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CHEST CT IN COVID-19 PNEUMONIA'S FOLLOW-UP: ABOUT 30 CASES

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Dedications

To the memory of my late grandparents

To my beloved parents

Who always believed in me, encouraged and supported me in all my endeavors, your prayers for me are what sustained me this far.

To my ever loving brother

Who taught me to persevere.

To my aunts, uncles, their husbands, wives and children

A profound feeling of love and gratitude

To all friendships that stood the test of time and change

Acknowledgments

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Professor of Radiology

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My profound respect and appreciation go to you.

To all my radiology professors

My highest consideration and deepest gratitude go to you professors. Through this work, I express to you my respect and appreciation. I am very honored to have been able to work beside you, and would like to express my immense indebtedness to you, for your patient guidance, enthusiastic encouragement, and useful appraisal throughout my training. Without your advice, assistance, and willingness to share your insights, this work would not have been possible.

Abbreviations List

ACE : Angiotensin-converting enzyme

ARDS : Acute respiratory distress syndrome

COPD : Chronic obstructive pulmonary disease

COVID-19 : Coronavirus disease

CRP : C-reactive protein

CRP : C-Reactive protein

CT : Computed tomography

CXR : Chest X-ray

DAD : Diffuse alveolar damage

D-E : Dual-energy

DLco : Diffusion capacity of lung for carbon monoxide

DTA : Data Driven Textural Analysis

DVT : Deep venous thrombosis

GGO : Ground-glass opacity

HRCT : High-resolution computed tomography

Il-6 : Interleukin 6

ILD : Interstitial lung disease

IPF : Idiopathic pulmonary fibrosis

LDH : Lactate dehydrogenase

LLL : Left Lower Lobe

LUL : Left Upper Lobe

MERS : Middle East Respiratory Syndrome

MPR : Multi-planar reconstruction

NSIP : Non-specific interstitial pneumonia

OP : Organizing pneumonia

PACS : Post-acute COVID syndrome

PE : Pulmonary Embolism

PFT : Pulmonary function test

RLL : Right lower lobe

RML : Right middle lobe

RNA : Ribonucleic acid

RT-PCR : Reserve transcription polymerase chain reaction

RUL : Right upper lobe

SARS-COV-2: Severe acute respiratory syndrome Coronavirus 2

UIP : Usual interstitial pneumonia

WHO : World Health Organization


Summary



Introduction


On March 11, 2020 the World Health Organization (WHO) proclaimed Coronavirus disease 19 (COVID-19) as a pandemic. It generated a critical planetary health crisis, and contaminated almost 277.6 million until 23 December 2021. It has caused over 5.3 million deaths across the world [1]. Its diagnosis relies on reverse transcriptase polymerase chain reaction (RT-PCR)'s detection of viral nucleic acid in the respiratory discharges. Using chest-computed tomography (CT) as a standard COVID-19 diagnostic tool is not advised by radiological societies. Nonetheless, CT performance is necessary in severe presentations and patients with respiratory degradation throughout the disease evolution. CT monitors the disease evolution and therapeutic response as well [2–4]. COVID-19 survivors present diverse clinical courses. Some recover fully while some experience residual symptoms or functional impairment [5].

As COVID-19's long-term effects are not entirely elucidated yet, the informations from former coronavirus infections could offer valuable understandings. In a study of SARS patients, 36% presented remaining chest X-ray (CXR) lung anomalies at 3 months that lowered to 30% at 6 months. At 6 months, 16% of survivors suffered from diminished diffusion capacity of lungs (DLco), indicating that remaining imaging anomalies had significant physiological repercussions [6]. Likewise, 36% of MERS survivors had remaining radiographic anomalies after a 1 to 8 months follow-up [7].

The initial data indicate that lung abnormalities do not fully clear-up in each Covid-19 survivor and in some progress to pulmonary fibrosis [5]. Some published reports have evaluated longitudinal variations of post-COVID lung parenchyma anomalies, however they primarily concentrated on short-term modifications [8–11].

Understanding post-COVID lung changes on CT could help identify risk factors for lasting COVID-19-provoked pulmonary sequelae, and thus precipitate the introduction of suitable treatment. It might help select patients for antifibrotic drugs trials' enrollment.

This study aims to report residual radiological lung findings, and identify the percentage of full radiographic resolution on intermediate- and long-term follow-up (3 months or more).


Physiopathology


Coronaviruses are sizable, encased, RNA viruses identified in humans and different mammalians. They adjust through genetic recombination to contaminate novel hosts. Bats constitute a natural SARS-CoV-2 reservoir, but it humans become contaminated by means of an intermediate host, namely the pangolin [9,10]. Coronaviruses induce respiratory, gastrointestinal, and neurological signs. SARS-CoV-2 is the 3rd coronavirus to occasion severe, universally spread illness in humans [11], succeeding to the severe acute respiratory syndrome (SARS), and Middle East respiratory syndrome (MERS) outbreaks [12]. SARS-CoV-2 has a 60 - 140 nm diameter and characteristic 9 - 12 nm spikes, responsible for its solar corona appearance [13].

1. THE HOST'S IMMUNE RESPONSE

In the initial stage, SARS-CoV-2 attacks nasal, bronchial cells and pneumocytes, by means of the spike (S) protein attached to the ACE2 receptor [14]. Lymphopenia can result from SARS-CoV-2 infecting and killing T lymphocytes. Moreover, the inflammatory riposte diminishes lymphopoiesis and accentuates lymphocyte apoptosis.

In late-stage Covid-19, viral replication increases, and the epithelial-endothelial wall is disrupted. SARS-CoV-2 targets endothelial cells as well, magnifying inflammation and setting-off a monocytes and neutrophils influx. Interstitial infiltration and edema form and present as GGO on CT. Pulmonary edema with hyaline membrane develops, filling the alveoli, corresponding to ARDS (Figure.1 [15]) [16].

In severe COVID-19, uncontrollable coagulation activation and clotting factors consumption take place [17, 18]. Inflammation might cause microthrombi explaining the elevated prevalence of thromboembolism in severe patients [19]. The host's dysregulated response to infection induces sepsis, which could lead to multi-systemic dysfunction.

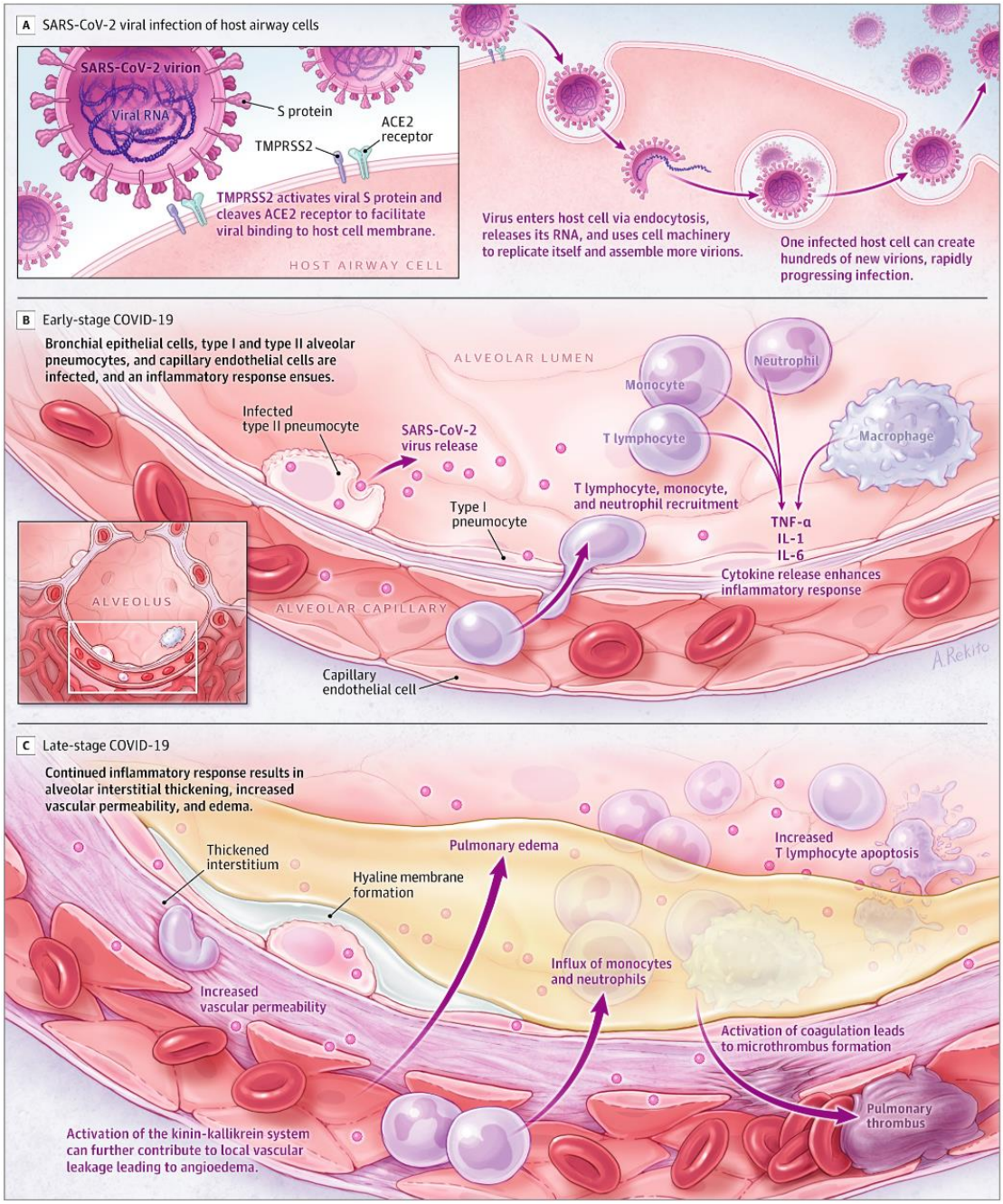


Figure 1: SARS-Cov-2' immunopathogenesis

From: Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. JAMA. 2020; 324(8):782-793. doi:10.1001/jama.2020.12839

2. Transmission

Face-to-face contact droplets expulsion is the most frequent transmission mode. Touching contaminated surfaces is another mode of transmission. It is believed that the viral load found on surfaces drops quickly between 48 to 72 hours [20]. Aerosol spread may occur as well [21,22]. Maternal COVID-19 is thought to be linked to a low vertical transmission hazard [23,24]. Viral shedding starts around 2 to 3 days before symptoms onset, and peaks over symptoms' onset [25]. An estimated 48% to 62% of spread might be due to pre-symptomatic carriers [26]. Transmission does not occur when exposed to the index case 5 days following symptoms' start [27], suggesting that patients' isolation release can be based on clinical recovery. The Centers for Disease Control and Prevention advise no less than ten days isolation ensuing clinical manifestations' onset and three days following recovery [28].

Anatomy – CT radiological anatomy

1. AIRWAYS

The airways consist of the trachea, bronchi, bronchioles and distal small airways.

1.1. TRACHEA

9–12 cm in length. It starts at the cricoid (C6) and bisects at the carina (T5).

Formed by 12–16 partial cartilage rings. Its posterior wall is fibrous.

1.2. BRONCHI

At the carina, the trachea bifurcated to 2 major bronchi.

- Right main bronchus:
  - ✓ Short and vertically oriented (Figure.2).
  - ✓ From which the right upper lobe bronchus emerges.
  - ✓ Enters the hilum and extends as the bronchus intermedius.
- Left main bronchus:
  - ✓ Longer and more horizontal (Figure.2).

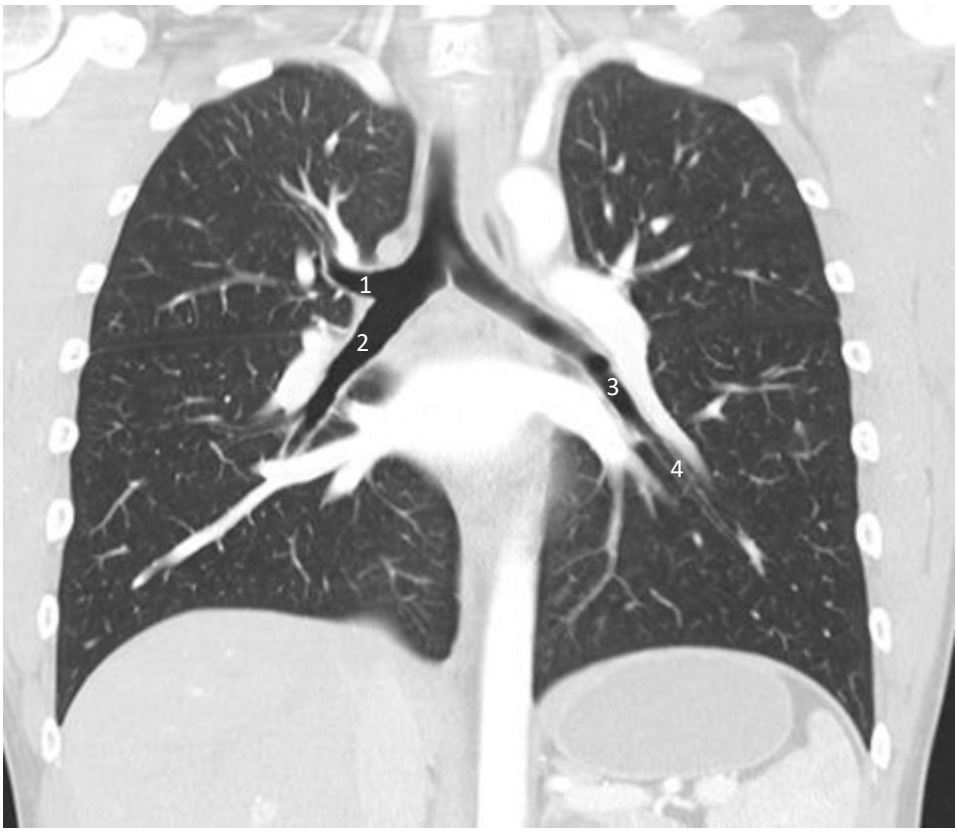


Figure 2: Coronal MPR Lung window CT image

1: Right upper lobe bronchus, 2: Bronchus intermedius, 3: Left lower lobe bronchus,

4: Left Lateral basal segmental bronchus

The lung lobes are divided into segments supplied by segmental bronchi, arteries and veins.

The segmental bronchi are designated using the Boyden system; 1961 (Figures. 3):

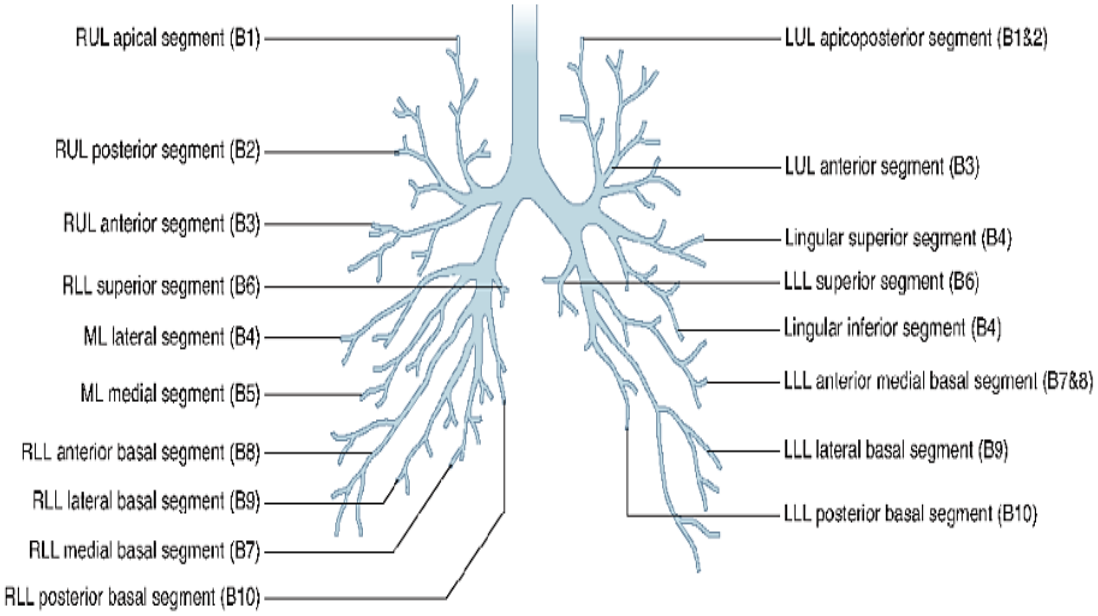


Figure 3: Line drawing of bronchial tree

- Right upper lobe bronchus :
  - apical (B1)
  - posterior (B2)
  - anterior (B3)
- Right middle lobe bronchus:
  - lateral (B4)
  - medial (B5)
- Right lower lobe bronchus:
  - apical (B6)
  - medial basal (B7)
  - anterior basal (B8)
  - lateral basal (B9)
  - posterior basal (B10).
- Left upper lobe bronchus

- ·apico-posterior (B1 + B2)
- anterior (B3)
- lingular – superior (B4)
- lingular – inferior (B5)

- Left lower lobe bronchus
  - apical (superior) (B6)
  - antero-medial basal (B7 + 8)
  - lateral basal (B9)
  - posterior basal (B10)

The segmental bronchi split into smaller bronchioles (6–20 divisions), until the terminal bronchiole and the acinus.

1.3. SECONDARY PULMONARY LOBULE

Smallest unit – 1–2.5 cm in diameter, polyhedron shape.

Supplied by a lobular bronchiole, artery and vein (Figure.4)

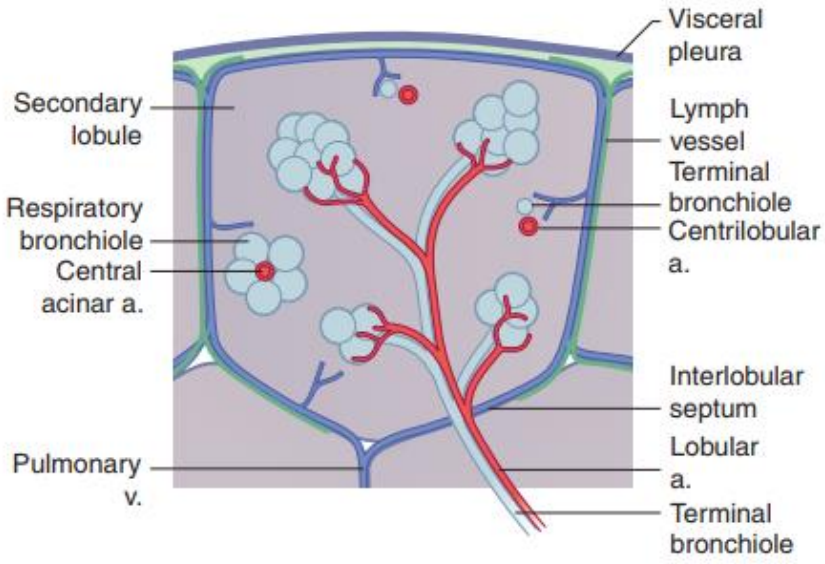


Figure 4: Line drawing of secondary lobules

Bordered by interlobular septae.

Normally not observed on CT; can be seen on HRCT (Figure.5).

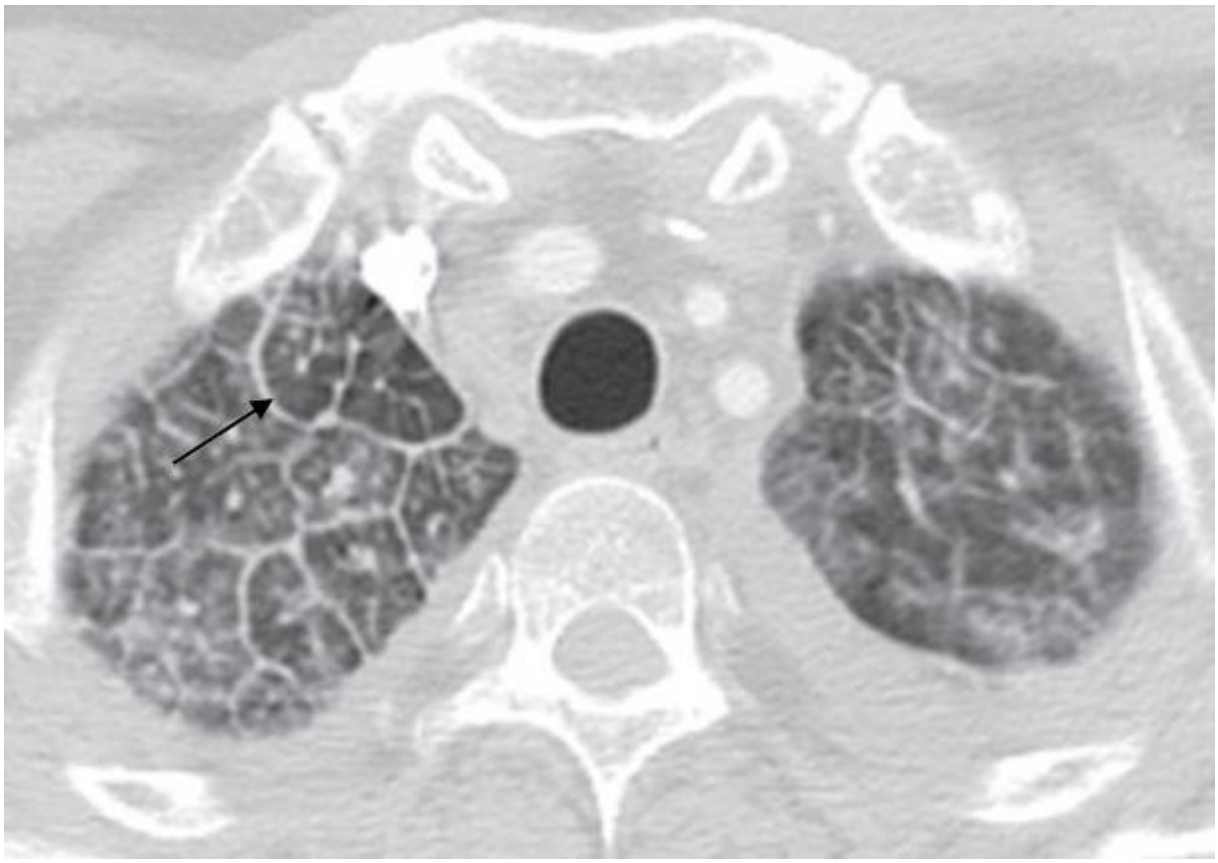


Figure 5: Thickened interlobular septae (arrow).

2. LOBAR ANATOMY

The right lung is bigger than the left and presents 3 lobes and 10 segments; the left lung possesses 2 lobes and 8 segments; nominated following the bronchi (Figure.6).

Right upper lobe – 3 segments:

- apical
- posterior
- anterior

Right middle lobe – 2 segments

- medial
- lateral

Right lower lobe – 5 segments

- superior
- medial basal
- anterior basal
- lateral basal
- posterior basal

Left upper lobe – 4 segments

- apico-posterior
- anterior
- lingula – superior
- inferior

Left lower lobe – 4 segments

- superior
- anterior basal
- lateral basal
- posterior basal

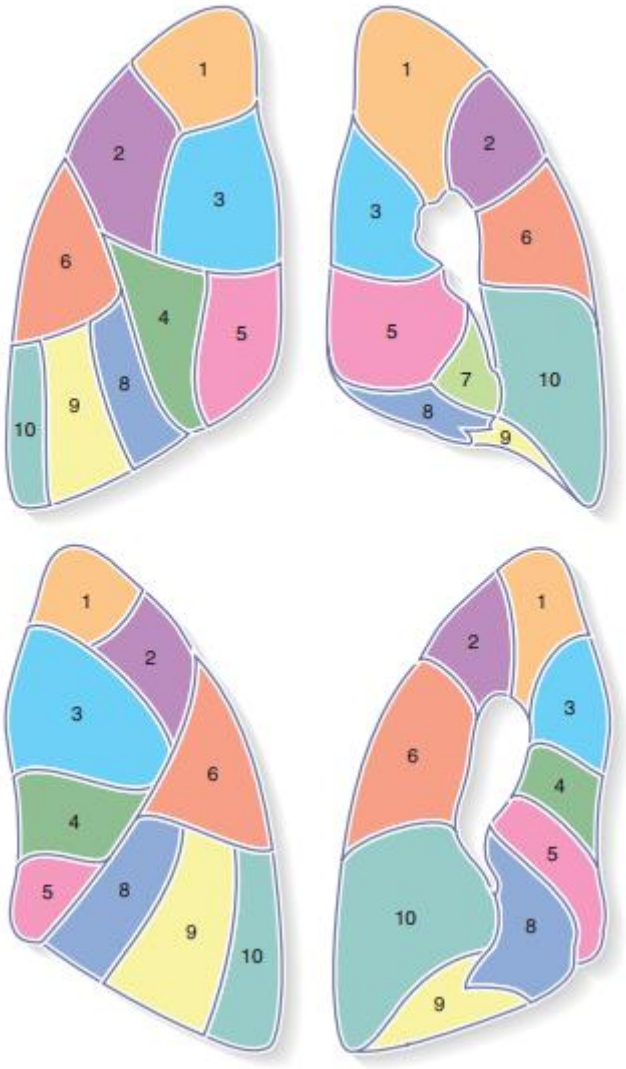


Figure 6: Line drawing of lobar anatomy

3. PULMONARY VESSELS

3.1. PULMONARY ARTERIES

The right ventricle gives rise to the main pulmonary trunk that parts into :

- The longer right pulmonary artery splits into:

  - upper truncus arteriosus to the RUL
  - descending interlobar artery to the RML and RLL

- The shorter left pulmonary artery divides into (Figure.7):

  - a LUL ascending branch
  - an interlobar artery for the lingula and LLL.

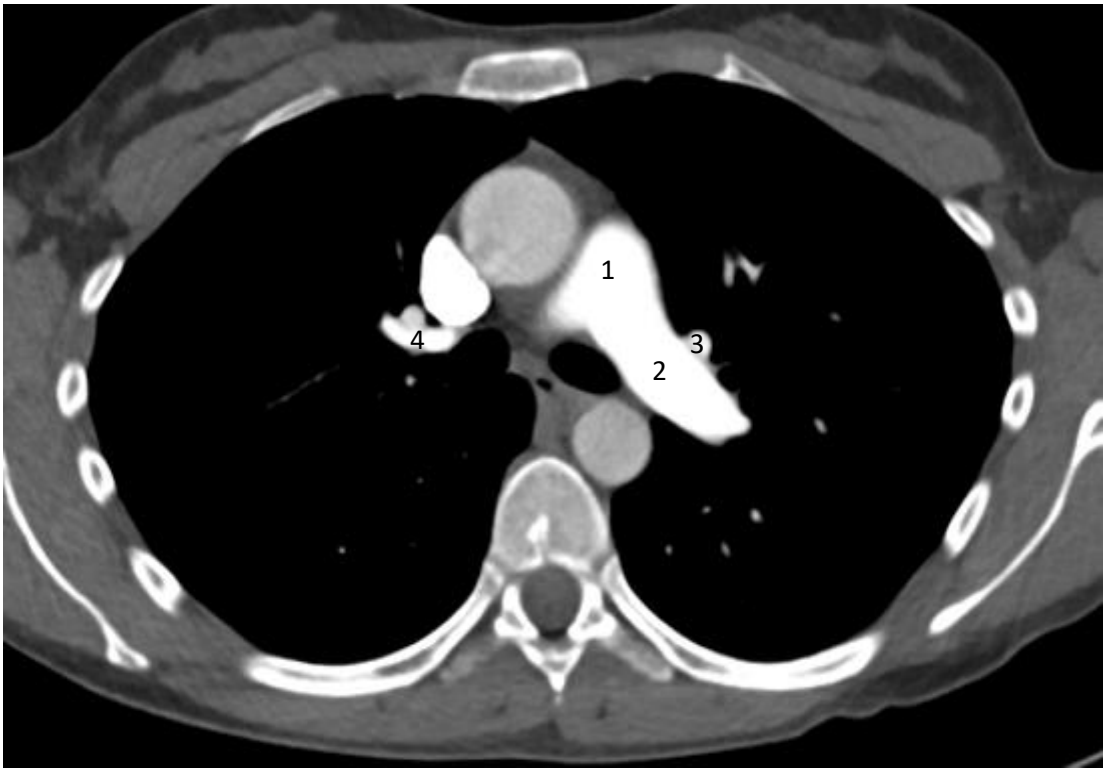


Figure 7: Axial CT pulmonary angiogram image

1: Pulmonary trunk, 2: Left pulmonary artery, 3: Left superior pulmonary vein, 4: Upper truncus arteriosus

3.2. PULMONARY VEINS

In 70% of people; 2 pairs of veins – superior and inferior– are present on each side.

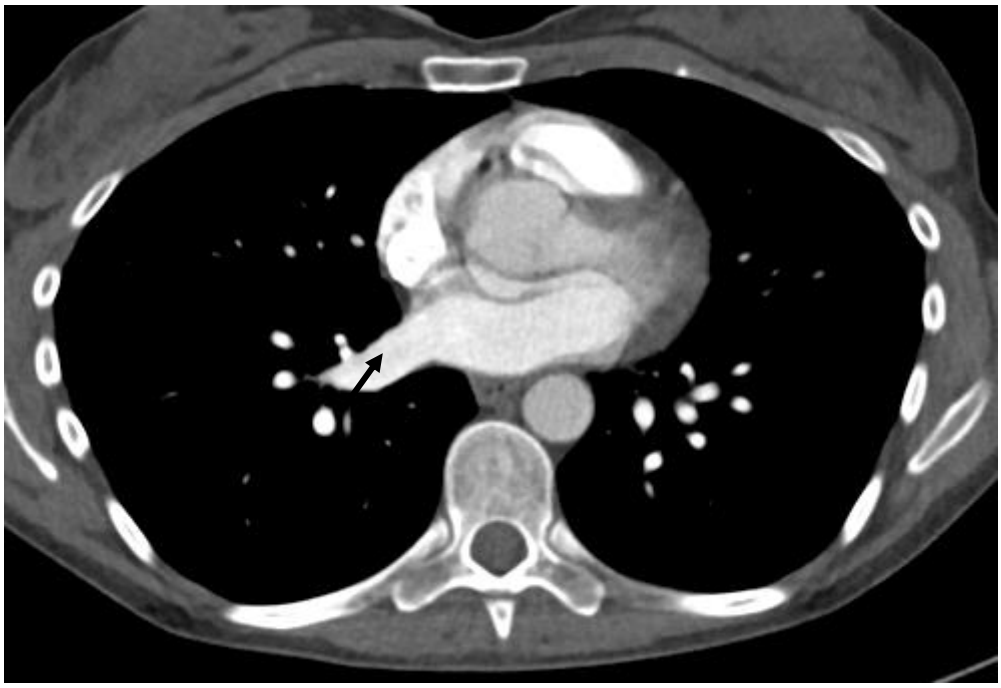


Figure 8: Axial CT through the right inferior pulmonary vein (arrow)

In 12–25% of the population, a common trunk for the superior and inferior veins is present and is more frequent on the left.

4. HILUM

It consists of the pulmonary artery, pulmonary vein, bronchus and nodes.

In 97% of people; the right hilum is lower than the left.

5. PLEURA

A fine membrane composed of:

- Parietal pleura: contours the non-pulmonary planes (diaphragm, pericardium and mediastinum)
- Visceral pleura: contours the pulmonary planes.

The two attach at the hilum, and extend inferiorly as a double layer– the pulmonary ligament.

The two layers cannot be delineated on CT.

The intercostal strip, visualized on CT between the ribs, consists of the two layers of pleura, extra-pleural fat, the extra-thoracic fascia and the innermost intercostal muscle (Figure.9).

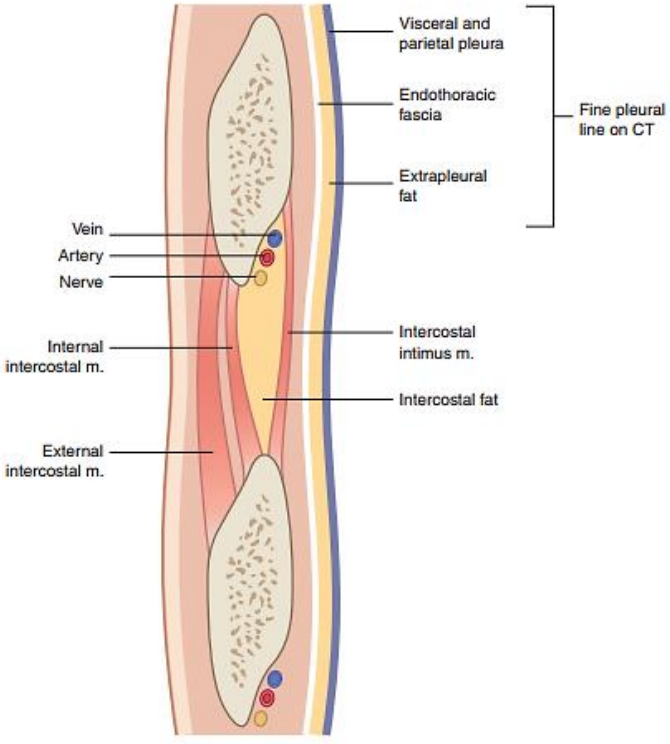


Figure 9: Line drawing of chest wall

Pleural fissures separate the lung lobes.

- Right oblique (major) fissure:

Splits up the RLL on one side, and the RUL and middle lobe on the other side.

- Left oblique fissure:

Sets apart the upper lobe from the lower lobe.

The oblique fissure is not visualized on a PA Chest X-ray, but is identified on a lateral Chest X-ray and on CT (Figure.10).

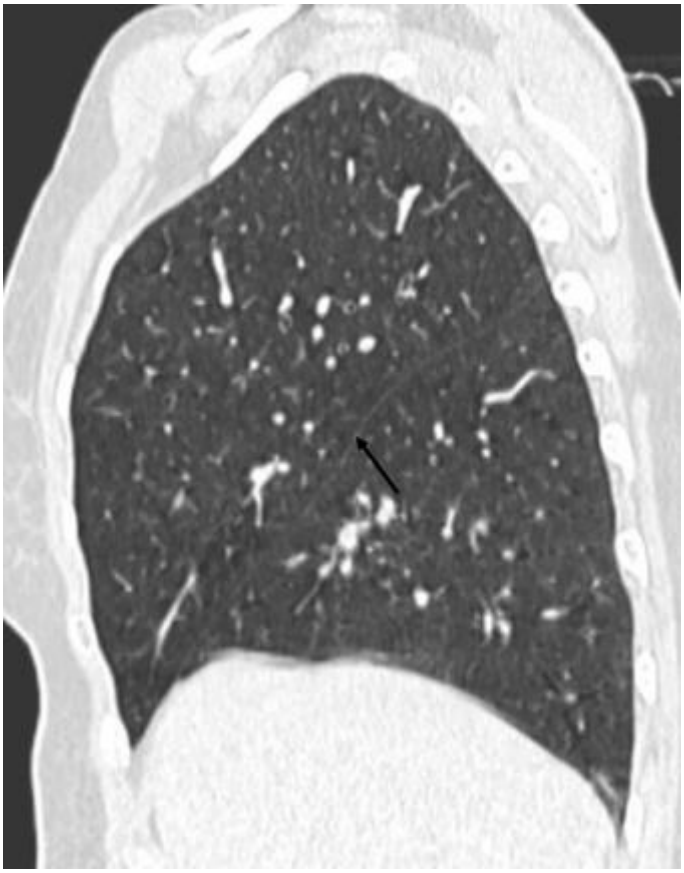


Figure 10: Sagittal CT shows the oblique fissure (Arrow).

- Horizontal (minor) fissure:

Splits up the RML and the RUL. On CT it appears as an area devoid of vessels.

- Azygous fissure:

On the right.

Owing to an abnormal azygous vein development (Figure.11).

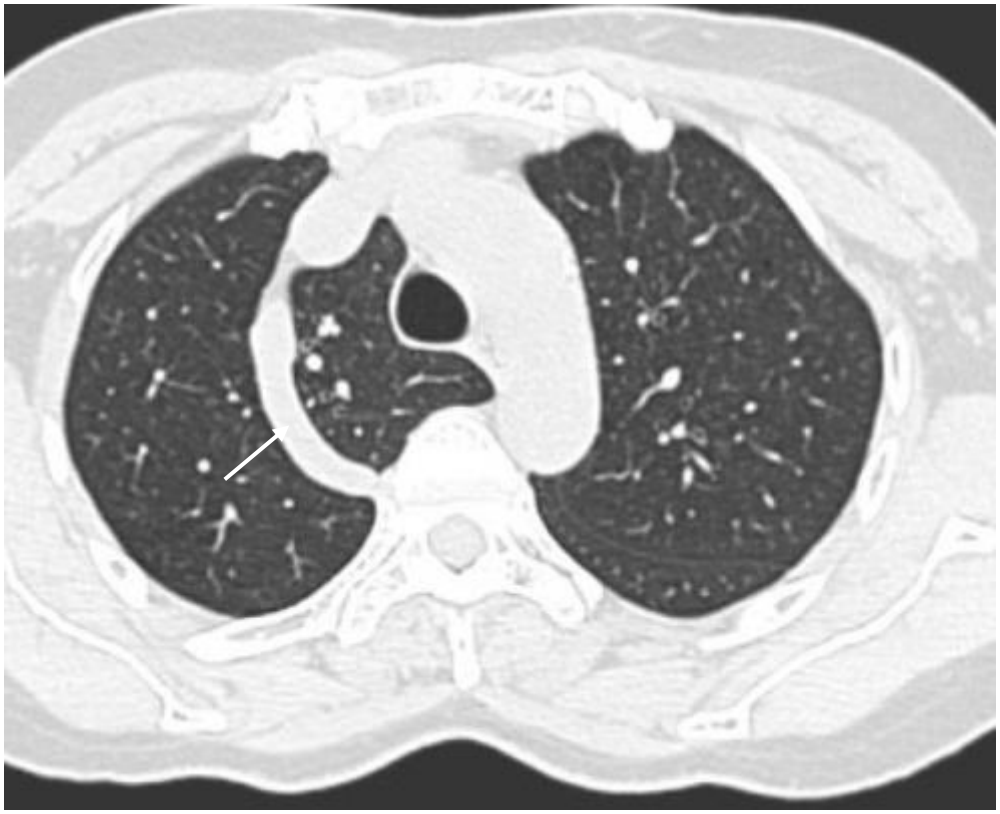


Figure 11: Axial CT showing the azygous fissure (arrow).

- Incomplete fissures:

Fail to reach the hilum.

Commoner on the right, they occur in 73% of oblique fissures and up to 60–90% of horizontal fissures.

- Accessory fissures:

Present 30–50% of people and visualized in 16–21% of CTs.

A fissure setting apart the LUL from the lingula in 8–18%.

Superior accessory: sets apart the LLL basal segments from the superior segment.

Inferior accessory: sets apart the medial basal segment from the rest; commoner on the right.

6. MEDIASTINUM

Expands from the sternum to the dorsal spinal column and from the thoracic entrance to the diaphragm. Sub-divided into:

- Superior mediastinum : from the thoracic inlet to T4/5, comprises the thymus, great vessels, and the trachea.
- Inferior mediastinum : underneath, divided into :
  - ➔ anterior –anterior to the pericardium, ascending aorta and superior vena cava
  - ➔ middle – comprises the heart, great vessels, the hilum and carina
  - ➔ posterior – (retro-cardiac and paravertebral spaces) contains descending aorta, oesophagus, azygous system and spinal column.

• On CT mediastinal structures are well seen (Figures 12-13).

6 5

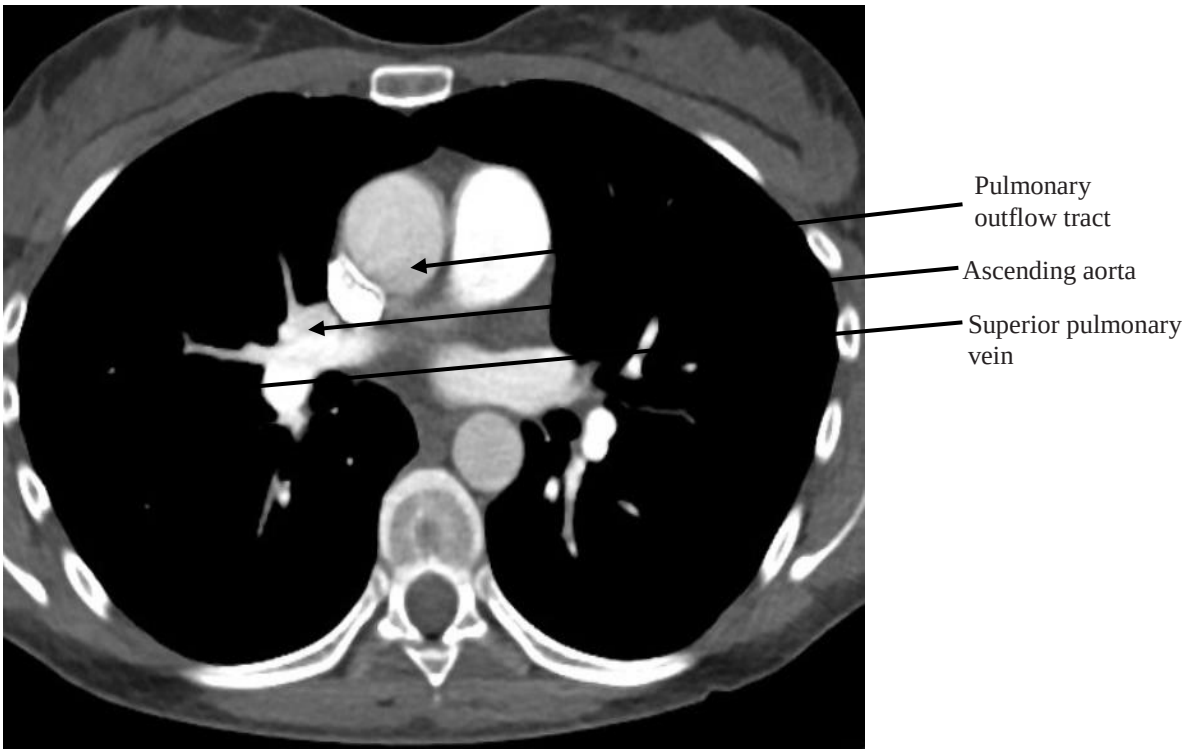


Figure 12: Axial CT of mediastinum

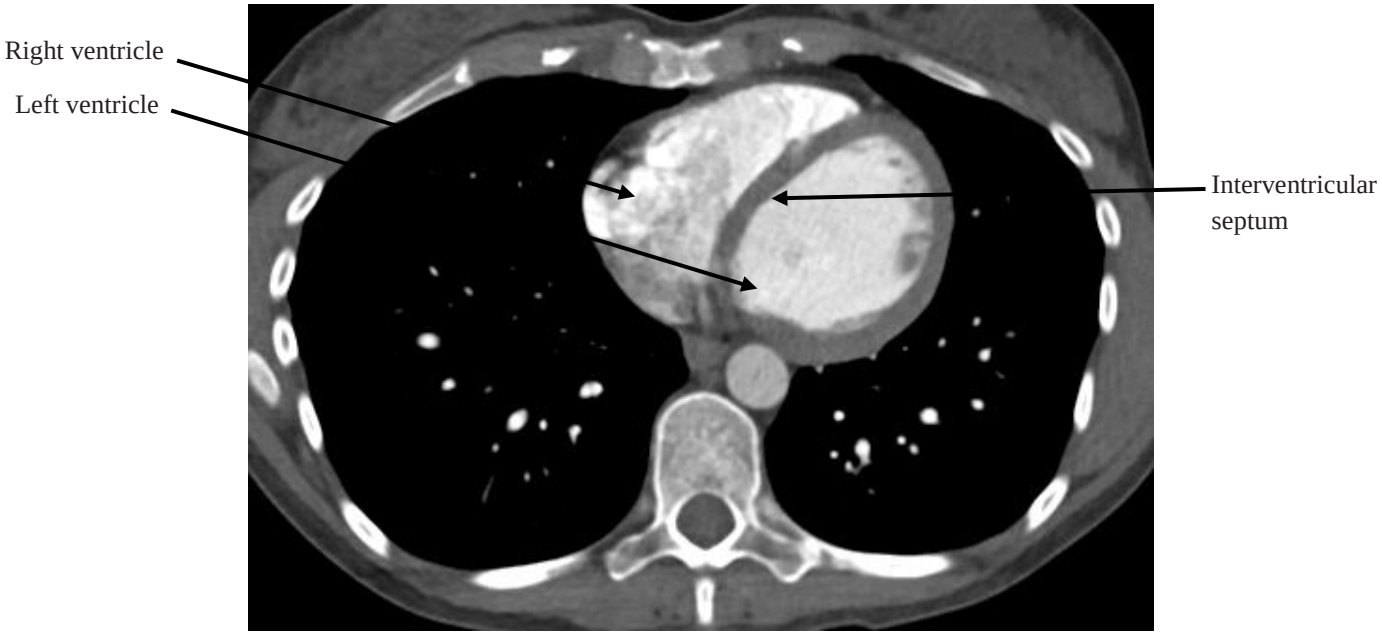


Figure 13: Axial CT of mediastinum

7. LYMPH NODES

Soft tissue masses seen on CT. Normal lymph nodes's short axis measures less than 1 cm and are oval rather than round. The nodal stations usually used are determined by the AJCC/UICC.

Level 1

Low cervical – superior to a horizontal line at the upper left brachiocephalic vein.

Level 2

Upper para-tracheal – lies superior to a tangent to the aortic arch upper margin and underneath level 1.

Level 3

Pre-vascular and retro-tracheal

Level 4

Lower paratracheal – inferior to the aortic arch upper margin and above the upper margin of the right main bronchus on the right.

Between the aortic arch superior border and the left main bronchus, medial to the ligamentum arteriosus on the left.

Level 5

Sub-aortic – lateral to the ligamentum arteriosus, aorta or left pulmonary artery

Level 6

Para-aortic – anterior and lateral to the aortic arch or ascending aorta or brachiocephalic artery underneath the upper aortic arch

Level 7

Subcarinal

Level 8

Paraoesophageal

Level 9

Within the pulmonary ligament, beside the posterior wall of the lower margin of the inferior pulmonary vein

Level 10

Hilar

Level 11: Interlobar [29].

Epidemiology

Since the first cases from Wuhan-China, by 2019's end, reports have been indexed world-wide. Universally, over 270 million COVID-19 affirmed cases were accounted. Up-to-date case accounts are present on the World Health Organization and European Centre for Disease Prevention and Control sites.

Since merely a fraction of infections is identified and declared, the announced case records underrate the overall weight of COVID-19. Seroprevalence investigations in America and Europe indicated that with consideration of possible false positives or negatives, seropositivity reflecting the proportion of anterior SARS-CoV 2 exposures, surpasses the number of announced cases by 10-times or beyond [30-31].

Clinical manifestations

Frequent symptoms among inpatients comprise hyperthermy, cough, dyspnea, astheny, myalgias, nausea/vomiting or diarrhea, migraine, and runny nose. Anosmia or ageusia are the sole manifestation in almost 3% of cases [32].

Usual complications in hospitalized patients comprise pneumonia (75%); ARDS (15%); liver dysfunction (19%); heart injury, namely troponin rise (7%-17%), cardiac insufficiency, arrhythmias, and myocarditis; coagulopathy causing thromboembolisms (10%-25%); kidney lesions (9%); neurologic symptoms, including altered mental status (8%) and stroke (3%); and shock (6%) [32-33-34].

Cytokine storm and macrophage activation syndrome are unusual complications that critically ill patients might present.

Materials and methods

1. STUDY DESIGN

We carried out a retrospective study at Ibn Sina University Hospital-Rabat.

30 RT-PCR positive COVID-19 patients with no less than one follow-up CT and a time interval of at least 3 months separating the RT-PCR and the CT performance were enrolled.

Follow-up CT's major indications were residual symptoms or functional deterioration.

We gathered and studied the pertinent demographic, clinical, and scannographic features retrospectively.

2. CT PROTOCOL AND INTERPRETATION

We carried-out all CTs on a 16-Slice Siemens Multidetector scanner without administration of intravenous contrast medium. In cases of pulmonary embolism suspicion, CT pulmonary angiography was carried-out.

The patient was set up in a supine head-first position.

The used voltage was 100–120 kVp, and current 90–130 mAs. Images reconstruction into a 1.5 mm slice thickness was obtained. The images were analyzed in lung window (Width: 1500 HU; Level: - 600 HU) and mediastinal window (Width : 350 HU; Level : 50 HU).

We analyzed the following elements: (1) existence or not of lung opacities; (2) distribution: one vs two-sided; (3) dominant lung opacity: ground glass opacity (GGO), consolidation, GGO and consolidation, and linear/curvilinear opacities, (4) Sub-pleural bands, (5) Interlobular septal thickening, (6) Vascular dilatation, (7) Bronchiectasis, (8) Honey combing, (9) Architectural distortion,

(10) mosaic attenuation, and (11) Additional findings: Enlarged lymph nodes, Pleural fluid, and Pericardial fluid.

To evaluate the degree of lung opacification, a score built on the visual appraisal of the percentage of lung involvement was employed [35]. Every lobe was graded from 0 to 5: no involvement (0), < 5% (1), 5–25% (2), 26–50% (3), 51–75% (4) and 76–100% (5). The five lobes scores were totaled to get a whole CT severity score extending from 0 (no participation) to 25 (maximal participation).

Patients were then classified in two sets : (1) full resolution and (2) remaining pulmonary opacities.

Results

1. DEMOGRAPHIC CHARACTERISTICS

1.1. AGE

The age varied between 40 and 87 years with an average of 53.4 years.

1.2. GENDER

There were 16 males (53.3 %) and 14 females (46.7 %).

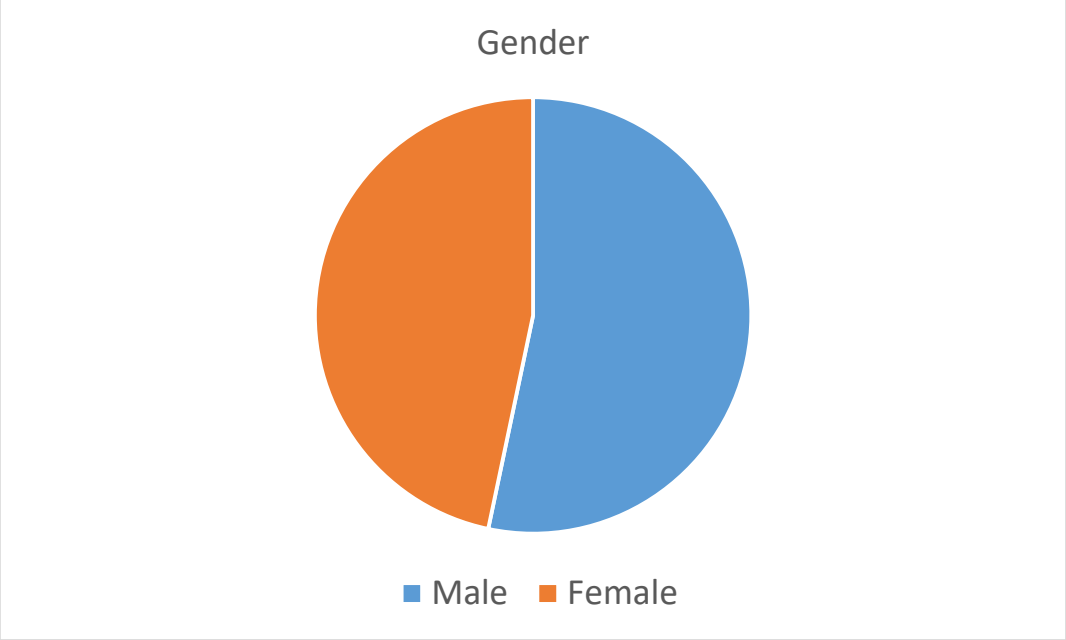


Figure 14: Gender

1.3. RESPIRATORY COMORBIDITIES

4 patients had chronic obstructive pulmonary diseases. 2 patients had pulmonary tuberculosis. 1 patient had recently diagnosed interstitial lung disease with indeterminate usual interstitial pneumonia pattern (UIP), and 2 patients had a pulmonary embolism.

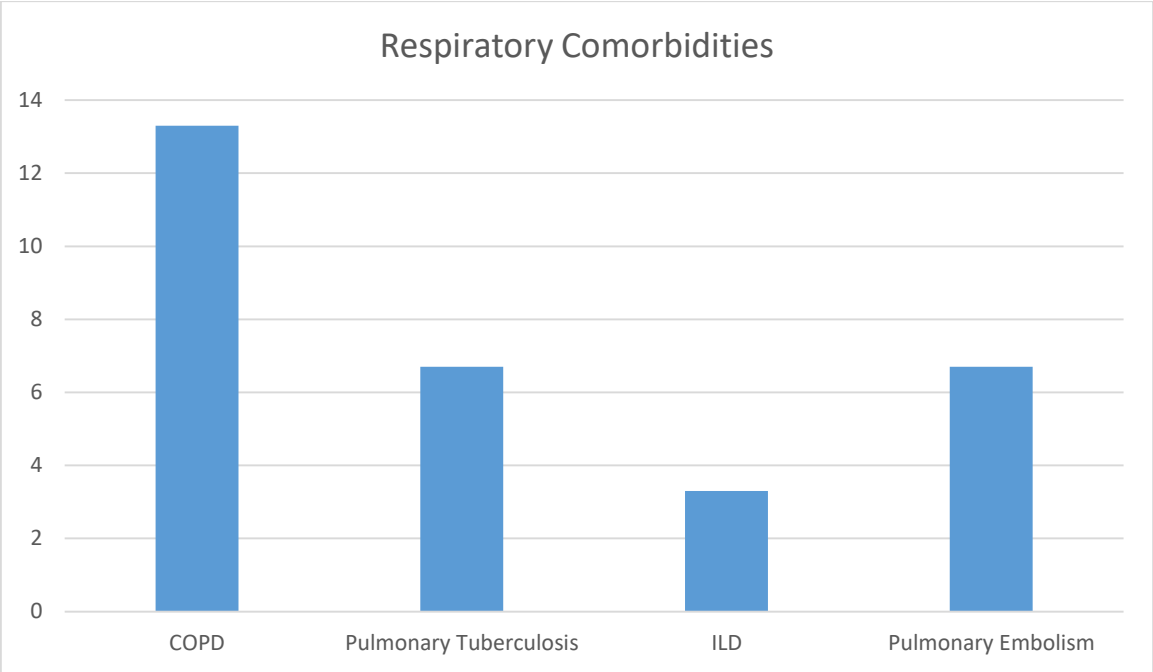


Figure 15: Respiratory Comorbidities

2. FOLLOW-UP CT INDICATIONS

CT was indicated for symptoms or functional impairment on follow-up in all cases.

3. TIME INTERVAL BETWEEN POSITIVE RT-PCR AND FOLLOW-UP CT

The time range between the positive RT-PCR and Follow-up CT varied between 3 and 12 months, with an average of 6 months.

4. CLINICAL MANIFESTATIONS

The major symptoms were Cough in 10 patients (33.3 % of cases), and dyspnea in 20 patients (66.7 % of cases).

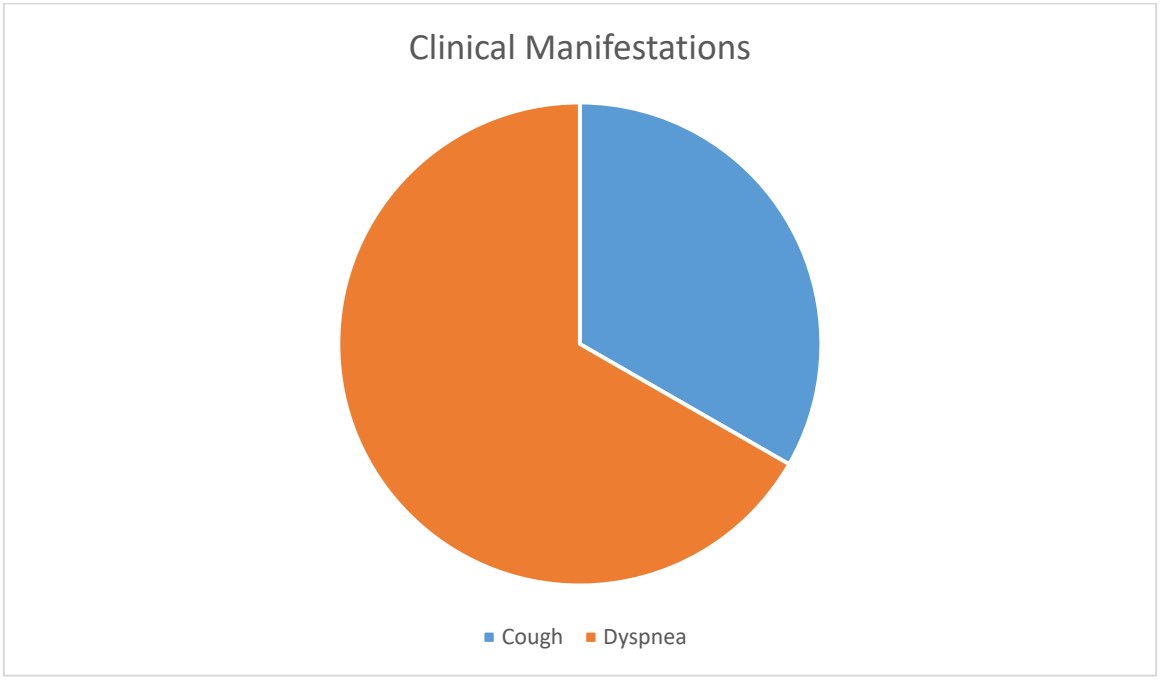


Figure 16: Clinical manifestations

5. FOLLOW-UP CHEST CT FEATURES

5.1. CT SEVERITY SCORE

Ct severity score ranged between o and 23. The mean score was 6.48.

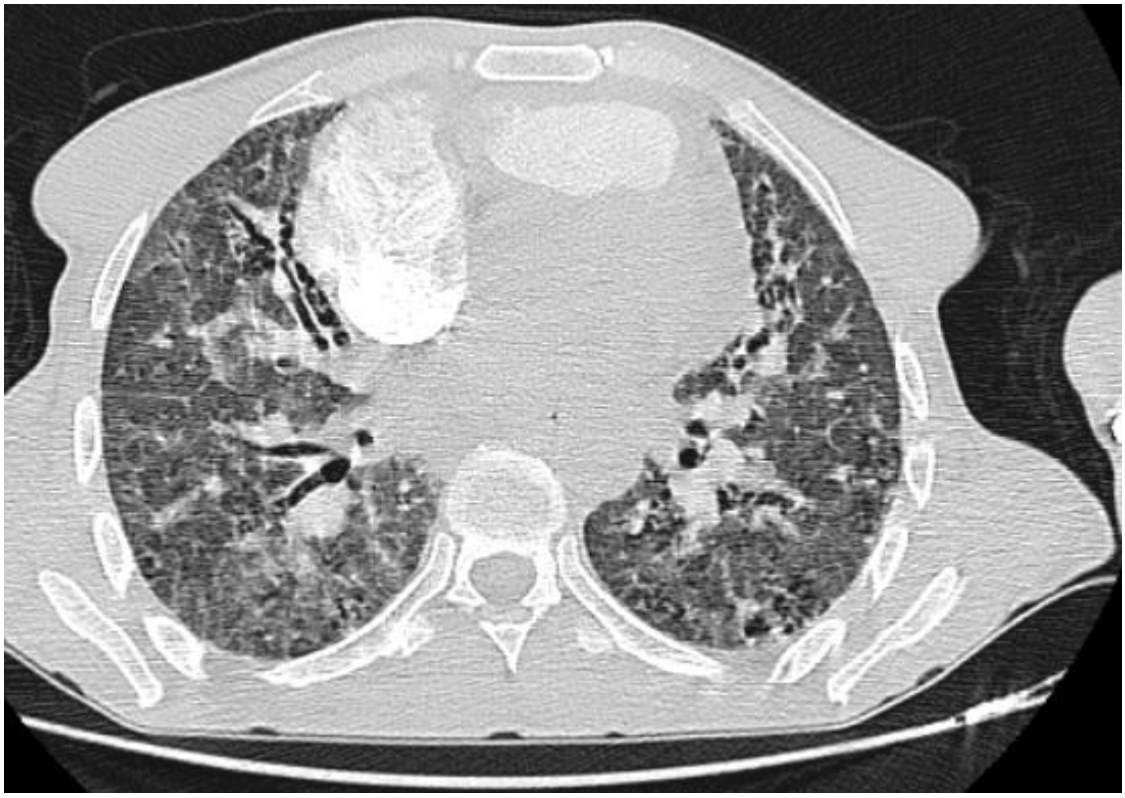


Figure 17: A 55-year-old man follow-up contrast-enhanced axial chest CT image in lung window, 5 months following initial presentation, showing extensive residual pulmonary ground glass opacities (23 CT severity score), and traction bronchiectasis.

5.2. DISTRIBUTION

Lesions' distribution was bilateral in 22 cases (73.3 %), unilateral in 2 cases (6.7%). No pulmonary opacities were detected in 6 cases (20 %).

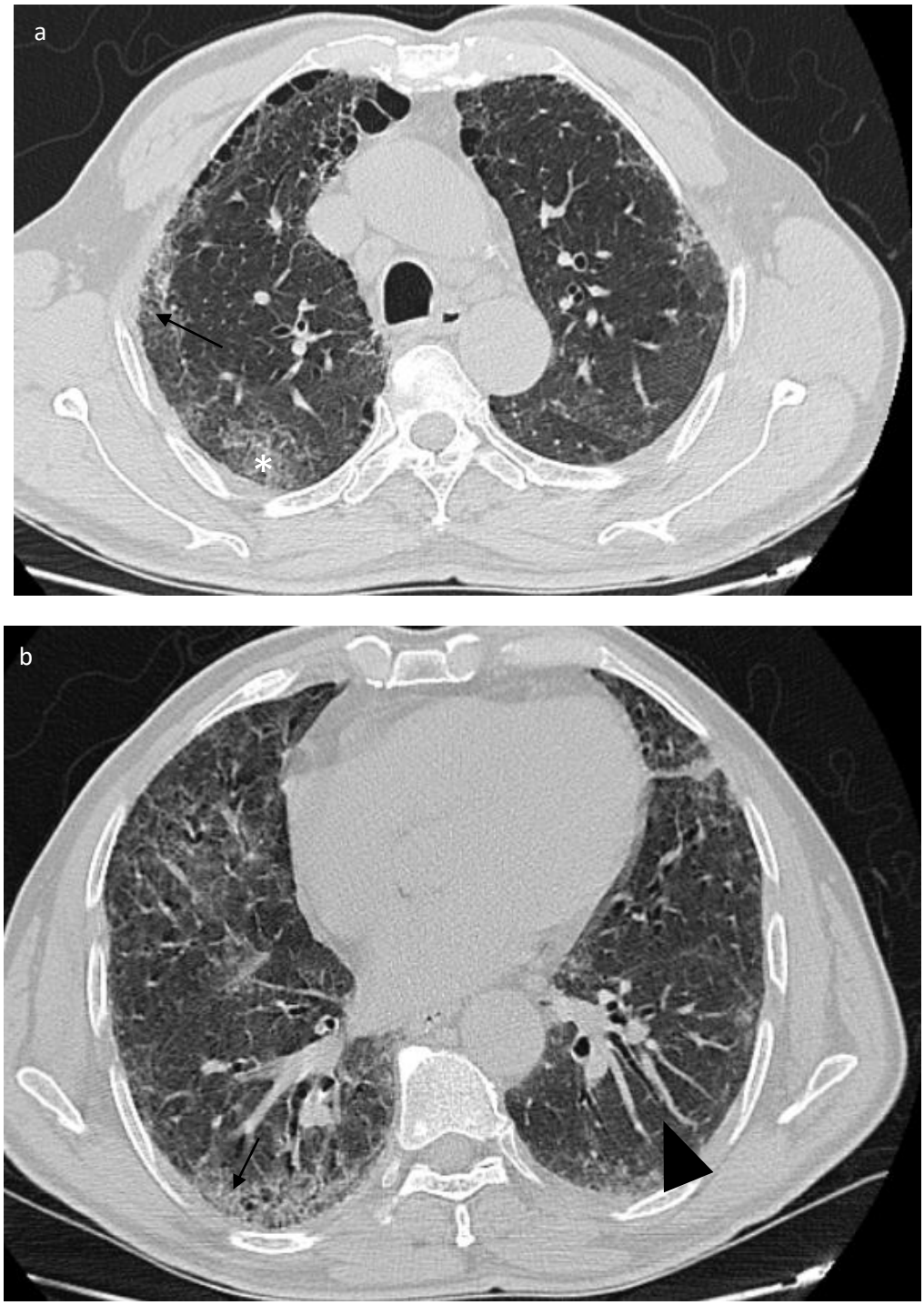


Figure 18: A 68-year-old male patient with COPD and severe coronavirus disease, 3 months following discharge. Axial non-enhanced chest CT images in lung window (a,b) showing bilateral involvement with residual light GGO (*), sub-pleural interlobular septal thickening (Black arrow), bronchiectasis, and vascular dilatation (Black arrow head).

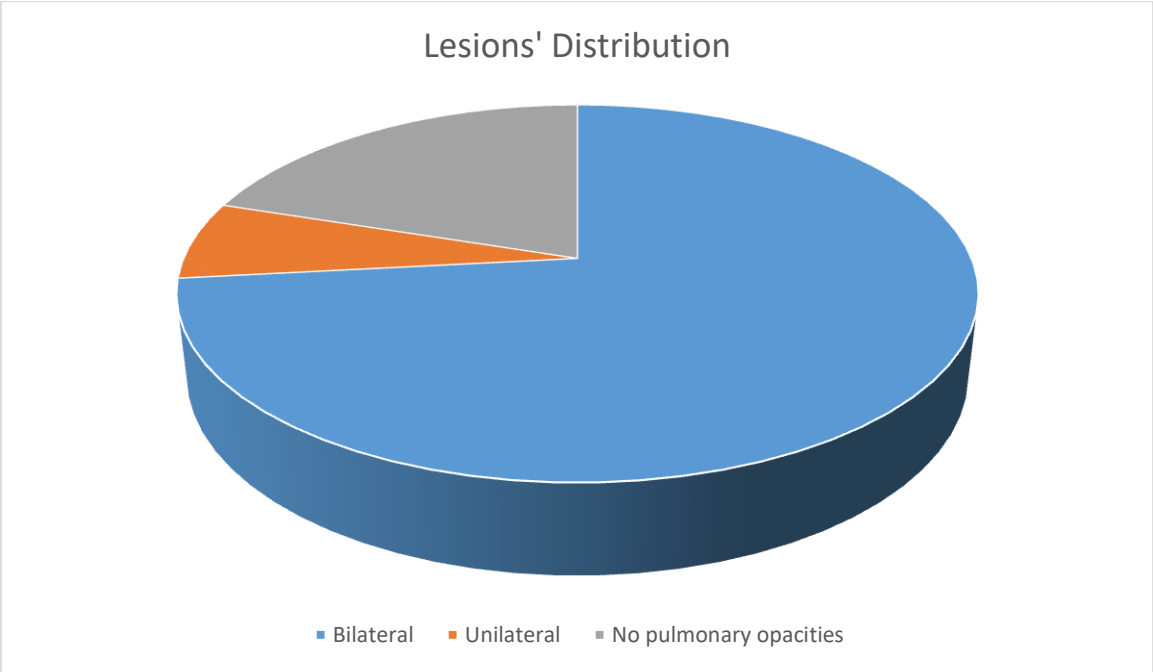


Figure 19: Lesion's distribution

5.3. IMAGING FINDINGS

Lung opacities were present in 24 cases (80 %).

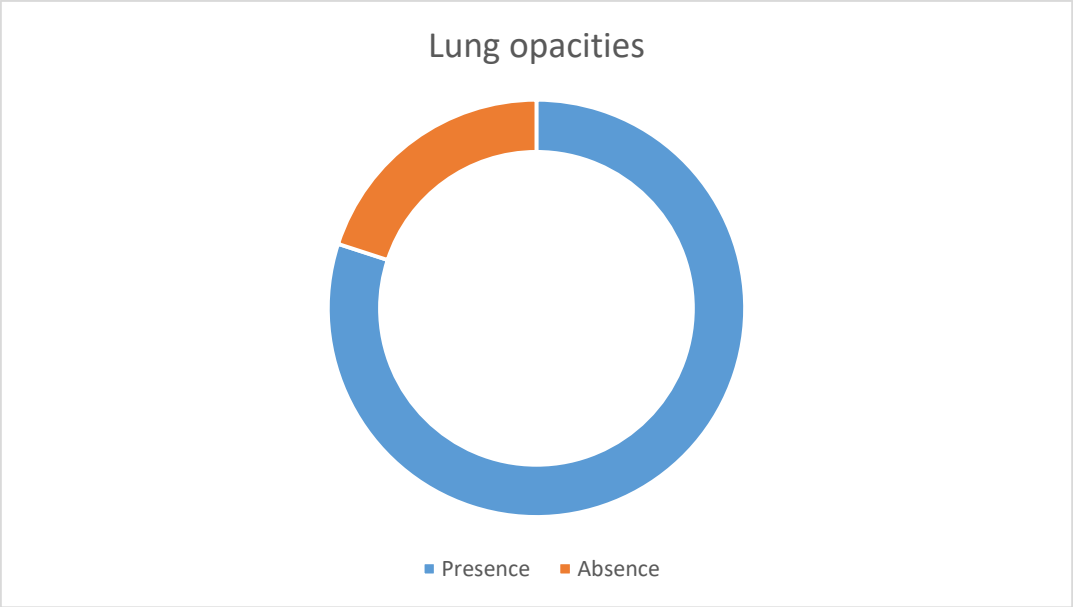


Figure 20: Lung opacities

The dominant lung opacities were Ground glass in 14 cases (46.7 %), Consolidations in 1 case (3.3 %), GGO + Consolidations in 2 cases (6.7 %), and linear/curvilinear opacities in 7 cases (23.3 %).

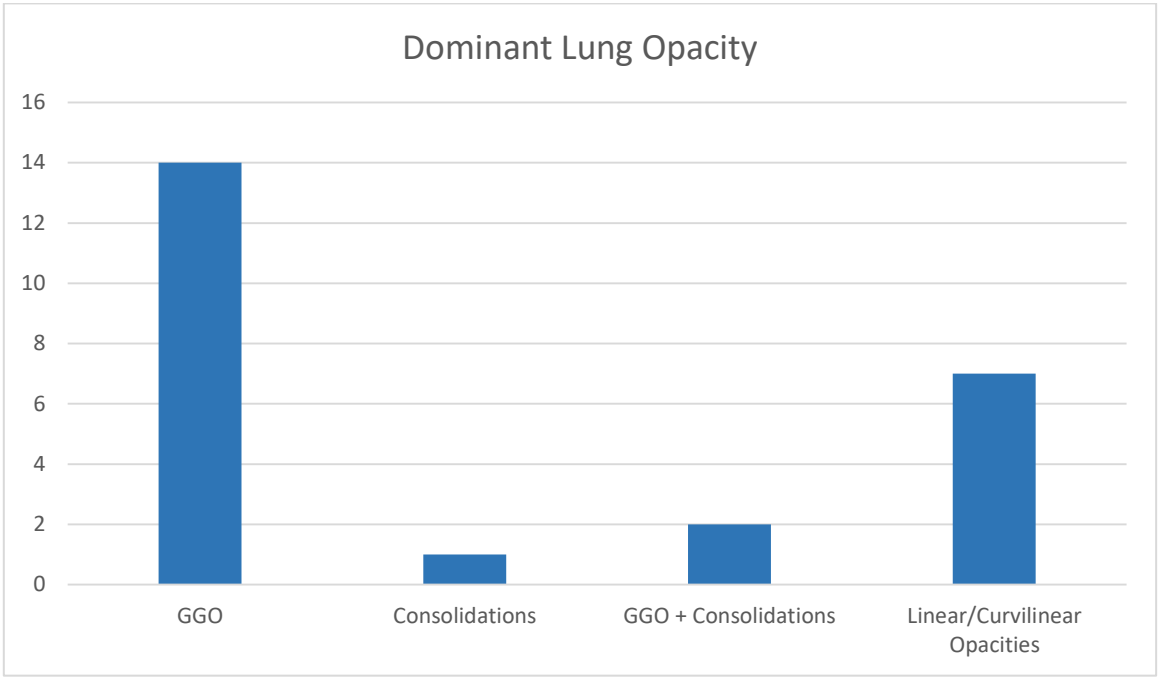


Figure 21: Dominant Lung Opacity

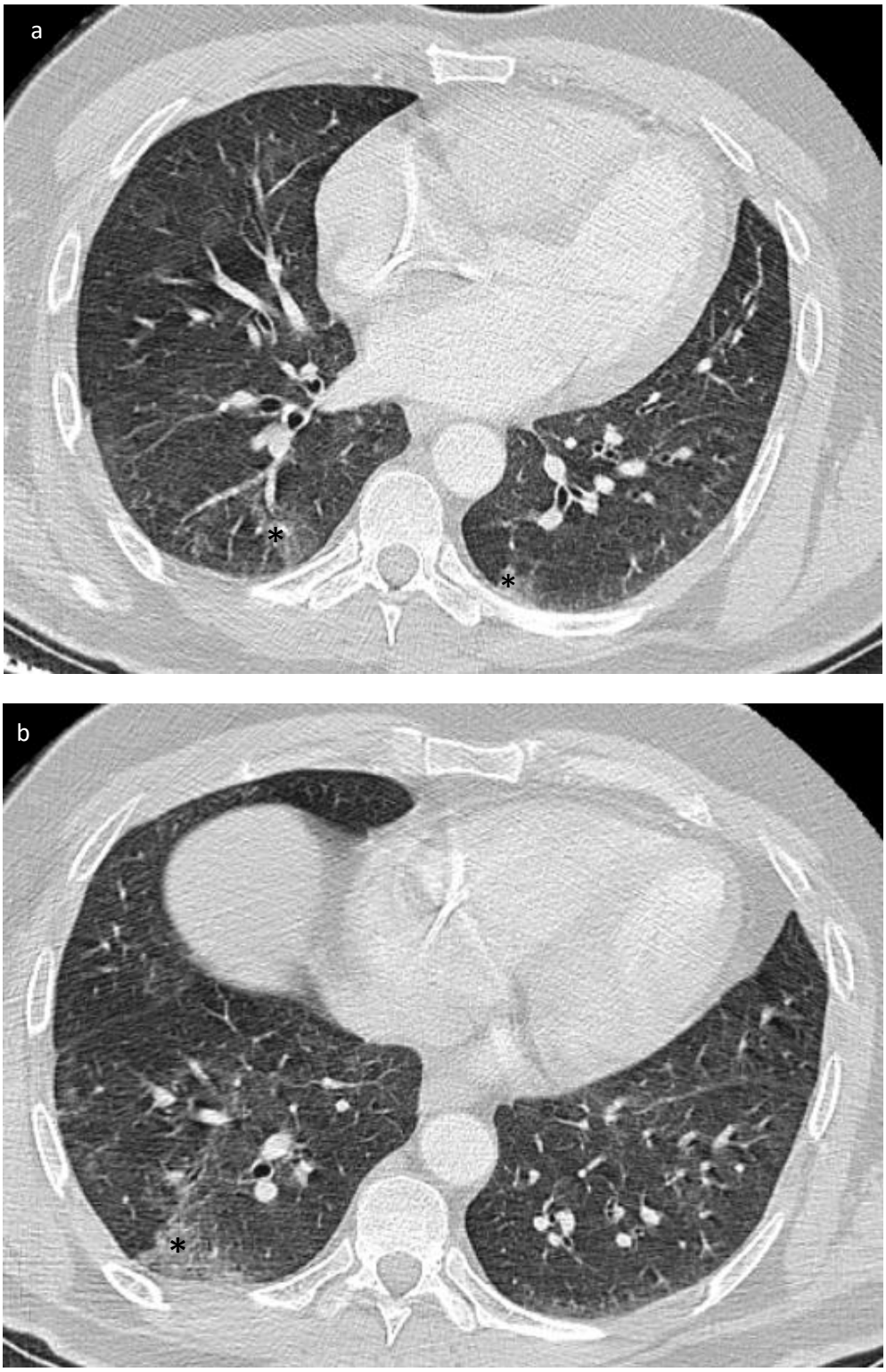
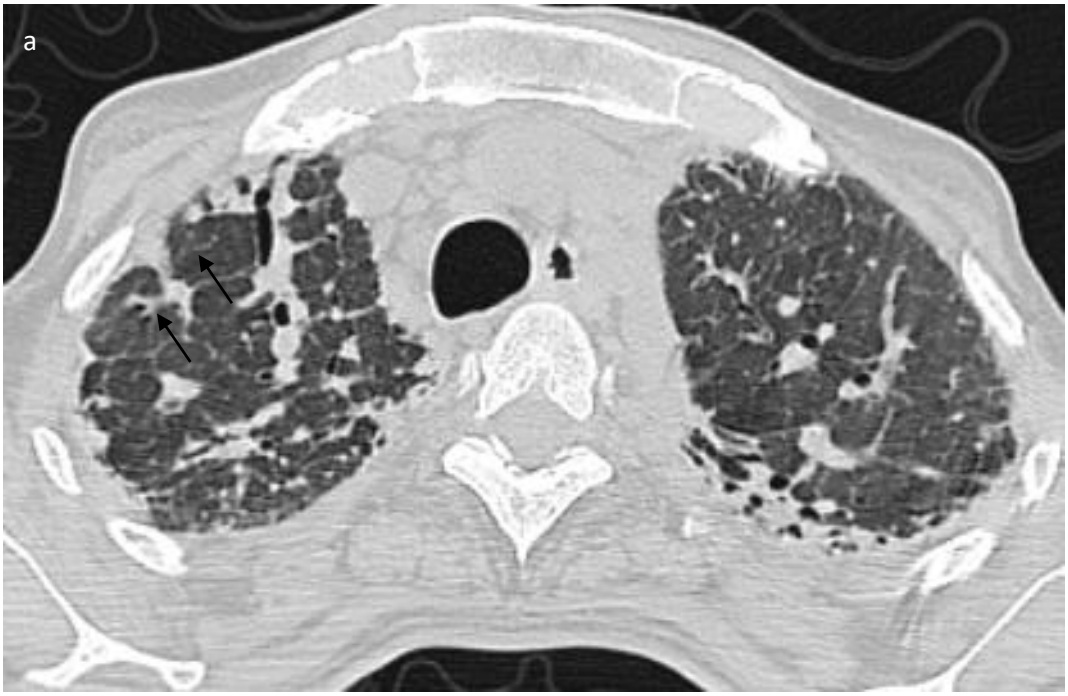
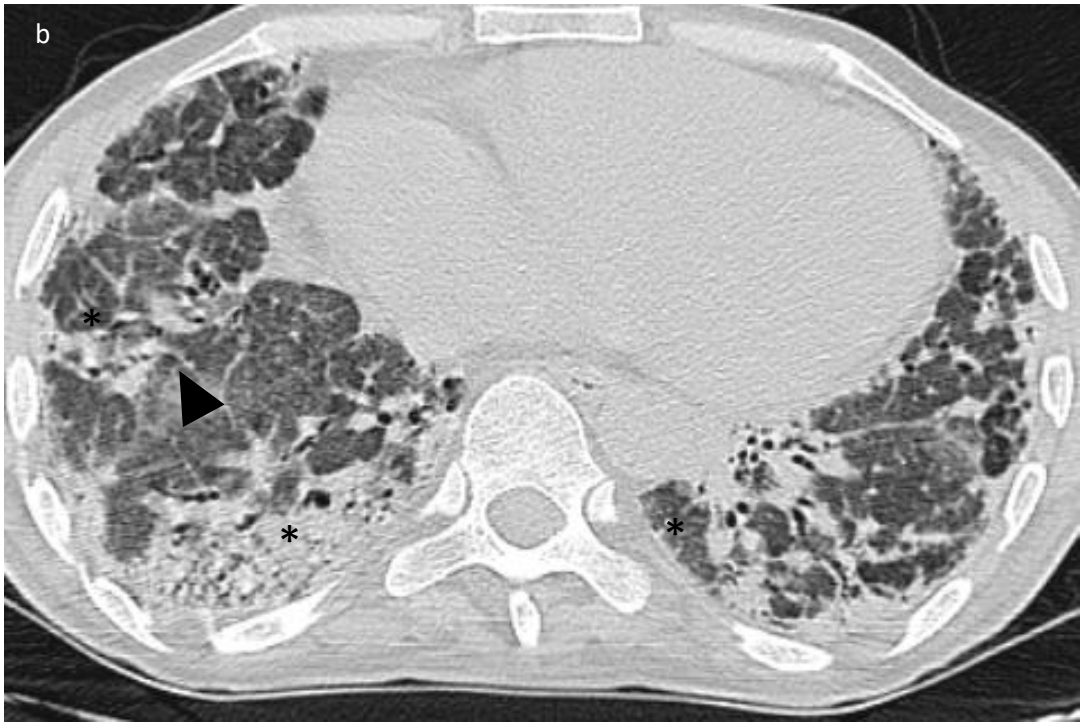


Figure 22: A 42-year-old-man 9 months follow-up axial non-enhanced chest CT images (a,b) showing residual, multi-focal, bilateral, sub-pleural, patchy ground glass opacities (*).


a


b

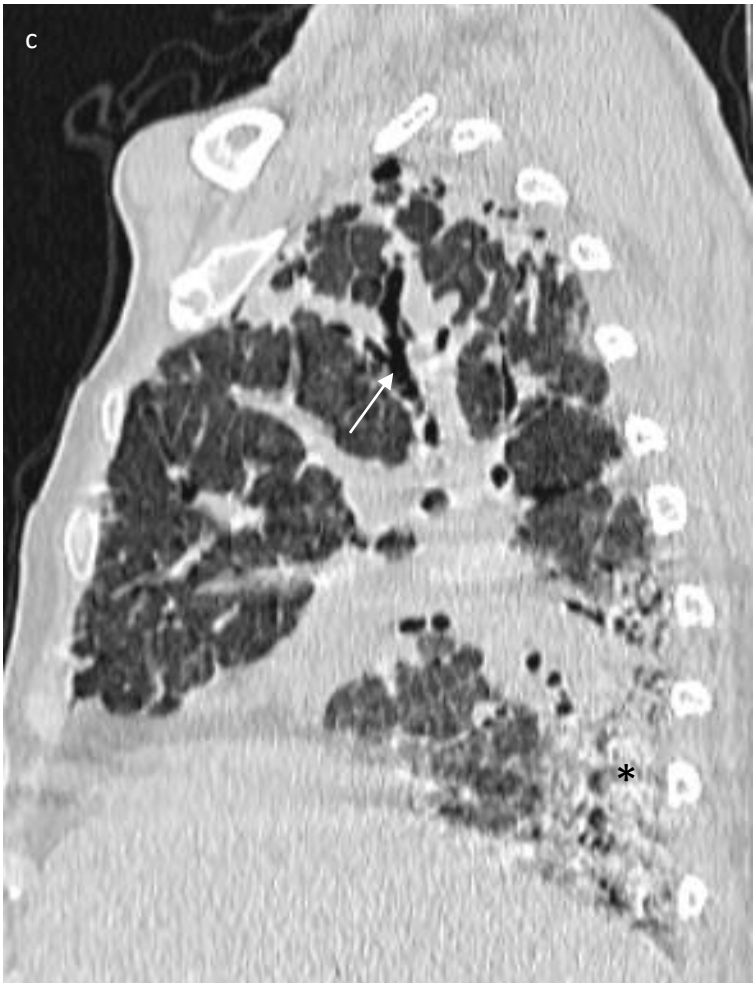


Figure 23: A 40-year-old-man 7 months follow-up non-enhanced chest CT axial (a,b) and sagittal images (c) showing residual, extensive multi-focal, bilateral, patchy dominant consolidations (*), some ground glass opacities (Black arrow head), alongside bronchiectasis (White arrow), and interlobular septal thickening (Black arrow).

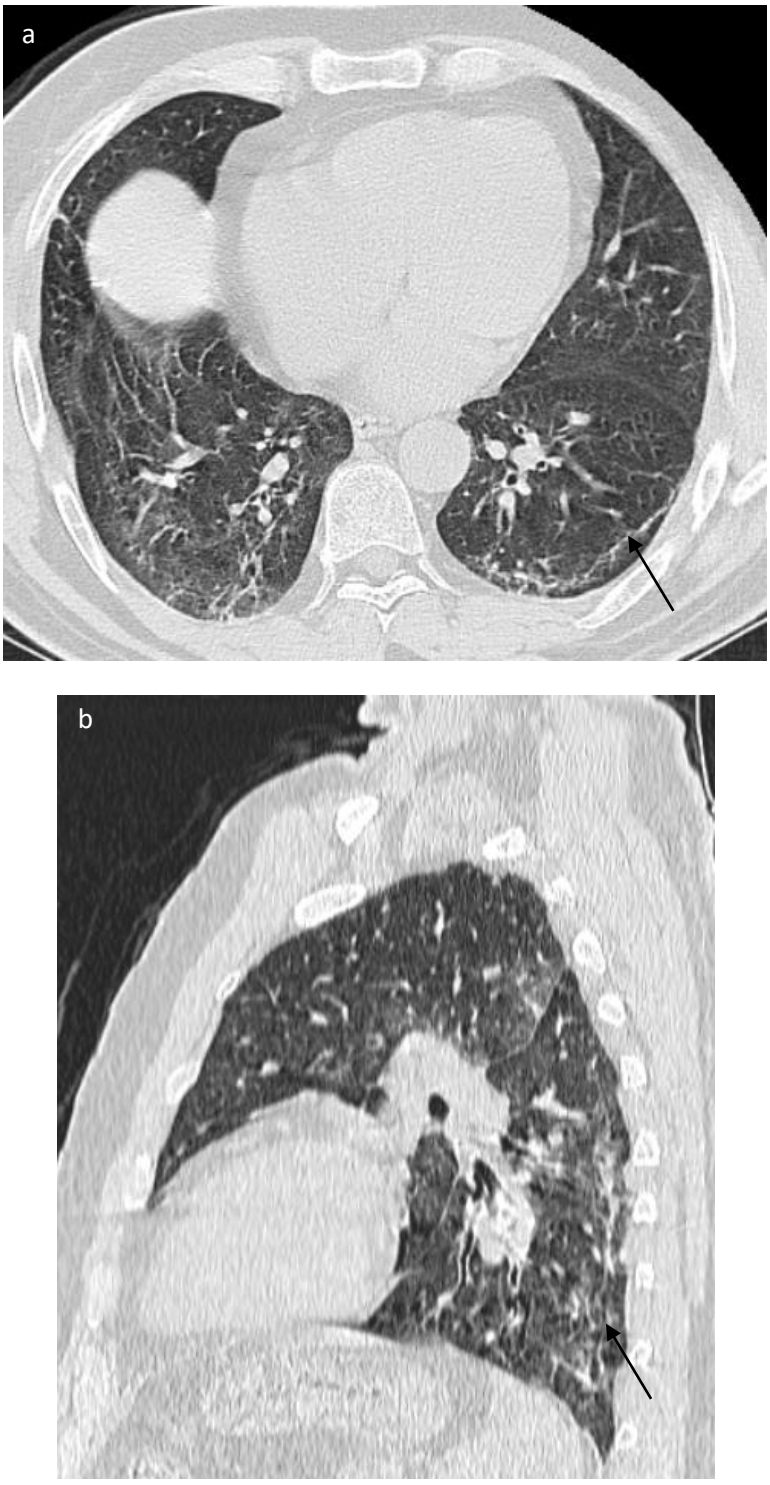


Figure 24: A 64-year-old man's 12 months follow-up non-enhanced chest CT axial (a) and sagittal (b) images showing residual curvilinear sub-pleural opacities (Black arrow) involving peripheral lung bases.

12 patients (40%) presented sub-pleural bands, and 13 patients (43.3%) presented vascular dilatation. Interlobular septal thickening was detected in 13 cases (43.3%), bronchiectasis in 12 cases (40%), honey combing in 2 cases (6.7%), mosaic attenuation in 3 cases (10 %), and architectural distortion in 3 cases (10%).

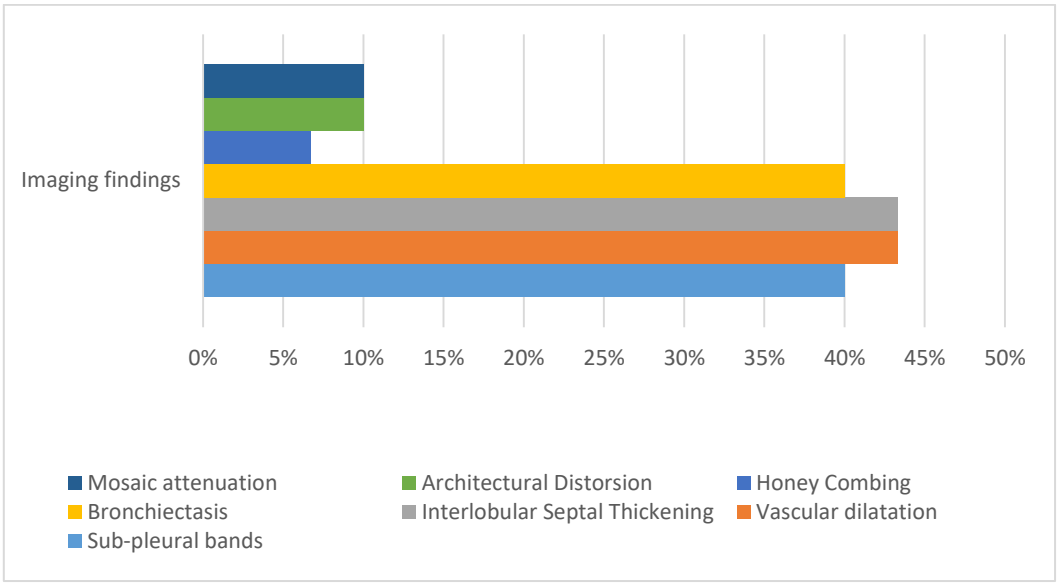
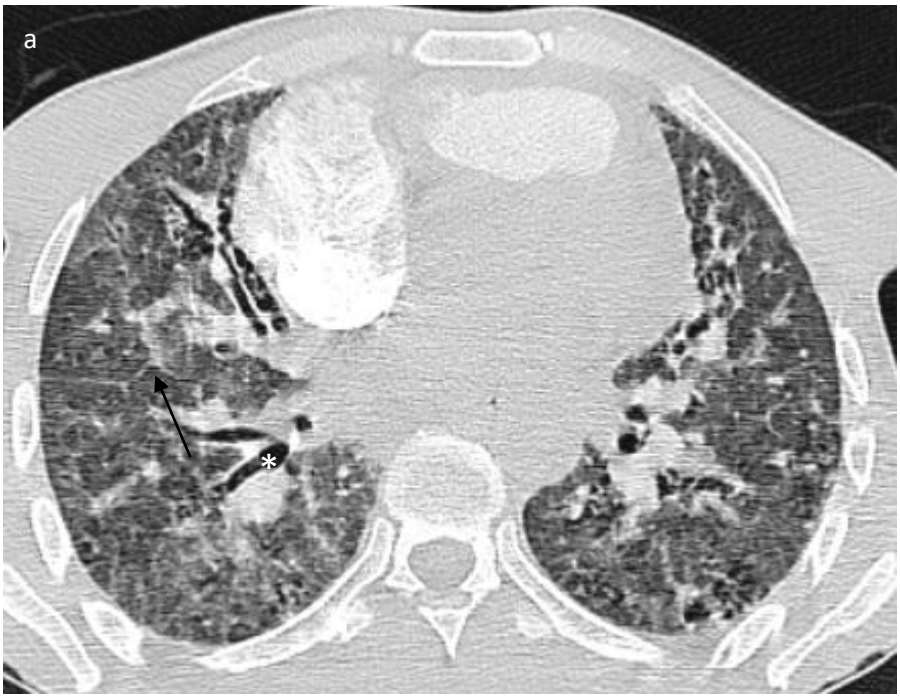


Figure 25: Imaging findings



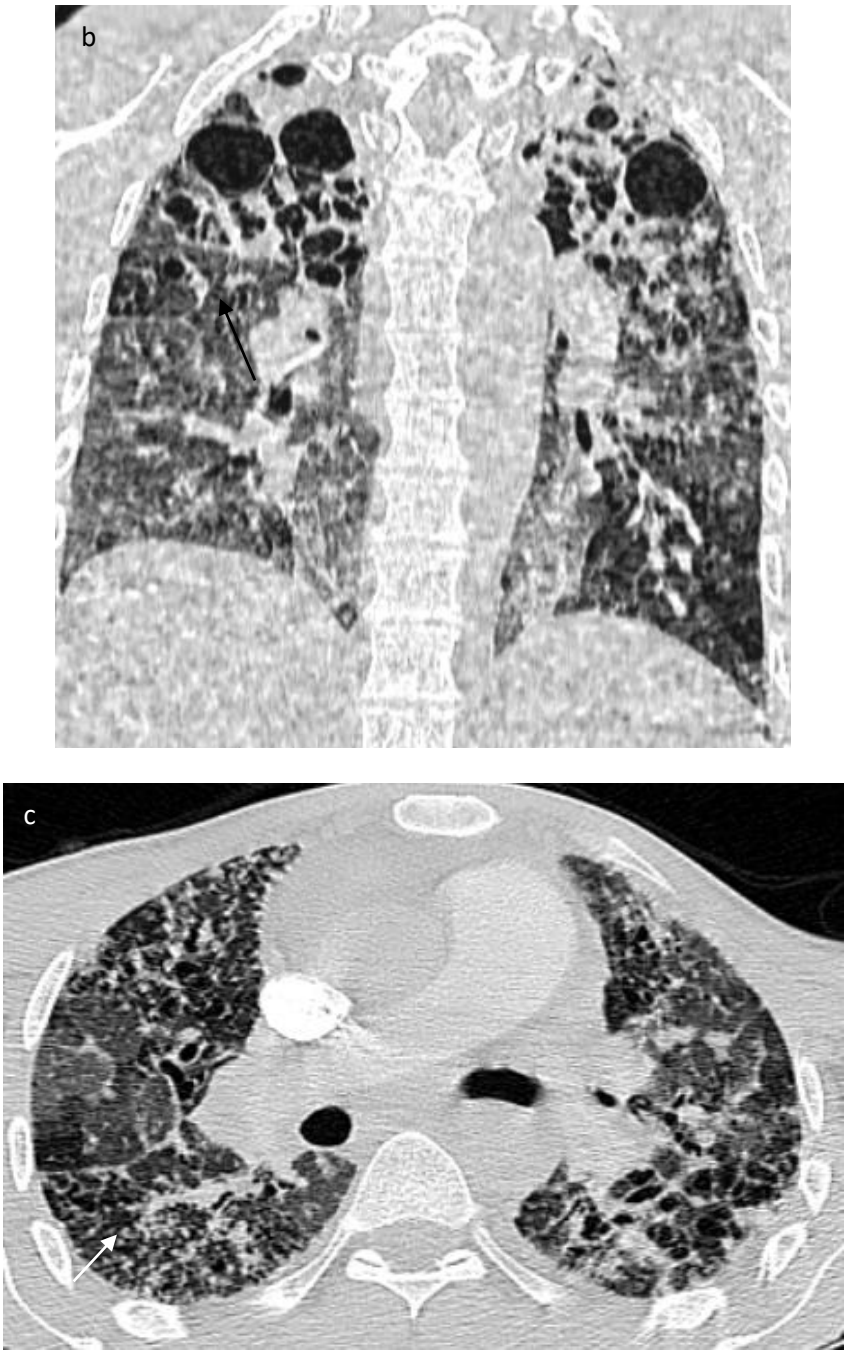


Figure 26: A 55-year-old man with COPD follow-up contrast-enhanced axial (a,c) and coronal (b) chest CT images in lung window, 5 months after initial presentation, showing extensive residual pulmonary opacities alongside with architectural distortion. Note the disruption of the normal course of the right oblique fissure (Black arrow), associated traction bronchiectasis (*), and extensive honey-combing (White arrow).

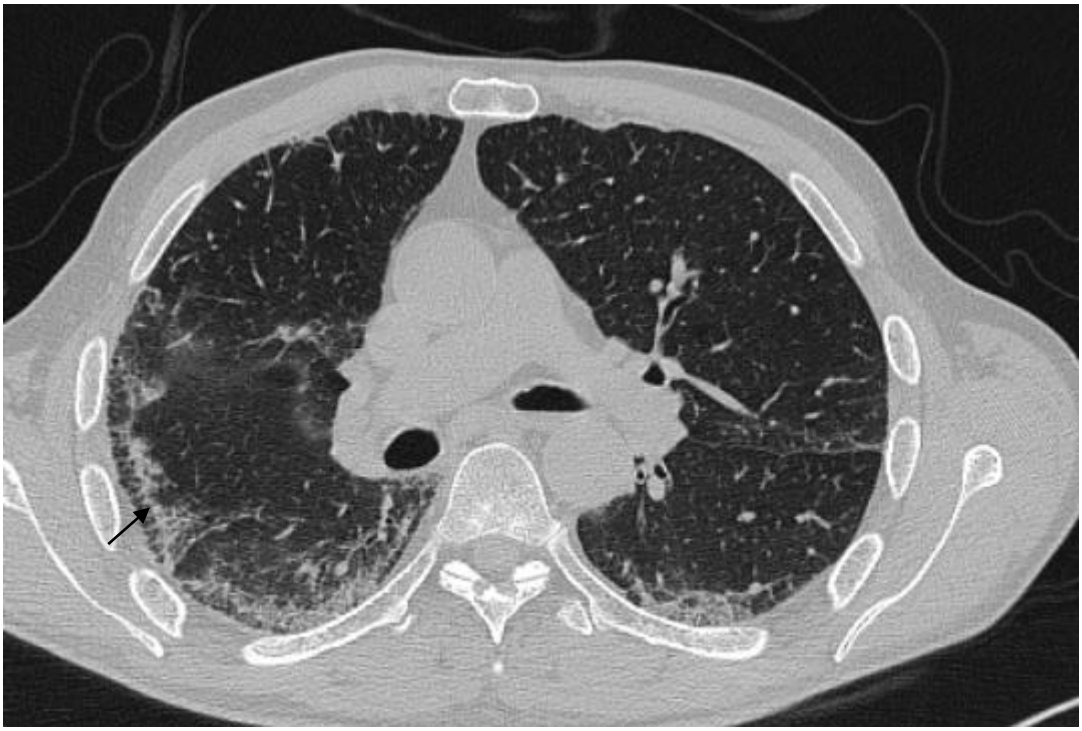


Figure 27: A 79-year-old man follow-up non-enhanced axial chest CT image in lung window,3 months after initial presentation, showing sub-pleural honey combing (Black arrow), and associated interlobular septal thickening, and peripheral bands.

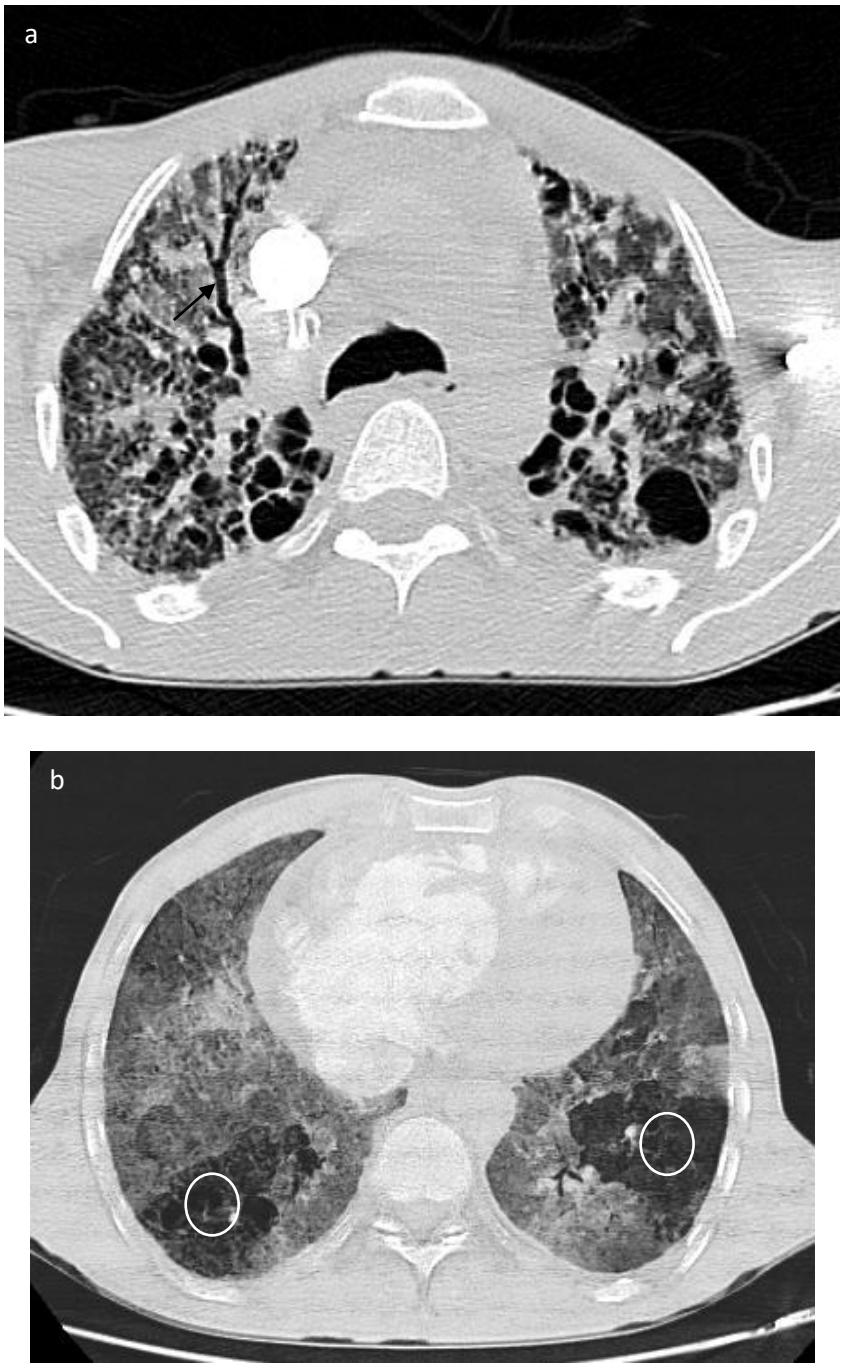


Figure 28: A 55-year-old man with COPD follow-up contrast-enhanced axial chest CT images in lung window, 5 months after initial presentation, showing extensive residual pulmonary opacities and emphysema. Note the right upper lobe bronchiectasis (Black arrow) (a). A mosaic attenuation pattern (White circles) in lower lung lobes best demonstrated on mIP reconstructions using narrow window parameters (b).

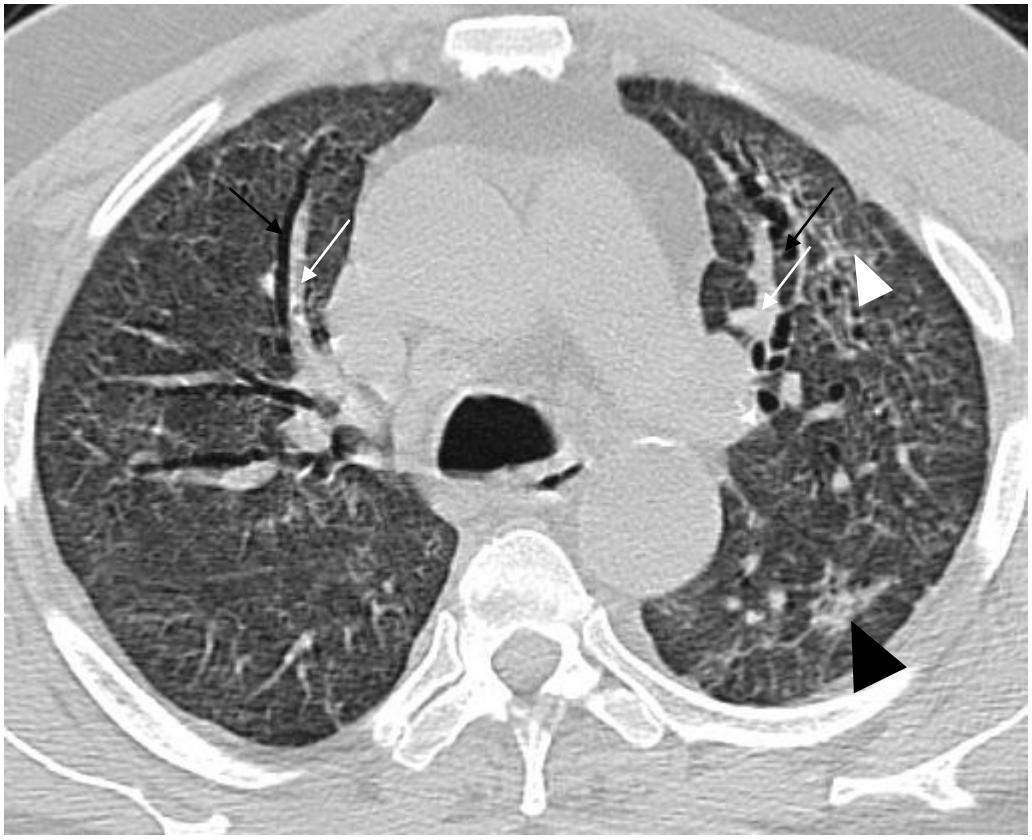


Figure 29: A 62-year-old man follow-up non-enhanced axial chest CT image in lung window, 3 months after initial presentation, showing traction bronchiectasis (Black arrows), vascular dilatation (White arrows), interlobular septal thickening (White arrow head), and a curvilinear sub-pleural opacity (Black arrow-head).

The additional findings detected were enlarged lymph nodes in 11 cases (36.7%), Pleural fluid in 2 cases (6.7%), and Pericardial fluid in 4 cases (13.3%).

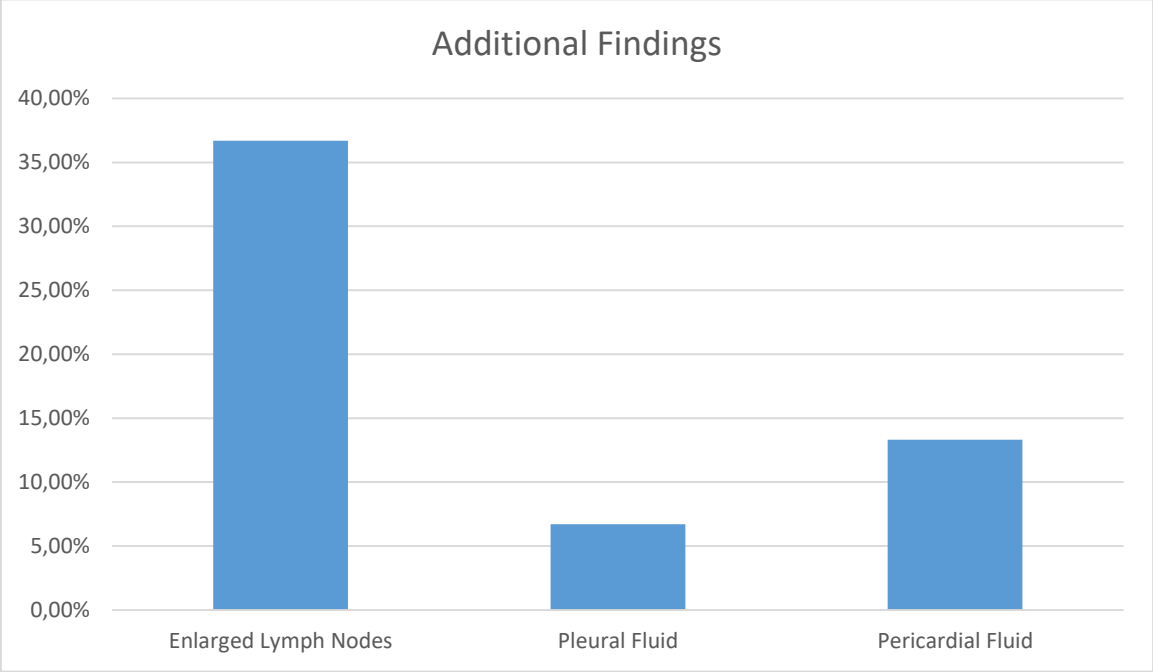


Figure 30: Additional findings

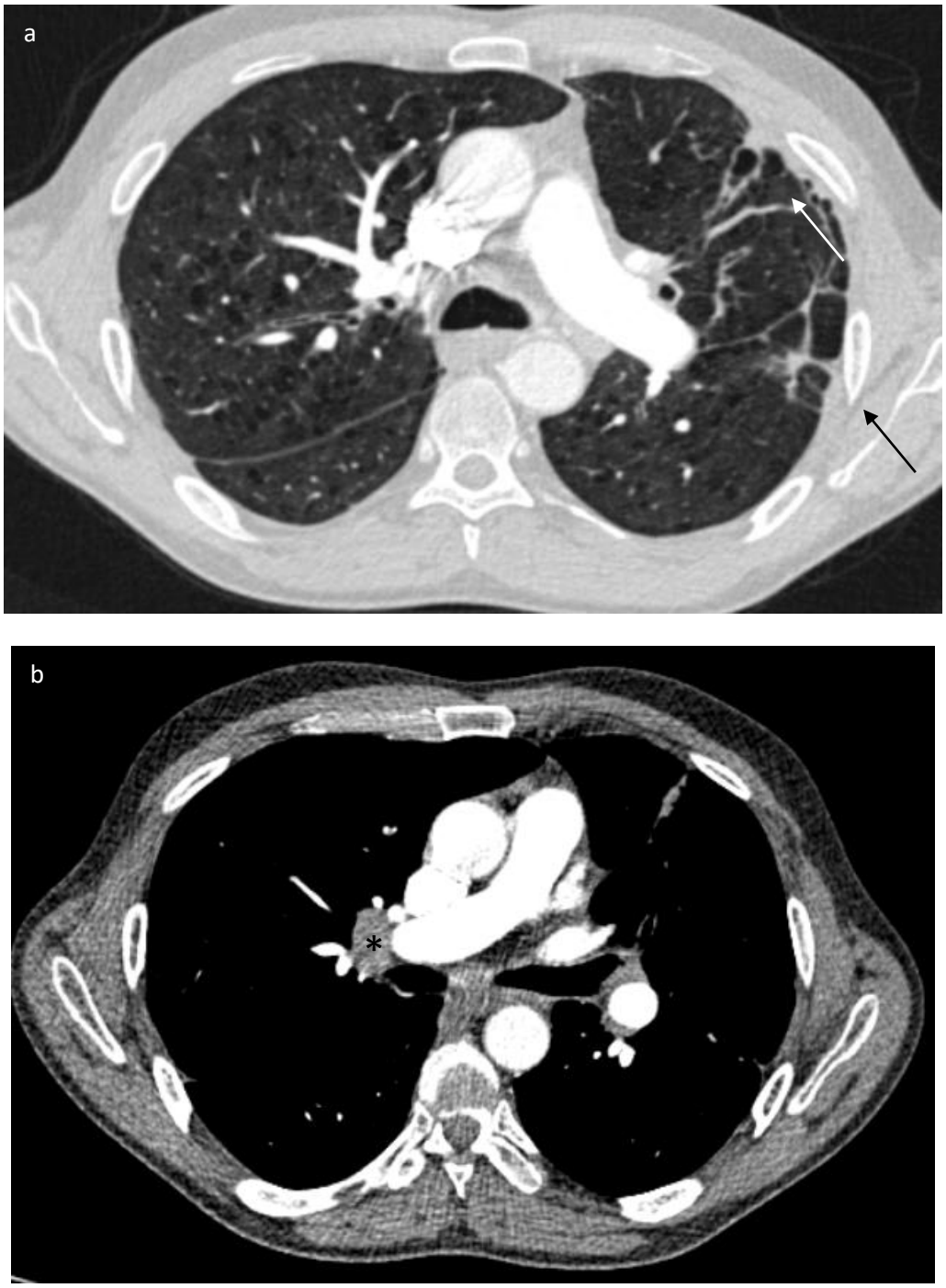


Figure 31: A 47-year-old man with antecedents of treated pulmonary tuberculosis, and pulmonary embolism presented for a 7 months follow-up chest CT-angiography. Axial images in lung (a) and mediastinal (b) windows show sub-pleural bands (Black arrow), traction bronchiectasis (White arrow), and a right hilar lymph node 10 R (*).

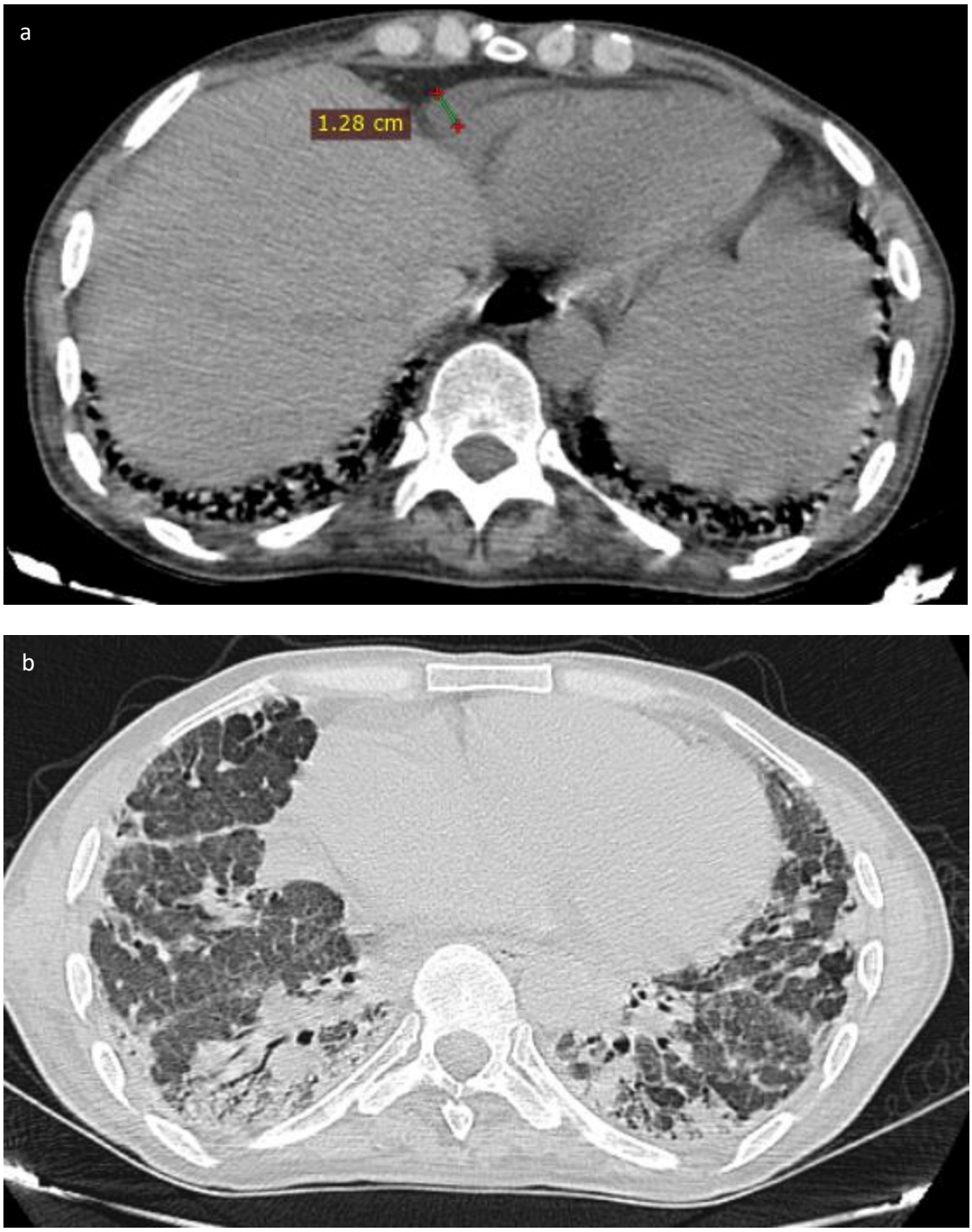


Figure 32: A 40-year-old-man 7 months follow-up non-enhanced chest CT axial mediastinal (a) and lung (b) window images (c) showing a small pericardial effusion, alongside residual, multi-focal, bilateral, patchy consolidations.

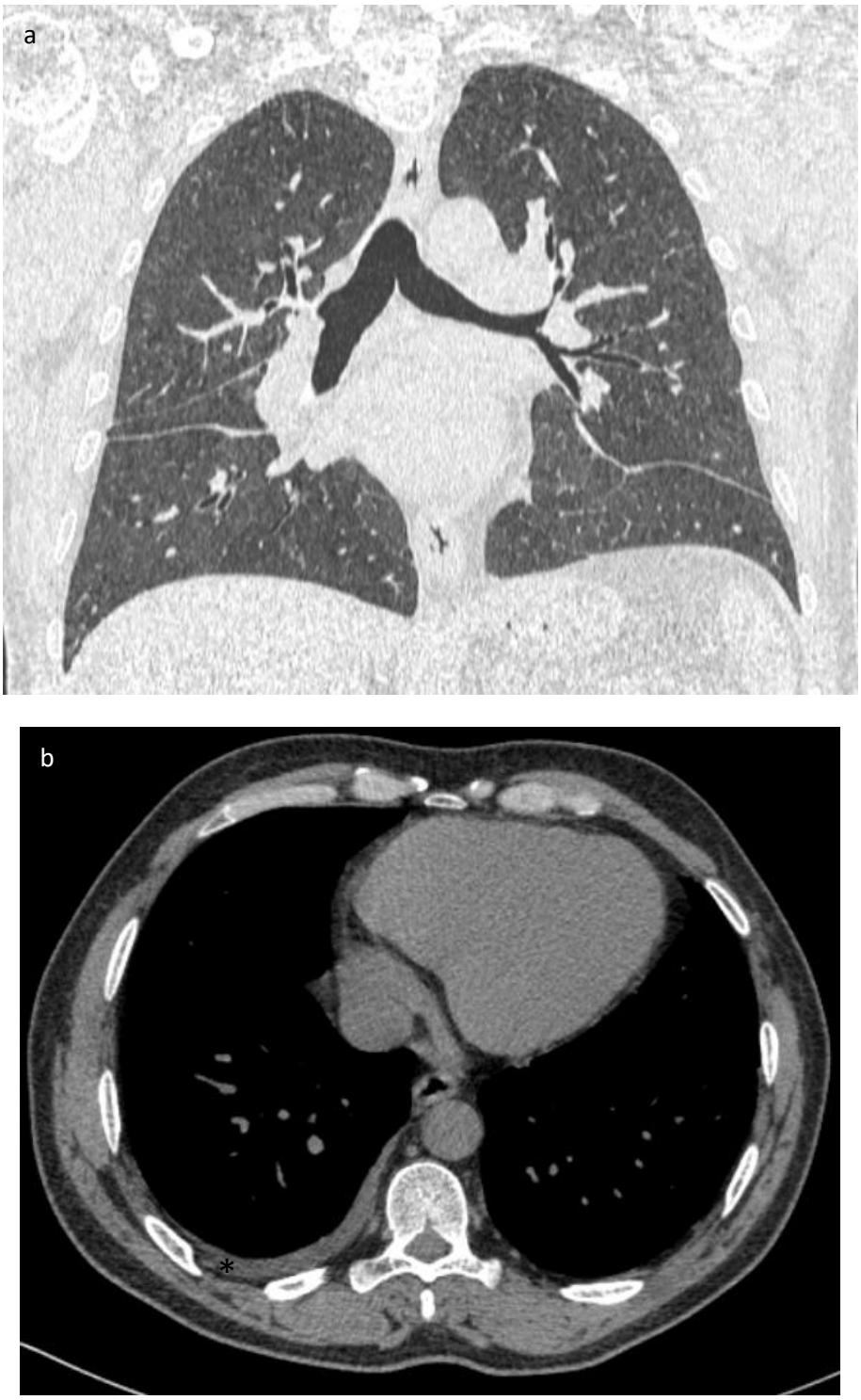


Figure 33: A 59-year-old-man 3 months follow-up non-enhanced chest CT axial lung (a) and mediastinal (b) window images (c) showing no residual pulmonary opacities, alongside a small right pleural effusion (*).

6 patients (20 %) presented no lung opacities whereas 24 patients (80 %) had residual pulmonary opacities. Fibrosis signs (Traction bronchiectasis, interlobular septal thickening, honeycombing and/or architectural distortion) were noted in 9 patients (30 %).

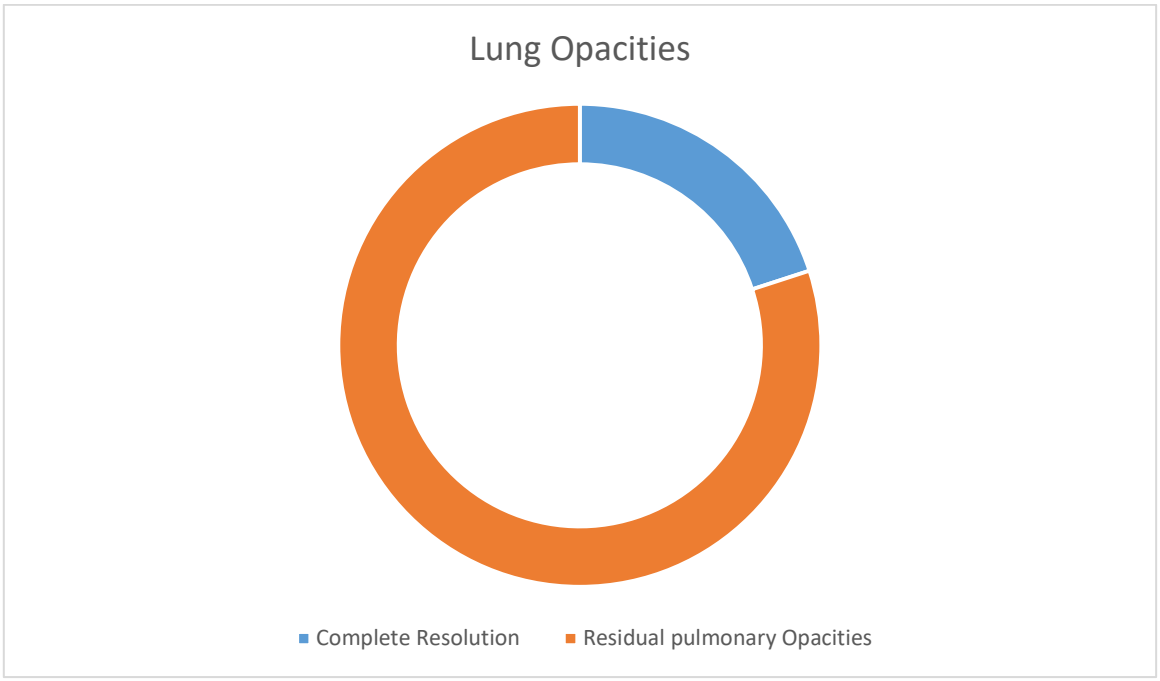


Figure 34: Lung opacities

Discussion

Considering the recognized link between viral pneumonias and fibrosis and the frequency of lung lesions during acute COVID-19 and residual respiratory manifestations following recovery, there is emphasis on the post-Covid-19 lung disease [36].

1. ETIOPATHOGENESIS OF POST-COVID LUNG DISEASE

There is uncertainty with regard to anomalies following acute COVID-19 are due to ARDS, mechanical ventilation, viral induced injuries, or the host's immune reaction to it [37]. Pulmonary fibrosis develops in a fraction of patients with ARDS [38] and is independently linked to the time span of acute respiratory failure [39]. Ventilator-induced lung injury is frequently observed in ARDS patients [40] and may lead to pulmonary fibrosis [41]. It can play a part in the occurrence of pulmonary sequelae following COVID-19 considering the mechanical ventilation prolonged duration [42] and increased barotrauma frequency [43] in COVID-19 ARDS patients in comparison to non-COVID-19 ones. Aggravation of pre-existing interstitial lung disease [44], a recognized complication in patients with fibrosis illness following pulmonary infection [45], appears to be another cause of lung disease following COVID-19.

2. HISTOLOGICAL, RADIOLOGICAL, and PFT CORRELATION

In a most recent Lancet Infectious disease publication in [46], 8 patients who died from COVID-19 underwent postmortem anatomo-pathologic examination. Substantial fibrotic lung parenchymal remodeling, defined by proliferation of fibroblasts, honeycombing, and airspace obliteration were noted.

Lung biopsies carry an elevated hazard of pneumothorax and are not practical. Nonetheless, a novel publication of a transbronchial biopsy in a Covid-19 61-year-old patient showed organizing pneumonia [47].

An autopsy lung tissues' study of 38 COVID-19 patients demonstrated diffuse alveolar injury, hyaline membrane constitution, interstitial edema, and type 2 alveolar epithelial cells enlargement [48].

Histologic presentations of lung viral infections may be subdivided to 2 models:

1) Bronchiolitis and inflammation contiguous to airways. On imaging: bronchial wall thickening, centrilobular nodules, and tree-in-bud pattern are present. Concentric fibrosis round the bronchioles causing airway reduction, called constrictive (or obliterative) bronchiolitis may occur. It results in remaining dyspnea following recovery from the acute episode, and an obstructive physiology on pulmonary function tests. Constrictive bronchiolitis main CT features comprise mosaic attenuation, air trapping, and bronchiectasis.

2) Diffuse alveolar damage, manifesting as GGO and/or consolidation on imaging. Histologically, fibrosis forms 1-2 weeks following acute signs, and is affiliated with reticulations and traction bronchiectasis on CT. Within time, months usually, fibrosis might resolve, nonetheless remaining fibrosis is frequent [49], is usually positioned in the anterior peripheral lung and might be linked to a restrictive defect on PFT.

Organizing pneumonia (OP) is frequent, and usually very steroid-responsive with opacities that rapidly better or clear up under treatment. Remaining fibrosis might persist, and usually mimics nonspecific interstitial

pneumonia with basilar dominant interlobular septal thickening, bronchiectasis, and subpleural exemption [50]. OP and DAD can be associated with common radiological features.

Pulmonary fibrosis is not always persistent. Collagen might be absorbed months following the initial injury.

3. PREVALENCE and CT FEATURES

The prevalence of radiologic changes following Covid-19 differs based on the cohort studied, the time span following infection, and the initial episode gravity [37].

In our retrospective study addressing COVID-19 pneumonia's mid to long-term follow-up (3-12 months) chest CT findings, and involving 30 patients; 80 % had residual lung opacities, among which 30 % presented fibrotic changes. The predominant lung opacity was GGO; present in 14 patients (46.7 %). Mosaic attenuation was detected in 3 patients (10%).

Han et al [51]. described the remaining CT features of COVID-19 6 months following the acute illness. In their report, more than 1/3 of patients manifested signs of fibrosis.

Cho and Villacreses et al. [52] discuss these long-term lung abnormalities in a report of 100 cases with lasting (>30 days) respiratory signs following COVID-19 pneumonia. The mean interval from diagnosis to the post-COVID-19 consultation was merely 75 days. Air trapping was reported in 58% of patients, prevailed in the group of hospitalized patients (73%), and affected 25-35% of the lungs depending on illness severity. Restriction was detected on PFT in the COVID-19 hospitalized patients and ICU sub-groups. GGO, traction

bronchiectasis, and other fibrosis signs were much common in ICU patients (94%, 69%, 81% of patients in comparison to 36%, 8%, and 3% of non-hospitalized patients). GGO and/or fibrosis on CT were prevalent in the ICU groups and are probably related to post-OP and/or DAD fibrosis. The contribution of airways disease to post-COVID fibrosis is greater in the non-hospitalized patients, and that of OP/DAD is higher in ICU admissions.

114 grave COVID-19 patients' control at six months revealed that thirty-five percent presented fibrosis and a subset of them had DLco diminutions [53]. GGO was described in 21% of cases. GGO and consolidation extent lowered in comparison to the initial scans, while reticular abnormalities increased.

Only 4 % of the three-months follow-up CTs of fourty eight grave SARS-Cov-2 survivors, with previous mechanical ventilation, were normal [54]. Eighty-nine percent presented GGO, while fibrotic anomalies (namely parenchymal bands, parenchymal distortion, and bronchiectasis) were observed in sixty-seven percent. The sannographic scores of severity were high. Associated lung volumes and DLco reductions were reported. In forty six percent, diminished attenuation due to hypoperfusion or rather bronchioles injury was present. In 25%, novel emphysema and cysts were noticed.

In 12 COVID-19 survivors, follow-up CTs performed at six months noted the occurrence of fibrosis in the same zones affected during the initial infection phase anomalies [55].

40% of patients showed fibrotic changes while 56% of CTs demonstrated ground-glass or consolidative opacities in a meta-analysis of 60 reports [56], analyzing follow-up radiological features of MERS, influenza, and COVID-19 pneumonia.

The changing definitions of CT features and absence of histologic correspondence complicate the COVID-19 follow-up studies' interpretation. It is suggested to classify PASC CT appearances like this: mainly GGO, mixed GGO and fibrotic, and mainly fibrotic. GGO or fibrotic bands or their association in the original infection areas, may represent early fibrosis or interstitial lung pathology [57].

A broad definition of fibrosis may inflate its prevalence, thus the designation fibrosis must be kept for particular features: bronchiectasis or bronchiolectasis, honeycombing, or architectural distortion [58]. These anomalies might resolve or progress on follow-up. It is not known yet if there is overlap between remaining COVID-19 pulmonary abnormalities and NSIP or UIP.

To appraise COVID-19 infection in the initial phase, different techniques are used, including densitometry and deep learning methods [59, 60]. Early phase quantitative CT assessment of severity is an autonomous forecaster of ICU hospitalization and mortality [61–63]. It could as well be used to appraise serial variations in lung volumes and pulmonary opacity [63]. A study of 41 COVID-19 survivors and an identical report of 29 patients demonstrated that quantitative pneumonia CT measures reduced gradually in 6–7 months [64, 65].

In order for quantitative CT assessment of severity to be beneficial in evaluating PASC, distinct metrics that differentiate between GGO and fibrotic abnormality are necessary. In a pilot evaluation, DTA effectively discriminated between GGO and fibrosis and helped perceive betterment over time. Nonetheless, further technical and clinical confirmation is still needed for quantitative CT to play a clinical part in PACS evaluation.

4. CT EVALUATION

COVID-19 follow-up Chest CT examination must comprise supine inspiratory and expiratory acquisitions with thin reconstructions (1.5 mm). Novel emphysematous lesions, cysts, and mosaic pattern suggest airflow obstruction. Lung bases prone imaging elucidates if basal anomalies at supine scanning correspond to atelectasis or authentic abnormalities. An acute or chronic pulmonary thromboembolism would also cause PACS symptoms, and computed tomography pulmonary angiograms must be acquired for low suspicion indexes. To understand the abnormalities temporal course, juxtaposition with initial phase CT is crucial. The majority of studies repeat HRCTs, however considering the irradiation risk, low-dose or ultra-low-dose CTs may have a role in longitudinal follow-ups [66].

The best time for follow-up CT is not known. The British Thoracic Society current guidelines advise a follow-up at 3-months, a convenient interval for lung anomalies to clear that guarantees at the same time that residual findings are handled promptly [67]. For cases with no pneumonia at the acute phase of illness, and those for which lung abnormalities completely resolve on follow-up CXR at discharge, a follow-up CT is not advised. High-resolution CT is recommended for remaining substantial lung anomalies on follow-up CXR and lasting respiratory symptoms or physiological dysfunction [67, 68].

The international guidelines were respected in our report. The time gap between the acute infection phase and the follow-up was 3 months at least, and all imaged patients presented respiratory symptoms, namely cough in 10 patients (33.3 %), and dyspnea in 20 patients (66.7 %).

5. PULMONARY EMBOLISM'S ROLE

Considering the proof of direct endothelial injury by SARS-CoV-2 [69] and the associated hypercoagulable state [70], there is worry that venous thromboembolism might take a part in Post-acute COVID syndrome. Since the hypercoagulable state's duration is not known, recovering patients might still be at a high hazard for novel or undiagnosed pulmonary embolisms. Seventeen percent and fifteen percent of patients presented PE and DVT, respectively, in a meta-analysis that studied 3342 Covid-19 survivors [71], mainly during the initial stage, and most frequently in the ICU. Pulmonary perfusion scans are suggested as a method of sorting Sars-Cov-2 patients, when pulmonary emboli is suspected, in the presence of pulmonary symptoms and/or DLco reductions that are unexplained by imaging [72].

We performed CT pulmonary angiography in 7 patients who had a pulmonary embolism suspicion (discrepancy between no or minimal parenchymal lung involvement and severe respiratory symptoms, or highly increased D-dimers). No thromboembolism was identified.

Dual-energy CT could play a part in assessing residual signs following COVID-19. Fifty-five D-E computed-tomography angiograms obtained three months post-COVID-19 pneumonia, to explore residual signs, showed disruption of normal opacification correspondent to embolism in 3 cases, and perfusion defects in 32 cases (58%) (4 of which with normal pulmonary parenchyma) implying residual micro-vascular anomalies [73]. Regions of augmented perfusion were noted in 15 cases, and corresponded to tree-in-bud, ground-glass opacities and sub-pleural bands. It was concluded to the frequency of vascular disturbance following Sars-Cov-2 pneumonia.

6. PREDICTORS OF POST-COVID LUNG DISEASE

In a study that analyzed CTs 5 months following discharge, a link was found between the abnormalities magnitude and the illness severity evaluated by the necessity of hospitalization, oxygen, and mechanical ventilation [74]. DLco reduction was correlated to the gravity of disease, and women and older patients had an augmented probability of presenting a diffusion anomaly. Other reports identified high inflammatory indicators (CRP, LDH, and Il-6) [75,76,77,78], D-dimers [79], white blood cells [75], albumin [76], older age [80,79], male sex [79,81], comorbidities [79], ICU hospitalization [81], longer hospital stay [82,77], the implementation and duration of mechanical ventilation [80,78], and ARDS [80,82] as factors linked to worsened fibrosis when monitored. Among the risk factors of fibrotic pulmonary illnesses comprising IPF, a short leukocyte telomere length was linked to fibrosis following COVID-19 [78]. In patients with anterior pulmonary fibrosis, COVID-19 might accelerate it.

Progressive interstitial lung disease development following COVID-19 may be due to autoimmune incitement sparked by SARS-CoV-2 or evolution of previously existing interstitial pulmonary anomalies to clinically considerable ILD [83].

Our cohort comprised one patient with interstitial lung disease indeterminate for UIP pattern and moderate COVID-19 infection. The 3 months follow-up CT showed moderate lung involvement (CT severity score = 14) with signs of fibrosis.

7. TREATMENT

Corticosteroids are considered in the initial phases with CT features of organizing pneumonia. Anti-fibrotic drugs utilized in chronic lung fibrosis are reviewed, specifically nintedanib [84], an inhibitor of tyrosine-kinase that retards advancement in IPF [85]. Genistein is an agonist of estrogen receptor beta, whose stimulation regulates cell cycle, facilitates DNA reparation, reduces inflammation, and has anti-fibrotic properties [86]. A National Institute of Allergy and Infectious Diseases–endorsed COVID-19 clinical trial is currently testing it.

8. LIMITATIONS

This study has many limitations. First, merely 30 patients were enrolled. A larger population size is advisable to better analyze the COVID-19 sequelae. Second, baseline imaging and pulmonary function tests were not available. Follow-up PFT were not performed. They offer more accurate informations on the lungs physiological anomalies. Third, the time gap between the positive RT-PCR and Follow-up CT ranged between 3 and 12 months, with an average of 6 months. Longer-term reports are necessary to investigate the durable features of post-COVID fibrosis. Fourth, a prone position acquisition was not performed; however, most lung lesions did not meet the criteria of dependent artifactual abnormalities. Fifth, our CT protocol did not include intravenous contrast administration; therefore pulmonary emboli was not searched, nonetheless in 7 patients who benefited from a pulmonary CT angiography, no pulmonary embolus was detected.

Conclusion

CT abnormalities following Covid-19's prevalence varies based on the extent of the original lung affection and the time gap since the acute phase. Longitudinal studies indicate that anomalies could remain in patients with established factors of risk. Many areas of incertitude remain and need more studies, namely CT findings clinical and functional impact, the relationship between post-COVID fibrosis and preexisting interstitial lung disease, pathologic correlation of CT abnormalities, long-term outcome, and improvement versus progressive fibrosis predictors. Even if no drug is endorsed for post-COVID lung fibrosis, therapies trials are continuing. The long-lasting effect of CT anomalies on respiratory manifestations, physiology, or life quality is not known. Post-discharge surveillance is crucial to avert a population with lasting lung injury. Consequently, maintained monitoring of released COVID-19 patients with clinical examination, iterative pulmonary function testing, and HRCT is advised.


Abstract


Abstract

Title: Chest CT in Covid-19 pneumonia's Follow-up : About 30 cases

Author: Hanae RAMDANI

Keywords: Chest CT, Covid-19, Pneumonia, Follow-up

Background: Lung abnormalities do not fully resolve in all Covid-19 survivors and may progress to fibrosis. Understanding post-COVID lung changes helps identify patients susceptible of post-COVID-19 sequelae. We analyzed scannographic residual lung abnormalities, and the full resolution percentage on intermediate- and long-term follow-up (3 months or more).

Methods: Data from 30 RT-PCR positive COVID-19 patients undergoing at least one follow-up chest CT at Ibn Sina Hospital, with a minimal time interval of 3 months between the RT-PCR and the CT performance were gathered retrospectively. The following elements were analyzed: lung opacities, distribution, dominant lung opacity, Sub-pleural bands, Interlobular septal thickening, Vascular dilatation, Bronchiectasis, Honey combing, Architectural distortion, mosaic attenuation, and Additional findings: Enlarged lymph nodes, Pleural and Pericardial fluid. To evaluate the degree of lung opacification, a score founded on visual evaluation of the lung involvement's percentage was employed. Patients were then subdivided into two categories: no residual opacities and remaining pulmonary opacities.

Results: 30 patients were enrolled. The age ranged between 40 and 87 years. CT was indicated for symptoms or functional impairment. The time range between the positive RT-PCR and Follow-up CT varied between 3 and 12 months. CT severity score ranged between o and 23. Residual lung opacities were present in 24 cases (80 %). The dominant lung opacities were Ground glass (46.7 %), and linear/curvilinear opacities (23.3 %). Signs of fibrosis were present in 9 patients (30 %).

Conclusion: CT abnormalities following Covid-19 pneumonia's prevalence varies based on the extent of the original lung affection and the time gap since the acute phase. Residual anomalies' effects on respiratory physiology, symptoms, and quality of living are unknown. Maintained monitoring of COVID-19 survivors with clinical examination, iterative pulmonary function tests, and HRCT is advised.

RÉSUMÉ

Titre : Scanner thoracique dans le suivi de la pneumopathie type Covid-19 : à propos de 30 cas

Auteur : Hanae RAMDANI

Mots-clés : Scanner thoracique, Covid-19, Pneumopathie, Suivi

Contexte : Les anomalies pulmonaires ne se résolvent pas complètement chez tous les survivants de Covid-19 et peuvent évoluer vers la fibrose. Comprendre les modifications post-COVID identifie les patients à risque de séquelles. Nous rapportons les anomalies pulmonaires scannographies résiduelles et le pourcentage de résolution complète à moyen et long terme (≥ 3 mois).

Méthodes : Les données de 30 patients COVID positifs ayant eu au moins un scanner thoracique de contrôle à l'hôpital Ibn Sina, avec au moins 3 mois entre PCR et scanner ont été recueillies rétrospectivement. Les éléments suivants ont été analysés : opacités pulmonaires, distribution, opacité dominante, Bandes sous-pleurales, Épaississement septal interlobulaire, Dilatation vasculaire, Bronchiectasie, rayon de miel, Distorsion architecturale, Mosaïque et Adénopathies médiastinales, épanchements pleural et péricardique. Pour évaluer le degré d'opacification pulmonaire, un score fondé sur l'appréciation visuelle du pourcentage d'atteinte pulmonaire a été utilisé. Les patients ont été divisés en 2 catégories : résolution complète et opacités résiduelles.

Résultats : 30 patients ont été recrutés, âgés entre 40 et 87 ans. La TDM était indiquée en cas de symptômes ou troubles fonctionnels. L'intervalle PCR-scanner variait entre 3 et 12 mois, et le score de sévérité entre 0 et 23. Des opacités pulmonaires résiduelles étaient présentes dans 24 cas (80 %). Les opacités pulmonaires dominantes étaient le verre dépoli (46,7 %), et les opacités linéaires/curvilignes (23,3 %). Des signes de fibrose étaient présents chez 9 patients (30 %).

Conclusion : Les anomalies scannographiques résiduelles post-Covid-19 dépendent de l'étendue de l'atteinte pulmonaire initiale et du temps écoulé depuis la phase aiguë. L'effet des anomalies résiduelles sur la physiologie et les manifestations respiratoires, ou la qualité de vie est inconnu. Une surveillance avec examen clinique, tests de la fonction pulmonaire et scanner thoracique est conseillée.

خلاصة

العنوان: التصوير المقطعي المحوسب للصدر في متابعة الالتهاب الرؤوي كوفيد 19 : حول 30 حالة

الكاتب: هناء رمضاني

الكلمات الأساسية: التصوير المقطعي المحوسب؛ الالتهاب الرؤوي؛ كوفيد 19؛ متابعة

خلفية: تغيرات الرئة لا تختفي تمامًا لدى جميع الناجين من فيروس كوفيد -19 وفي بعض الحالات تتقدم نحو التليف. يساعد فهم التغييرات الرئوية على التصوير المقطعي في تحديد المرضى المعرضين للإصابة بالعواقب الرئوية على المدى الطويل. أبلغنا عن تشوهات الرئة المتبقية في التصوير المقطعي المحوسب، و النسبة المئوية لا لرئات السليمة خلال المتابعة المتوسطة والطويلة الأجل (3 أشهر أو أكثر).

أساليب: تم جمع البيانات بأثر رجعي من 30 مصابا بفيروس*COVID-19* ممن لديهم فحص صدري واحد على الأقل في مستشفى ابن سينا، مع فاصل زمني لا يقل عن 3 أشهر بين *PCR* و الفحص الصدري. تم تحليل العناصر التالية: عتامات رئوية. التوزيع؛ عتامة الرئة السائدة، الشرائط تحت الغشاء الرئوي، سماكة الحاجز بين الفصوص، تمدد الأوعية الدموية، توسع القصبات، قرص العسل، تشوه معماري، مظهر فسيفساء و تضخم العقد اللمفية، الانصباب الجنبي وانصباب التامور. لتقييم درجة عتامة الرئة، تم استخدام درجة بناءً على التقييم البصري للنسبة المئوية لتضرر الرئة. ثم تم تصنيف المرضى إلى مجموعتين: رئات سليمة و عتامة رئة متبقية.

نتائج: تم تسجيل 30 مريضا. تراوحت الاعمار ما بين 40 و 87 سنة. تم الحصول على التصوير المقطعي المحوسب للأعراض أو الضعف الوظيفي . تراوح النطاق الزمني بين فحص تفاعل البوليميراز التسلسلي الموجب و التصوير المقطعي بين 3 و 12 شهرًا. تراوحت شدة عتامة الرئة بين 0 و 23. كانت حالات عتامة الرئة المتبقية موجودة في 24 حالة (80٪). عتامة الرئة السائدة كانت الزجاج المغشى(46.7) والعتامة الخطية / المنحنية (23.3٪). تواجدت علامات التليف في 9 مرضى(30٪) .

خاتمة:على مدى تأثر الرئة الأصلي والفجوة الزمنية منذ*19* تعتمد تغيرات الرئة في التصوير المقطعي بعد فيروس كوفيد المرحلة الاولى. لا يُعرف التأثير طويل المدى لنتائج التصوير المقطعي على اعراض أو فسيولوجيا الجهاز التنفسي أو نوعية الحياة. يُنصح بالمراقبة المستمرة من خلال الفحص السريري واختبار وظائف الرئة و التصوير المقطعي.

References

[1]. World Health Organization. WHO coronavirus disease (COVID-19) dashboard. https://covid19.who.int/ Accessed 23 Dec 2021.

[2]. Revel MP, Parkar AP, Prosch H, Silva M, Sverzellati N, Gleeson F, Brady A (2020) COVID-19 patients and the Radiology department–advice from the European Society of Radiology (ESR) and the European Society of Thoracic Imaging (ESTI). European radiology. 30(9):4903–4909.

[3]. https://www.acr.org/Advocacy-and-Economics/ACR-Position-Statements/Recommendations-for-Chest-Radiography-and-CT-for Suspected-COVID19-Infection. Accessed 30 Oct 2020.

[4]. Rubin GD, Ryerson CJ, Haramati LB, Sverzellati N, Kanne JP, Raoof S, Schluger NW, Volpi A, Yim JJ, Martin IB, Anderson DJ (2020) The role of chest imaging in patient management during the COVID-19 pandemic: a multinational consensus statement from the Fleischner Society. Chest. 158(1):106–116.

[5]. Zhao YM, Shang YM, Song WB, Li QQ, Xie H, Xu QF, Jia JL, Li LM, Mao HL, Zhou XM, Luo H (2020) Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery.EClinical Medicine. 25:100463

[6]. Hui DS, Joynt GM, Wong KT, Gomersall CD, Li TS, Antonio G, Ko FW, Chan MC, Chan DP, Tong MW, Rainer TH (2005) Impact of severe acute respiratory syndrome (SARS) on pulmonary function, functional capacity and quality of life in a cohort of survivors. Thorax. 60(5):401–409

[7]. Das KM, Lee EY, Singh R, Enani MA, Al Dossari K, Van Gorkom K, Larsson SG, Langer RD (2017) Follow-up chest radiographic findings in patients with MERS-CoV after recovery. Indian J Radiol Imaging. 27(3):342

[8]. Parry AH, Wani AH, Shah NN, Yaseen M, Jehangir M (2020) Chest CT features of coronavirus disease-19 (COVID-19) pneumonia: which findings on initial CT can predict an adverse short-term outcome? BJR| Open 2:20200016

[9]. Lu R, Zhao X, Li J, et al. Genomic characterization and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020;395(10224):565-574. doi:10.1016/

[10]. S0140-6736(20)30251-8

[11]. Lam TT, Jia N, Zhang YW, et al. Identifying SARS-CoV-2-related coronaviruses in Malayan pangolins. Nature. Published online March 26, 2020. doi:10.1038/s41586-020-2169-0

[12]. Zhu N, Zhang D, Wang W, et al; China Novel Coronavirus Investigating and Research Team.

[13]. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382(8):727-733.doi:10.1056/NEJMoa2001017

[14]. Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RA. Isolation of a novel

[15]. coronavirus from a man with pneumonia in Saudi Arabia. N Engl J Med. 2012;367(19):1814-1820. doi:

[16]. 10.1056/NEJMoa1211721

[17]. Goldsmith CS, Tatti KM, Ksiazek TG, et al. Ultrastructural characterization of SARS coronavirus. Emerg Infect Dis. 2004;10(2):320-326. doi:10.3201/eid1002.030913

[18]. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181(2):271-280. doi:10.1016/j.cell.2020.02.052

[19]. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. JAMA. 2020;324(8):782-793. doi:10.1001/jama.2020.12839

[20]. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020;8(4):420-422. doi:10.1016/S2213-2600(20)30076-X

[21]. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18(4):844-847. doi:10.1111/jth.14768

[22]. Thachil J, Tang N, Gando S, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost. 2020;18(5):1023-1026. doi:10.1111/jth.14810

[23]. Klok FA, Kruip MJHA, van der Meer NJM, et al.Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res. 2020;191: 145-147. doi:10.1016/j.thromres.2020.04.013

[24]. van Doremalen N, Bushmaker T, Morris DH, et al. Aerosol and surface stability of SARS-CoV-2 as

[25]. compared with SARS-CoV-1. N Engl J Med. 2020;382(16):1564-1567. doi:10.1056/NEJMc2004973

[26]. Bourouiba L. Turbulent gas clouds and respiratory pathogen emissions: potential implications for reducing transmission of COVID-19. JAMA. Published online March 26, 2020. doi:10.1001/ jama.2020.4756

[27]. Lewis D. Is the coronavirus airborne? Experts can’t agree. Nature. 2020;580(7802):175. doi:10. 1038/d41586-020-00974-w

[28]. Dashraath P, Wong JLJ, Lim MXK, et al. Coronavirus disease 2019 (COVID-19) pandemic and pregnancy. Am J Obstet Gynecol. 2020;222(6): 521-531. doi:10.1016/j.ajog.2020.03.021

[29]. Zeng L, Xia S, Yuan W, et al. Neonatal early-onset infection with SARS-CoV-2 in 33 neonates born to mothers with COVID-19 in Wuhan, China. JAMA Pediatr. Published online March 26, 2020.

[30]. He X, Lau EHY, Wu P, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19.

[31]. Nat Med. 2020;26(5):672-675. doi:10.1038/s41591-020-0869-5

[32]. Ganyani T, Kremer C, Chen D, et al. Estimating the generation interval for coronavirus disease (COVID-19) based on symptom onset data, March 2020. Euro Surveill. 2020;25(17). doi:10.2807/1560-7917.ES.2020.25.17.2000257

[33]. Cheng HY, Jian SW, Liu DP, et al. Contact tracing assessment of COVID-19 transmission dynamics in

[34]. Taiwan and risk at different exposure periods before and after symptom onset. JAMA Intern Med.

[35]. Published online May 1, 2020. doi:10.1001/jamainternmed.2020.2020

[36]. Symptom-based strategy to discontinue isolation for persons with COVID-19. Centers for

[37]. Disease Control and Prevention website. Updated May 3, 2020. Accessed July 6, 2020. https://www.

[38]. cdc.gov/coronavirus/2019-ncov/community/ strategy-discontinue-isolation.html

[39]. Butler, P., Mitchell, A. W., & Ellis, H. (Eds.). (2012). Applied radiological anatomy. Cambridge University Press.

[40]. Stringhini S, Wisniak A, Piumatti G, et al. Seroprevalence of anti-SARS-CoV-2 IgG antibodies in Geneva, Switzerland (SEROCoV-POP): a population-based study. Lancet 2020; 396:313.

[41]. Havers FP, Reed C, Lim T, et al. Seroprevalence of Antibodies to SARS-CoV-2 in 10 Sites in the United States, March 23-May 12, 2020. JAMA Intern Med 2020.

[42]. Mao R, Qiu Y, He JS, et al. Manifestations and prognosis of gastrointestinal and liver involvement in patients with COVID-19: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2020;

[43]. 5(7):667-678. doi:10.1016/S2468-1253(20)30126-6

[44]. Long B, Brady WJ, Koyfman A, Gottlieb M. Cardiovascular complications in COVID-19. Am J Emerg Med. Published online April 18, 2020. doi:10.1016/j.ajem.2020.04.048

[45]. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, et al; Latin American Network of ACoronavirus Disease 2019-COVID-19 Research (LANCOVID-19). Clinical, laboratory and imaging features of COVID-19: a systematic review and meta-analysis. Travel Med Infect Dis. 2020;34:101623.

[46]. doi:10.1016/j.tmaid.2020.101623

[47]. Pan F, Ye T, Sun P, Gui S, Liang B, Li L, Zheng D, Wang J, Hesketh RL, Yang

[48]. L, Zheng C (2020) Time course of lung changes at chest CT during recovery

[49]. from coronavirus disease 2019 (COVID-19). Radiology. 295(3):715–721

[50]. Spagnolo P, Balestro E, Aliberti S, et al. Pulmonary fibrosis secondary to COVID-19: a call to arms? Lancet Respir Med 2020;8(8):750–752.

[51]. Elicker BM. What Are the Long-term Pulmonary Sequelae of COVID-19 Infection?. Radiology. 2022 Mar 15:220449.

[52]. Zapol WM, Trelstad RL, Coffey JW, Tsai I, Salvador RA. Pulmonary fibrosis in severe acute respiratory failure. Am Rev Respir Dis 1979;119(4):547–554.

[53]. Ichikado K, Muranaka H, Gushima Y, et al. Fibroproliferative changes on high-resolution CT in the acute respiratory distress syndrome predict mortality and ventilator dependency: a prospective observational cohort study. BMJ Open 2012;2(2):e000545.

[54]. International consensus conferences in intensive care medicine: Ventilatorassociated Lung Injury in ARDS. This official conference report was cosponsored by the American Thoracic Society, The European Society of Intensive Care Medicine, and The Societé de Réanimation de Langue Française, and was approved by the ATS Board of Directors, July 1999. Am J Respir Crit Care Med 1999;160(6):2118–2124.

[55]. Cabrera-Benitez NE, Laffey JG, Parotto M, et al. Mechanical ventilationassociated lung fibrosis in acute respiratory distress syndrome: a significant contributor to poor outcome. Anesthesiology 2014;121(1):189–198.

[56]. Bain W, Yang H, Shah FA, et al. COVID-19 versus Non-COVID-19 Acute Respiratory Distress Syndrome: Comparison of Demographics, Physiologic Parameters, Inflammatory Biomarkers, and Clinical Outcomes. Ann Am Thorac Soc 2021;18(7):1202–1210.

[57]. McGuinness G, Zhan C, Rosenberg N, et al. Increased Incidence of Barotrauma in Patients with COVID-19 on Invasive Mechanical Ventilation. Radiology 2020;297(2):E252–E262.

[58]. Fonseca M, Summer R, Roman J. Acute Exacerbation of Interstitial Lung Disease as a Sequela of COVID-19 Pneumonia. Am J Med Sci 2021;361(1):126–129.

[59]. Leuschner G, Behr J. Acute Exacerbation in Interstitial Lung Disease. Front Med (Lausanne) 2017;4:176.

[60]. Grillo F, Barisione E, Ball L, Mastracci L, Fiocca R (2020) Lung fibrosis: an undervalued finding in COVID-19 pathological series [published online ahead of print, 2020 Jul 28]. Lancet Infect Dis. https://doi.org/10.1016/S1473 3099(20)30582-X

[61]. Pogatchnik BP, Swenson KE, Sharifi H, Bedi H, Berry GJ, Guo HH (2020) Radiology-pathology correlation in recovered COVID-19, demonstrating organizing pneumonia Pneumonia [published online ahead of print, 2020 Jul 1]. Am J Respir Crit Care Med. https://doi.org/10.1164/rccm.202004-1278IM

[62]. L. Xie, Y. Liu, B. Fan et al., "Dynamic changes of serum SARS-coronavirus IgG, pulmonary function and radiography in patients recovering from SARS after hospital discharge," Respiratory Research, vol. 6, no. 1, p. 5, 2005.

[63]. Nöbauer-Huhmann IM, Eibenberger K, Schaefer-Prokop C, et al. Changes in lung parenchyma

[64]. after acute respiratory distress syndrome (ARDS): assessment with high-resolution computed

[65]. tomography. European Radiology. 2001;11(12):2436–2443. doi: 10.1007/s003300101103.

[66]. Lee JW, Lee KS, Lee HY, et al. Cryptogenic organizing pneumonia: serial high-resolution CT

[67]. findings in 22 patients. AJR American journal of roentgenology.2010;195(4):916–922. doi:

[68]. 10.2214/ajr.09.3940.

[69]. Rubin GD, Ryerson CJ, Haramati LB, Sverzellati N, Kanne JP, Raoof S, Schluger NW, Volpi A, Yim JJ, Martin IB, Anderson DJ (2020) The role of chest imaging in patient management during the COVID-19 pandemic: a multinational consensus statement from the Fleischner Society. Chest 158:106–116. https://doi.org/10.1016/j.chest.2020.04.003

[70]. Tabatabaei SMH, Talari H, Moghaddas F, Rajebi H (2020) Computed tomographic features and short-term prognosis of coronavirus disease 2019 (COVID-19) pneumonia: a single-center study from Kashan, Iran. Radiology: Cardiothoracic Imaging 2(2):e200130. https://doi.org/10.1148/ryct.2020200130

[71]. Han X, Fan Y, Alwalid O, et al. Six-month Follow-up Chest CT Findings after Severe COVID-19 Pneumonia. Radiology 2021;299(1):E177–E186.

[72]. van Gassel RJJ, Bels JLM, Raafs A, et al. High Prevalence of Pulmonary Sequelae at 3 Months after Hospital Discharge in Mechanically Ventilated Survivors of COVID-19. Am J Respir Crit Care Med 2021;203(3):371–374.

[73]. Gulati A, Lakhani P. Interstitial lung abnormalities and pulmonary fibrosis in COVID-19 patients: a short-term follow-up case series. Clin Imaging 2021;77:180–186.

[74]. Fabbri L, Moss S, Khan F, et al. Post-viral parenchymal lung disease of COVID-19 and viral pneumonitis: A systematic review and meta-analysis. medRxiv. 2021:2021.03.15.21253593.

[75]. Huang Y, Yan Tan C, Wu J, Zhu Chen M, Guo Wang Z, Yun Luo L, Rong Zhou X, Ran Liu X, Ling Huang X, Can Yuan C, Lin Chen C (2020) Impact of coronavirus disease 2019 on pulmonary function in early convalescence phase. Respir Res 21(1):163. https://doi. org/10.1186/s12931-020-01429-6

[76]. Hansell DM, Bankier AA, MacMahon H, McLoud TC, Müller NL, Remy J. Fleischner Society: glossary of terms for thoracic imaging. Radiology 2008;246(3):697–722.

[77]. Zhang Y, Liu Y, Gong H, Wu L. Quantitative lung lesion features and temporal changes on chest CT in patients with common and severe SARS-CoV-2 pneumonia. PLoS One 2020;15(7):e0236858.

[78]. Wang YC, Luo H, Liu S, et al. Dynamic evolution of COVID-19 on chest computed tomography: experience from Jiangsu Province of China. Eur Radiol 2020;30(11):6194–6203.

[79]. Li K, Liu X, Yip R, et al. Early prediction of severity in coronavirus disease (COVID-19) using quantitative CT imaging. Clin Imaging 2021;78:223–229.

[80]. Chabi ML, Dana O, Kennel T, et al. Automated AI-Driven CT Quantification of Lung Disease Predicts Adverse Outcomes in Patients Hospitalized for COVID-19 Pneumonia. Diagnostics (Basel) 2021;11(5):878.

[81]. Pang B, Li H, Liu Q, et al. CT Quantification of COVID-19 Pneumonia at Admission Can Predict Progression to Critical Illness: A Retrospective Multicenter Cohort Study. Front Med (Lausanne) 2021;8(810):689568.

[82]. Liu M, Lv F, Huang Y, Xiao K. Follow-Up Study of the Chest CT Characteristics of COVID-19 Survivors Seven Months After Recovery. Front Med (Lausanne) 2021;8:636298.

[83]. Kassin MT, Varble N, Blain M, et al. Generalized chest CT and lab curves throughout the course of COVID-19. Sci Rep 2021;11(1):6940

[84]. Tofighi S, Najafi S, Johnston SK, Gholamrezanezhad A (2020) Low-dose CT in COVID-19 outbreak: radiation safety, image wisely, and image gently pledge. Emerg Radiol. 10:1–5. https ://doi.org/10.1007/s10140-020-01784-3

[85]. George PM, Barratt SL, Condliffe R, Desai SR, Devaraj A, Forrest I, Gibbons MA, Hart N, Jenkins RG, McAuley DF, Patel BV (2020) Respiratory follow-up of patients with COVID-19 pneumonia. Thorax. 75(11):1009–1016.

[86]. Raghu G, Wilson KC (2020) COVID-19 interstitial pneumonia: monitoring the clinical course in survivors. Lancet Respir Med. 8(9):839–842

[87]. Lowenstein CJ, Solomon SD. Severe COVID-19 Is a Microvascular Disease. Circulation 2020;142(17):1609–1611.

[88]. Bilaloglu S, Aphinyanaphongs Y, Jones S, Iturrate E, Hochman J, Berger JS. Thrombosis in Hospitalized Patients With COVID-19 in a New York City Health System. JAMA 2020;324(8):799–801.

[89]. Suh YJ, Hong H, Ohana M, et al. Pulmonary Embolism and Deep Vein Thrombosis in COVID-19: A Systematic Review and Meta-Analysis. Radiology 2021;298(2):E70–E80.

[90]. Dhawan RT, Gopalan D, Howard L, et al. Beyond the clot: perfusion imaging of the pulmonary vasculature after COVID-19. Lancet Respir Med 2021;9(1):107–116.

[91]. Remy-Jardin M, Duthoit L, Perez T, et al. Assessment of pulmonary arterial circulation 3 months after hospitalization for SARS-CoV-2 pneumonia: Dual-energy CT (DECT) angiographic study in 55 patients. EClinicalMedicine 2021;34:100778.

[92]. Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet 2021;397(10270):220–232.

[93]. Tabatabaei SMH, Rajebi H, Moghaddas F, Ghasemiadl M, Talari H. Chest

[94]. CT in COVID-19 pneumonia: what are the findings in mid-term follow-up? Emerg Radiol 2020;27(6):711–719.

[95]. Zou JN, Sun L, Wang BR, et al. The characteristics and evolution of pulmonary fibrosis in COVID-19 patients as assessed by AI-assisted chest HRCT. PLoS One 2021;16(3):e0248957.

[96]. Yu M, Liu Y, Xu D, Zhang R, Lan L, Xu H. Prediction of the Development of Pulmonary Fibrosis Using Serial Thin-Section CT and Clinical Features in Patients Discharged after Treatment for COVID-19 Pneumonia. Korean J Radiol 2020;21(6):746–755.

[97]. McGroder CF, Zhang D, Choudhury MA, et al. Pulmonary fibrosis 4 months

[98]. after COVID-19 is associated with severity of illness and blood leucocyte telomere length. Thorax 2021. 10.1136/thoraxjnl-2021-217031. Published online April 29, 2021.

[99]. Huang W, Wu Q, Chen Z, et al. The potential indicators for pulmonary fibrosis in survivors of severe COVID-19. J Infect 2021;82(2):e5–e7.

[100]. Han X, Fan Y, Alwalid O, et al. Six-month Follow-up Chest CT Findings after Severe COVID-19 Pneumonia. Radiology 2021;299(1):E177–E186.

[101]. Lerum TV, Aaløkken TM, Brønstad E, et al. Dyspnoea, lung function and CT findings 3 months after hospital admission for COVID-19. Eur Respir J 2021;57(4):2003448.

[102]. Gulati A, Lakhani P. Interstitial lung abnormalities and pulmonary fibrosis in COVID-19 patients: a short-term follow-up case series. Clin Imaging 2021;77:180–186.

[103]. Guler, Sabina A., et al. "Pulmonary function and radiological features 4 months after COVID-19: first results from the national prospective observational Swiss COVID-19 lung study." European respiratory journal 57.4 (2021).

[104]. George PM, Wells AU, Jenkins RG. Pulmonary fibrosis and COVID-19: the potential role for antifibrotic therapy. Lancet Respir Med 2020;8(8):807–815.

[105]. Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med 2014;370(22):2071–2082.

[106]. Hämäläinen M, Nieminen R, Vuorela P, Heinonen M, Moilanen E. Antiinflammatory effects of flavonoids: genistein, kaempferol, quercetin, and daidzein inhibit STAT-1 and NF-kappaB activations, whereas flavone, isorhamnetin, naringenin, and pelargonidin inhibit only NF-kappaB activation along with their inhibitory effect on iNOS expression and NO production in activated macrophages. Mediators Inflamm 2007;2007:45673.