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**“ROLE OF HIGH RESOLUTION  
COMPUTED TOMOGRAPHY THORAX  
IMAGING IN FOLLOW-UP OF COVID-19  
PATIENTS – A ONE YEAR HOSPITAL  
BASED CROSS-SECTIONAL STUDY”**

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**BY**

**REG. NO. BS0120010**

**Dissertation**

*Submitted to*

*KAHER, Belagavi, Karnataka,*

*In partial fulfilment of the requirements for the degree of*

**M.D.**

**In**

**RADIO-DIAGNOSIS**

**DEPARTMENT OF RADIO-DIAGNOSIS,  
J. N. MEDICAL COLLEGE,  
BELAGAVI -590010. KARNATAKA**

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**JUNE /JULY – 2023**

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With reference to the above, we wish to inform you that your proposed research project titled  
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SECTIONAL STUDY”**, is ethical and justifiable. The proposed research project has been cleared  
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## **LIST OF ABBREVIATIONS**

COVID-19	Coronavirus Disease 2019
HRCT	High-resolution computed tomography
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
RT-PCR	Reverse transcriptase polymerase chain reaction
RAT	Rapid antigen test
CN	Cranial nerve
CT	Computed tomography
PHEIC	Public Health Emergency of International Concern
nCoV	Novel coronavirus
MERS-CoV	Middle east respiratory syndrome coronavirus
ssRNA	Single-stranded ribonucleic acid
CoV	Coronavirus
RBD	Receptor-binding domain
ACE2	Angiotensin-converting enzyme 2
RNA	Ribonucleic acid
AGPs	Aerosol-generating procedures
MODS	Multiple organ dysfunction syndrome
PT	Prothrombin time
LDH	Lactate dehydrogenase
ESR	Erythrocyte sedimentation rate

CRP	C-reactive protein
LFT	Liver function test
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
GGT	Gamma-glutamyl transferase
ALP	Alkaline phosphatase
PPE	Personal protective equipment
CDC	Centre for Disease Control and Prevention
ACR	American College of Radiology
NCCT	Non-contrast computed tomography
CTPA	Computed tomography pulmonary angiogram
GGO	Ground glass opacification
WHO	World Health Organization
ILD	Interstitial lung disease
FDG	Fluorodeoxyglucose
PET	Positron emission tomography

## **ABSTRACT**

**BACKGROUND AND OBJECTIVES:** Since the outbreak of Coronavirus Disease 2019 (COVID-19) in Wuhan, China, in December 2019, multiple studies have been conducted focused on the radiological changes in patients who have tested positive for reverse transcriptase polymerase chain reaction (RT-PCR) test or rapid antigen test (RAT). HRCT has been utilized as the primary imaging modality of choice in the radiological evaluation of such patients. Various imaging findings, ranging from ground glass opacities, consolidation, crazy paving pattern, and pleural thickening to pulmonary fibrosis, have been reported in the spectrum of temporal HRCT thorax changes in COVID-19 patients.

However, there is limited literature on the HRCT thorax imaging findings in COVID-19 patients who have tested negative on RT-PCR test / RAT after an initial confirmed diagnosis but continue to be symptomatic or have developed new symptoms after resolution of the initial illness and follow-up of post-COVID-19 patients.

This study was conducted to observe the spectrum of lung findings on the HRCT thorax and evaluate its role in the follow-up of the patients, as mentioned above.

**MATERIALS AND METHODS:** A one-year cross-sectional study was conducted in the Department of Radiodiagnosis at KLES Dr. Prabhakar Kore Hospital & MRC, Belagavi. The study included 223 patients who were either previously RT-PCR / RAT confirmed COVID-19 cases who were RT-PCR / RAT negative at the time of the start of the study or patients who were at the time symptomatic (cough, fever,

breathlessness) or had developed new symptoms (cough, fever, breathlessness) after resolution of the initial illness or had been referred to the Department of Radio-Diagnosis, KLES Dr. Prabhakar Kore Hospital & MRC for HRCT thorax scan. All patients were over 18 years and below 80 years of age. After taking written consent from the patient/carer, the patient underwent an HRCT thorax scan to detect and evaluate the lung findings. All imaging findings were noted, and the data was analyzed.

**RESULTS:** Of the 223 cases in our study, 175 were males, and 48 were females. 46.2% of the patients were of the 60-80 years age group, 39.5% of the 40-59 years age group, and 14.3% of the 18-39 years age group. At presentation, 58.3% of patients had breathlessness, 19.7% had cough, and 18.8% had fever. Rest were either asymptomatic or had non-respiratory complaints.

Among the various imaging findings, the most common were reticular opacities (50.2%,  $p=0.024$ ), ground-glass opacification (46.2%,  $p=0.013$ ), and fibrosis (45.3%,  $p=0.041$ ). Apart from the three imaging findings mentioned above, also statistically significant were pneumothorax ( $p=0.018$ ) and cardiomegaly ( $p=0.001$ ). The majority of these findings were more commonly seen in older age groups (40-59 years & 60-80 years age groups). None of the imaging findings showed statistically significant sex predilection.

**INTERPRETATION AND CONCLUSION:** After recovery from the acute disease, post-COVID-19 patients may continue to present with a myriad spectrum of clinical features or complications. HRCT is an essential diagnostic tool in evaluating patients in the post-COVID-19 recovery period to look for the resolution/evolution of the lung disease, detect its sequelae and identify complications.

The most common & statistically significant imaging findings were reticular opacities, followed by ground-glass opacities & fibrosis. These imaging findings are more commonly seen in middle-aged and older age groups. Pneumothorax and cardiomegaly were also found to be statistically significant. Knowledge of the imaging spectrum of post-COVID-19 lung and associated complications will help the radiologists diagnose the patient accurately, thus allowing appropriate and prompt treatment in this patient group.

**Keywords: HRCT thorax, post-COVID-19, lung sequelae**

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## **INTRODUCTION**

Since the outbreak of Coronavirus Disease 2019 (COVID-19) in Wuhan, China, in December 2019, it has spread across all the continents, causing a pandemic that has resulted in significant mortality & morbidity.<sup>1</sup> Governments worldwide have diverted considerable resources toward understanding the pathogenesis, clinical & imaging findings, and disease management.

High-resolution computed tomography (HRCT) thorax provides excellent visualization & evaluation of normal anatomy as well as pathological conditions of the lungs.<sup>2</sup> Since the lungs are the primary target organs of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)<sup>3</sup>, HRCT thorax has become an important imaging modality in the pulmonary evaluation of COVID-19 patients, detecting any pathological change in lung architecture.

Since the outbreak, multiple studies have been conducted, many of which concluded and some still ongoing, focused on the radiological changes in patients who have tested positive for reverse transcriptase polymerase chain reaction (RT-PCR) test or rapid antigen test (RAT). HRCT has been utilized as the primary imaging modality of choice in the radiological evaluation of such patients.<sup>4</sup>

Imaging findings, ranging from ground glass opacities, consolidation, crazy paving pattern, and pleural thickening to pulmonary fibrosis, have been reported in the spectrum of temporal HRCT thorax changes in COVID-19 patients.<sup>4</sup>

However, there is limited availability of literature on the HRCT thorax imaging findings in:

- COVID-19 patients who have tested negative on RT-PCR test / RAT after an initial confirmed diagnosis but continue to be symptomatic or have developed new symptoms after resolution of the initial illness, and
- Follow-up of post-COVID-19 patients.

This study aims to observe the spectrum of lung findings on the HRCT thorax and evaluate its role in the follow-up of the patients, as mentioned above.

## **AIMS AND OBJECTIVES**

### **Aim:**

- To evaluate the role of HRCT thorax scan in the follow-up of COVID-19 patients.

### **Objectives:**

- To evaluate persistent and new lung imaging findings in post-COVID-19 patients using HRCT thorax
- To assess temporal changes in the HRCT lung imaging findings in post-COVID-19 patients
- To evaluate post-COVID-19 lung complications using HRCT thorax

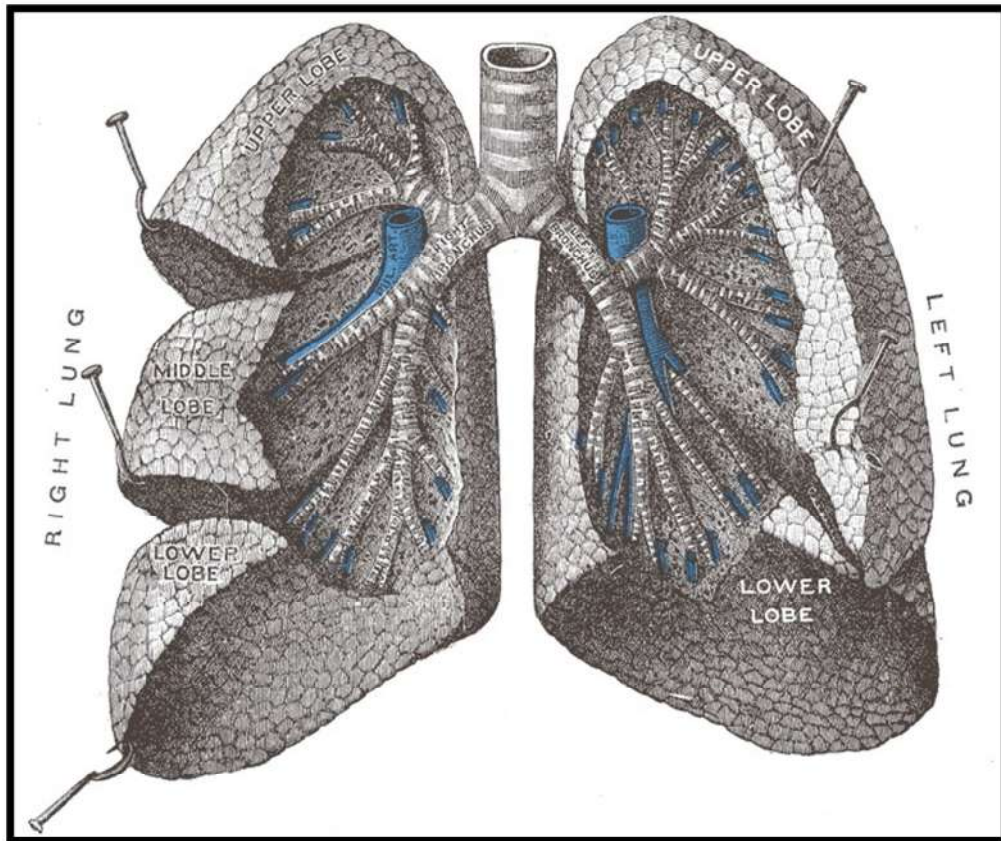
## **REVIEW OF LITERATURE**

A thorough understanding of the key aspects of normal lung anatomy is essential in accurately interpreting HRCT images of the thorax.

The lungs are essential paired organs of respiration wherein the gaseous exchange of oxygen and carbon dioxide occurs. They contain airways spanning 2400 km and approximately 480 million alveoli,<sup>5</sup> a combined surface area of 70 m<sup>2</sup> with each lung weighing about 1.1 kgs.<sup>6,7</sup>

**Gross Anatomy:** The paired lungs lie within the thoracic cavity and are separated by the cardia and the mediastinum. Each lung is covered by the pleura, a double-layered serous membrane consisting of parietal and visceral layers. The visceral pleura is closely adherent to the lung surface following the interlobar fissure and each lobe. The parietal pleura lines the lateral mediastinal margins, the respiratory diaphragm, and the thoracic wall. The potential space between the two pleural layers is called the pleural cavity, which contains a thin film of pleural fluid. 0.01-0.02 mL/kg/hr pleural fluid is produced daily and continuously absorbed, maintaining a pleural fluid level of 0.1-0.2 mL/kg — any disruption in the mechanism of normal resorption of fluid results in pleural effusion.<sup>7</sup>

**Lobar anatomy:** Each lung has lobes that are further subdivided into segments. The right lung has three lobes which are subdivided into ten segments. The left lung consists of two lobes subdivided into eight segments. The lobes are separated from each other by the interlobar fissures. The right lung has an oblique fissure separating the upper & lower lobes and a horizontal fissure separating the upper & middle lobes. In contrast, the left lung has a singular oblique fissure separating the upper & lower lobes.<sup>7</sup>



**Fig. 1 Illustrative anatomy of the lungs**

**Bronchopulmonary segments:** The bronchopulmonary segmental anatomy is based on the tertiary/segmental bronchi. Each bronchopulmonary segment has its segmental bronchus and a pulmonary arterial branch. Each segment is anatomically & functionally discrete, which allows surgical resection of a single segment without affecting the other segments.<sup>8,9</sup>

The right lung consists of three lobes subdivided into the following ten segments:

<b>Lobe</b>	<b>Segment</b>
Right upper lobe	Apical segment Posterior segment Anterior segment
Right middle lobe	Lateral segment Medial segment
Right lower lobe	Superior segment Medial segment Anterior segment Lateral segment Posterior segment

The left lung consists of two lobes subdivided into the following eight segments:

<b>Lobe</b>	<b>Segment</b>
Left upper lobe	Apicoposterior segment Anterior segment Superior lingular segment Inferior lingular segment
Left lower lobe	Superior segment Anteromedial segment Lateral segment Posterior segment

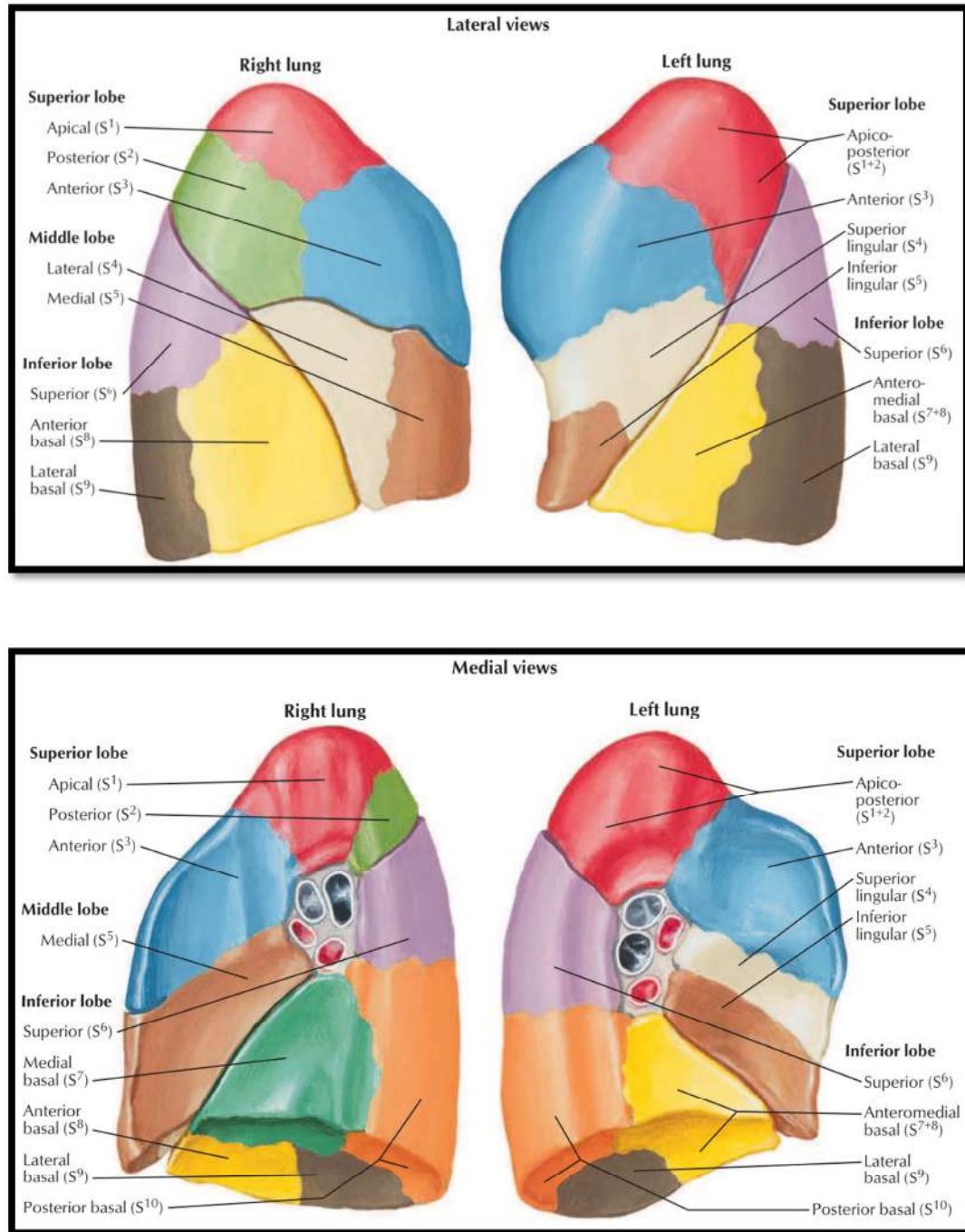


Fig. 2 Illustrative anatomy of the bronchopulmonary segments

**Tracheobronchial tree:** The tracheobronchial tree consists of a branching network of tubular pathways, progressively decreasing in diameter, beginning at the larynx and ending in the alveoli. It can be divided into two zones, the conduction zone, and the respiratory zone.<sup>10</sup>

- **Conduction zone:** The conduction zone consists of the trachea, bronchi, bronchioles & terminal bronchioles. Its primary function is to deliver the gas to the functional zone of the lung, i.e., the alveoli. The cilia in these pathways' walls help remove the particulates from the inspired air. The walls contain cartilage which prevents the collapse of the airways in expiration.
- **Respiratory zone:** The respiratory zone consists of respiratory bronchioles, alveolar ducts, and alveoli. It is the site where gas exchange occurs. Therefore, the respiratory zone forms the functional zone of the lungs.

**Arterial supply:** The lungs have a dual arterial supply in the form of pulmonary and bronchial arteries.

- Pulmonary arteries supply deoxygenated blood to the lungs from the right ventricle.
- Bronchial arteries are branches of the thoracic aorta supplying oxygenated blood.<sup>7,11</sup>

**Venous drainage:**

- Pulmonary veins drain the oxygenated blood from the lungs into the left atrium.
- Bronchial veins drain into the pulmonary veins, the superior vena cava & the azygos vein.<sup>7,11</sup>

**Innervation:** The lungs receive the sympathetic, parasympathetic & visceral afferent fibers from the pulmonary plexus. The pulmonary plexus comprises parasympathetic & visceral afferent fibers from the CN X (vagus) and fibers from the cervical & upper four sympathetic ganglia.

- **Parasympathetic supply:** It arises from the CN X (vagus) and supplies fibers from the pulmonary plexus. The pulmonary plexus comprises parasympathetic & visceral afferent fibers from the CN X (vagus) and fibers from the cervical & upper four sympathetic ganglia.
- **Sympathetic supply:** It arises from the T1-T4 sympathetic ganglia via the pulmonary plexus. It is responsible for vasodilation of the pulmonary vasculature, bronchodilatation, and suppression of glandular secretion.<sup>11</sup>

The phrenic nerve (C3,4,5) innervates the fibrous layer of the pericardium, the diaphragm, and parts of the visceral pleura.<sup>11</sup>

**Lymphatic drainage:** The pulmonary lymphatic system consists of a superficial subpleural lymphatic plexus and a deep lymphatic plexus that accompanies the bronchovascular structures & associated intrapulmonary lymph nodes. Both drain into the bronchopulmonary nodes located at the hilum.

## **HIGH RESOLUTION COMPUTED TOMOGRAPHY (HRCT)**

Computed tomography (CT) is an imaging modality based on the principle that the internal structure of any object can be reconstructed from multiple projections of the object. It utilizes x-rays to generate cross-sectional images or “slices” of the part of the body that is scanned. These cross-sectional images are then reconstructed based on the degree to which a tissue attenuates the passing x-ray beams, i.e., the

attenuation coefficients. High-resolution CT (HRCT) of the thorax refers to a CT imaging acquisition technique in which thin slices (0.625 mm to 1.25 mm) of thorax images are obtained, post-processed in a sharp, high-spatial-frequency, or high-resolution reconstruction algorithm which generate images with a reduction in smoothness and an increase in contrast resolution. These high-resolution images of the lung with exquisite detail are ideal for the assessment of lung pathologies, in particular, diffuse interstitial lung disease.<sup>12,13</sup>

## **COVID-19**

In December 2019, local health authorities in Wuhan, Hubei province, China, reported multiple respiratory infections linked to a wholesale seafood market due to a previously unknown coronavirus, subsequently named severe acute respiratory syndrome – coronavirus 2 (SARS-CoV2). In the following weeks, the disease quickly spread across other cities in China and subsequently to other countries.<sup>14,15</sup>

### **Brief timeline:**

- January 30, 2020: The WHO declared the outbreak in Wuhan a Public Health Emergency of International Concern (PHEIC)<sup>16</sup>
- February 12, 2020: The WHO named the disease “Coronavirus Disease 19 (COVID-19)”<sup>17</sup>
- March 11, 2020: The WHO declared COVID-19 a pandemic<sup>18</sup>

As of November 2022, more than 640 million documented cases and almost 6.6 million documented deaths have occurred due to COVID-19 worldwide, with India accounting for around 44 million cases and 0.5 million deaths.<sup>19</sup>

## **PATHOLOGY**

**Etiology:** Viral phylogenetic analysis in preliminary reports suggested that the virus belonged to subgenus Sarbecovirus and was more similar to two bat-derived SARS-like coronaviruses than to the SARS coronavirus that was known to infect humans, including the one responsible for the SARS outbreak in 2003. Hence, it was temporarily named 2019 novel coronavirus or 2019-nCoV at the time.<sup>20</sup>

Subsequently, the International Committee on Taxonomy of Viruses designated the virus as “Severe Acute Respiratory Syndrome – Coronavirus 2 (SARS-CoV2)”.<sup>21</sup>

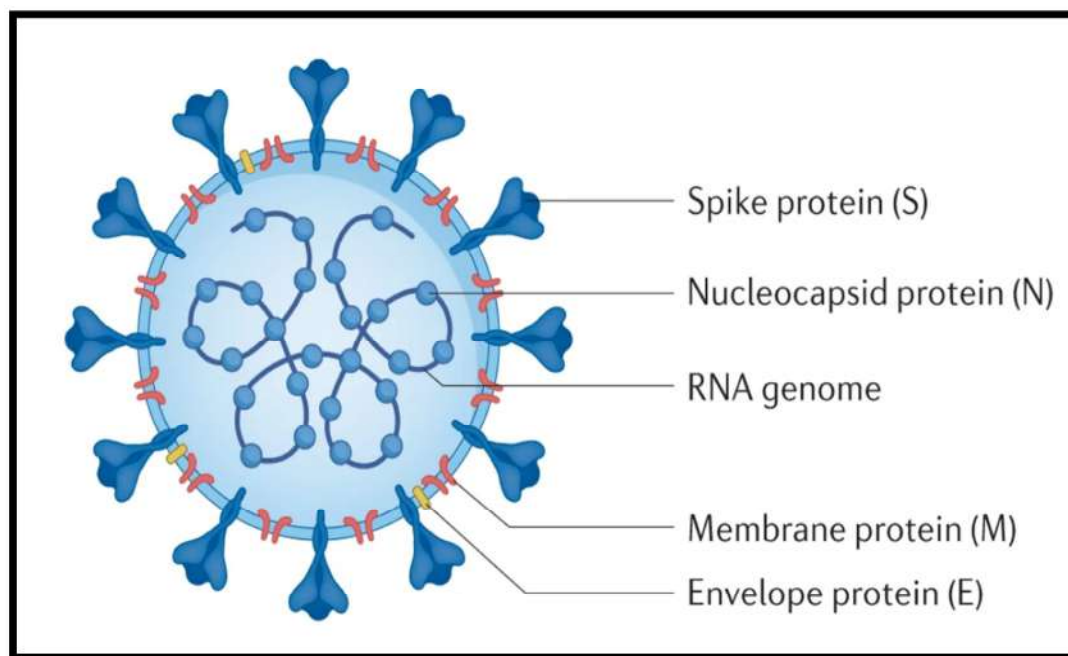
Coronaviruses (CoVs) form a group of pathogenic enveloped viruses containing single-stranded ribonucleic acid (ssRNA) genome.<sup>22</sup> They have characteristic surface spikes, approximately 9-12 nm long, which give them a solar corona-like appearance, hence the name.<sup>23</sup> SARS-CoV-2 has shown higher pathogenicity compared to the previously known SARS-CoV (2002) and MERS-CoV (2013).<sup>24</sup>

Coronaviruses belong to Coronaviridae family of order Nidovirales. CoVs are classified into 4 genera:  $\alpha$ ,  $\beta$ ,  $\gamma$ , and  $\delta$ . SARS-CoV, MERS-CoV & SARS-CoV-2 belong to the  $\beta$ -coronaviruses.<sup>25,26</sup>

**PATHOGENESIS:** Structurally, SARS-CoV-2 has four important proteins:

- Spike (S) protein
- Envelope (E) protein
- Membrane (M) protein
- Nucleocapsid (N) protein

The sequences of these four structural proteins have high similarity to the sequences of the corresponding structural proteins of MERS-CoV and SARS-CoV.<sup>20</sup>



**Figure 3. Structure of SARS-CoV-2 virion**

During cell entry, the CoVs depend on the spike (S) proteins to bind to the host cell-surface receptor. The S protein has two subunits, S1 & S2. The S1 protein binds to the host receptor via the receptor-binding domain (RBD). Following this, the S2 subunit fuses to the cell membrane.<sup>27</sup>

The RBDs of S proteins of different CoVs recognize different cell surface receptors for binding:

- MERS-CoV recognizes dipeptidyl peptidase 4 receptor.
- SARS-CoV & SARS-CoV-2 recognize ACE2 receptor.<sup>28</sup>

The expression and tissue distribution of the above-mentioned cell surface entry receptors consequently influence the tropism and pathogenicity of the virus.<sup>29</sup>

The ACE2 receptor is most commonly seen on the alveolar cells of the lung parenchyma, which explains the development of respiratory symptoms (cough & breathlessness) as the commonest clinical feature of COVID-19. The cardiovascular effects are believed to be mediated via the same receptor, as it is also commonly expressed on the myocardial cells.<sup>30</sup>

During its intracellular life cycle, CoV expresses and replicates its genomic RNA to produce multiple full-length copies that are subsequently incorporated into the newly produced viral particles.<sup>29</sup>

**TRANSMISSION:** COVID-19 is considered an indirect zoonosis since it is transmitted now primarily human-to-human. Its transmission can occur through various mechanisms:

- Contact with droplets of upper respiratory tract secretions of infected patients, e.g., from sneezing or coughing.<sup>31,32</sup>
- Via aerosol transmission (i.e., airborne transmission), e.g., by talking, coughing, singing, expiration, aerosol-generating procedures (AGPs) in hospitals.<sup>33-35</sup>
- Fomites transmission<sup>36</sup>

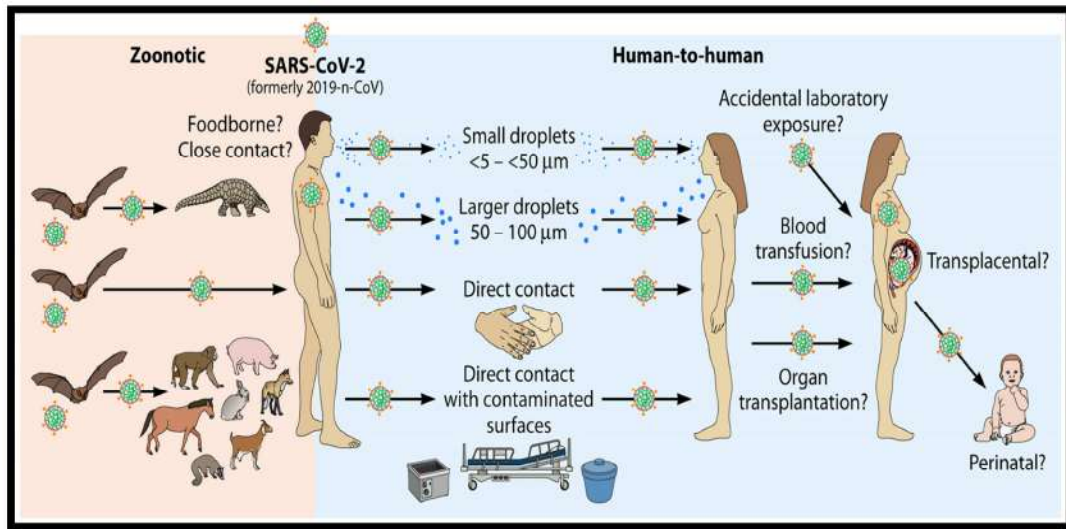
The oro-fecal transmission was seen with SARS-CoV in the SARS epidemic. There is some evidence of oro-fecal transmission of SARS-CoV-2, although it remains unclear.<sup>31,37</sup>

Although sexual transmission has not yet been confirmed in the field, it remains possible as the SARS-CoV-2 virus has been demonstrated in all secretions, including vaginal and seminal fluids.<sup>38</sup>

Transmission through blood transfusion remains unclear, although no cases have been documented so far. Nevertheless, some national bodies have advised that potential donors should not donate blood at least until 28 days after recovering from COVID-19.<sup>39</sup>

The possibility of mother-to-fetus transmission, i.e., vertical transmission of COVID-19, has not been ruled out by cohort studies. However, it seems to be a relatively rare event, if at all it does occur.<sup>40,41</sup>

Transmission from pre-symptomatic & asymptomatic carriers has been documented in many communities.<sup>42,43</sup>



**Figure 4. Potential transmission routes of SARS-CoV-2**

## CLINICAL PRESENTATION

COVID-19 patients typically have systemic and/or respiratory manifestations on presentation.<sup>44-46</sup> When the presentation is systemic, there can be multiple organ dysfunction, in which case it is termed MODS-SARS-CoV-2.<sup>46</sup> Gastrointestinal and cardiovascular symptoms can occur but are less common.<sup>47,48</sup>

The majority of infected individuals remain asymptomatic and, therefore, act as potential carriers throughout the duration of the illness.<sup>49,50</sup>

COVID-19 has a broad spectrum of clinical manifestations, with the majority of symptoms & signs being non-specific.<sup>51,52</sup>

<b>Common</b>	<b>Less common</b>	<b>Rare</b>
<ul style="list-style-type: none"> <li>• Fever (most common; 85%-90%)</li> <li>• Cough (second most common; 65%-70%)</li> <li>• Anosmia (45%)<sup>53</sup></li> <li>• Fatigue (40%)</li> <li>• Sputum production (35%)</li> <li>• Breathlessness (20%)</li> </ul>	<ul style="list-style-type: none"> <li>• Arthralgia/myalgia</li> <li>• Headaches<sup>54</sup></li> <li>• Dermatologic lesions – erythematous rash<sup>55</sup></li> <li>• Sore throat</li> <li>• Chills</li> <li>• Diarrhea<sup>56</sup></li> <li>• Splenomegaly</li> </ul>	<ul style="list-style-type: none"> <li>• Nausea &amp; vomiting<sup>45</sup></li> <li>• Abdominal pain, gastrointestinal bleeding<sup>45</sup></li> <li>• Stroke<sup>57,58</sup></li> <li>• Nasal congestion<sup>45</sup></li> <li>• Palpitations<sup>48</sup></li> <li>• Hemoptysis<sup>59</sup></li> <li>• Confusion, altered consciousness, paraesthesia, seizures<sup>54,60</sup></li> <li>• Ocular symptoms (e.g., epiphora, conjunctivitis)<sup>61</sup></li> <li>• Hiccups<sup>62</sup></li> </ul>

Pediatric patients usually have milder presentations as compared to adults. Children typically present with fever, sore throat, wheezing, dry cough, and myalgia. Diarrhea, rhinorrhea, lethargy & vomiting are less commonly seen.<sup>63,64</sup>

## **DIAGNOSIS**

### **RT-PCR Test**

The real-time reverse transcriptase polymerase chain reaction test, RT-PCR, is the gold standard diagnostic investigation for SARS-CoV-2. It is a highly specific test for SARS-CoV-2. However, the reported sensitivity of the test varies, ranging from as

low as 60% to as high as 97%.<sup>65</sup> Pooled sensitivity of the test based on meta-analysis is reported to be about 89% which suggests that false negatives can be of significant clinical concern and multiple negative tests are required in a case to exclude the disease confidently.<sup>66</sup>

The test's sensitivity depends on the duration since exposure to the virus. The false-negative rate drops from 100% on the 1<sup>st</sup> day after exposure to 67% on the 4<sup>th</sup> day, further falling to 38% on the day of onset of symptoms and reaching a nadir of 20% about three days after symptom onset. Following this, it begins to rise again and reaches 66% on day 21 after the date of exposure.<sup>67</sup>

### **Rapid Antigen Test or Lateral Flow Assays**

Rapid antigen tests (RATs) are lateral flow immuno-chromatographic assays in which analytes (antigen in RAT) are detected in a sample from the patient's upper respiratory tract.<sup>68</sup>

### **HRCT as a Diagnostic Test**

Multiple radiological societies have stated that HRCT imaging findings should not be relied upon as a screening or diagnostic tool for COVID-19. HRCT imaging findings are not part of the COVID-19 diagnostic criteria in multiple panel recommendations.<sup>69-71</sup> However, HRCT as a diagnostic tool has been utilized by many despite the recommendations not to do so.<sup>72,73</sup>

### **LABORATORY TESTS**

The common laboratory findings in COVID-19 patients include the following<sup>51,72,74,75</sup>:

- Lymphopenia
- Thrombocytosis
- Raised Prothrombin Time (PT)
- High Lactate Dehydrogenase (LDH)

Other commonly identified laboratory abnormalities include:

- Mildly elevated inflammatory markers (ESR & CRP)
- Raised D-dimer
- Mildly raised serum amylase
- Mildly deranged LFTs are common, primarily raised aspartate aminotransferase (AST) & alanine aminotransferase (ALT)
  - Mild increase in bilirubin
  - Normal gamma-glutamyl transferase (GGT) & alkaline phosphatase (ALP)

## **IMAGING IN COVID-19**

### **Imaging indications**

There is a great degree of global variation in the threshold for imaging potential/ confirmed COVID-19 patients due to local resources, regionally published guidelines, and the sociocultural approach to radiological imaging.

The use of HRCT as a primary imaging screening tool is not encouraged, not least because these studies tended to suffer from selection bias, with a meta-analysis,

in April 2020 reporting a pooled sensitivity of 94% and specificity of 37%. In countries with low prevalence (<10%), the positive predictive value of RT-PCR was ten-fold that of HRCT chest.<sup>66,70,76,77</sup>

On April 7, 2020, the Fleischner Society published a multinational consensus statement,<sup>78</sup> a summary of recommendations of which is described below:

- **Main recommendations:**

- Imaging as a screening tool is not routinely indicated for COVID-19 in asymptomatic individuals.
- Imaging is not indicated for cases with mild clinical features of COVID-19 unless they are at risk for disease progression.
- Imaging is indicated for cases with moderate-to-severe features of COVID-19 regardless of COVID-19 test results.
- Imaging is indicated in COVID-19 cases with features indicative of worsening respiratory status.
- In a resource-constrained environment with limited access to HRCT, chest radiography may be a preferred imaging modality in COVID-19 cases unless features of deteriorating respiratory status warrant the use of HRCT.

- **Additional recommendations:**

- Daily chest radiographs are not indicated in stable intubated patients with COVID-19.

- CT is indicated in patients with functional impairment and/or hypoxemia after recovery from COVID-19.
- COVID-19 testing is indicated in patients incidentally found to have findings suggestive of COVID-19 on a CT scan.

Moreover, there are additional risks in performing HRCT routinely for large patient cohorts<sup>76</sup>:

- depletion of limited & finite resources (e.g., due to excessive usage of PPE)
- increased risk of transmission of the virus (to healthcare workers, patients, and carers) because of the proximity of the COVID-19-positive & negative patients in the radio-diagnosis department
- additional exposure to ionizing radiation.

### **Infection precautions**

Clear guidelines regarding infection control are imperative, given that the healthcare workers in a radio-diagnosis department are often at the frontline when handling COVID-19 patients. Various precautionary measures include:

- Precautions against droplet-type transmission: Medical masks, whole-body gowns, gloves, & protection of eyes (aerosol-generating procedures require whole-body aprons & N95 masks)<sup>79</sup>
- Portable radiography for patients requiring general radiography (to limit transportation of patients) or in dedicated auxiliary imaging units. Patients requiring transport to departments must wear an N-95 mask during transportation. All machines, including any ancillary equipment used in the

examinations, should be cleaned after the examinations are over. It is also recommended that two radiographers be present during any imaging examination, using the system of 'one clean and one in contact with the patient' to minimize cross-contamination. SARS-CoV-2 is known to survive on a surface for as long as 72 hours, which reinforces the need to protect the equipment with barriers (e.g., covers) and the importance of thorough cleaning of the equipment between patients.<sup>80</sup>

### **Non-urgent care**

The Centre for Disease Control and Prevention (CDC) & the American College of Radiology (ACR) recommend rescheduling all non-urgent outpatient appointments.<sup>81</sup>

The British Society of Skeletal Radiologists recommends that soft tissue, perineural, and intra-articular steroid injections may decrease viral immunity and, hence, should be avoided unless they are absolutely necessary. However, this decision has been criticized for its highly uncompromising approach, particularly due to a lack of clear underlying evidence, with many suggesting that the risk-benefit calculation favors performing the procedure in many patients.<sup>82</sup>

### **CT protocol**

For the majority of patients requiring HRCT, a non-contrast CT scan of the thorax with slice thickness between 0.625 mm to 1.5 mm is indicated.<sup>70</sup>

If an iodinated contrast study or CT pulmonary angiogram is indicated, an NCCT scan should be done prior to the administration of the contrast. This is because the interpretation of GGO patterns can be impacted by the contrast medium.<sup>72</sup>

Although there is a higher risk of pulmonary thromboembolism in severe COVID-19, current recommendations suggest that D-dimer values should be used to justify a CTPA. At present, there is no clear evidence to suggest that there is a benefit to performing CTPA on initial presentation as first-line imaging in patients suspected of COVID-19.<sup>83-85</sup>

## **RADIOGRAPHIC FEATURES**

The primary imaging findings of COVID-19 seen on chest radiographs & HRCT are those of organizing pneumonia or atypical pneumonia.<sup>73,80,86,87</sup>

When patients have a mild disease or are early in the disease course, about 18% of patients show normal chest radiographs or HRCT. This number can decrease to about 3% in severe COVID-19. As a result, the imaging has shown limited sensitivity for the diagnosis of COVID-19.<sup>45,72</sup>

COVID-19 commonly involves both lungs and multiple lobes.<sup>88,89</sup>

Currently, the majority of radiological associations recommend that imaging should not be employed for screening or diagnosing, instead reserved for the evaluation of complications due to COVID-19.<sup>76</sup>

### **Plain radiograph:**

Chest radiography is the first-line imaging modality in cases with suspected COVID-19, although it is less sensitive than HRCT thorax.<sup>90</sup> Portable radiography units are preferred because of the ease of decontamination.<sup>69</sup>

Early/mild disease usually has normal chest radiographs. In a retrospective study conducted by Wong et al in 2020, it was shown that 69% of COVID-19 cases

that required hospitalization had chest radiograph abnormalities at the time of admission, and about 80% of patients had abnormal chest radiographic findings sometime during the hospitalization period. Chest radiographic findings were most extensive 10-12 days after the onset of symptoms.<sup>90</sup>

Airspace opacities are the most frequent findings. These can be in the form of consolidation or GGO. Most often, these are distributed bilaterally, peripherally, and predominantly in the lower zone. GGO is more common early in the course and may precede the development of consolidation. Pleural effusion is rarely seen.<sup>72,90</sup>

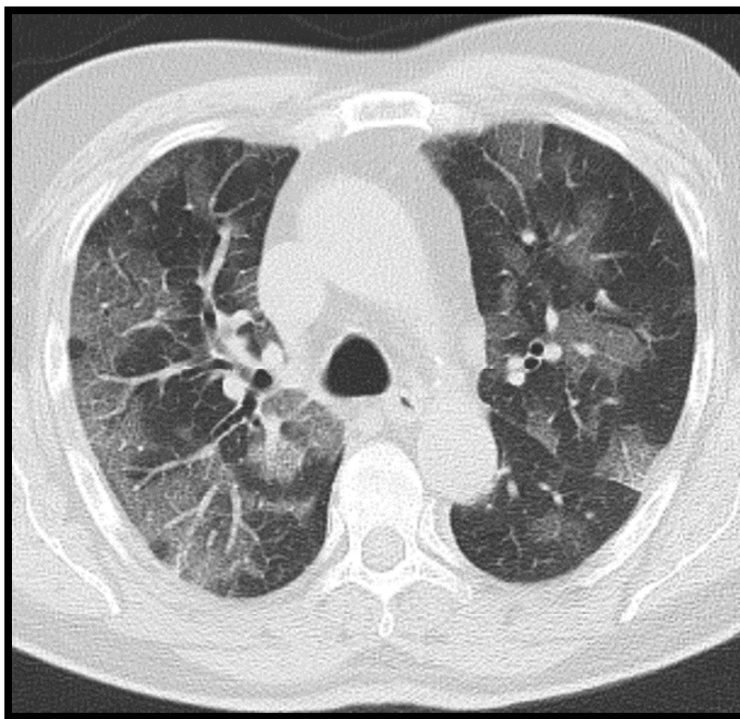
There are no published data regarding cardiac disease evaluation on chest radiographs even though cardiac involvement is a well-recognized feature of COVID-19.<sup>91</sup>

#### **HRCT:**

COVID-19 pneumonia typically presents on HRCT thorax imaging as bilateral peripheral opacities with a predominant lower lung distribution. The opacities are most commonly ground-glass opacities (GGOs) with areas of consolidation. They are often nodular or mass-like and resemble organizing pneumonia pattern.<sup>92</sup>

An important imaging sign noted in COVID-19 is the reverse halo sign, which is a focal and rounded area of GGO surrounded by a ring or arc of denser consolidation.<sup>93</sup>

GGOs can also follow a diffuse pattern, in which case COVID-19 may mimic other infections, inhalational lung disease, and drug toxicities.<sup>94</sup>



**Fig. 5 Axial HRCT thorax image (lung window) showing bilateral ground-glass opacities and dilated segmental and subsegmental vessels**

Many patients will present with some but not all of the prototypical features of COVID-19 that have been well described, e.g., the patient may present with unilateral opacities which have rounded morphology, or the opacities may be distributed predominantly in the upper lobes and still retain subpleural or peripheral distribution.<sup>95</sup>

<b>RSNA Expert consensus reporting system for COVID-19:<sup>96</sup></b>	
<b>Category</b>	<b>Description</b>
<b>Typical appearance</b>	<p>Bilateral, peripheral GGOs ± consolidation or visible intralobular lines (i.e., crazy paving pattern)</p> <p>Multifocal rounded GGOs ± consolidation or visible intralobular lines (i.e., crazy paving pattern).</p> <p>Reverse halo sign / other findings suggestive of organizing pneumonia.</p>
<b>Indeterminate appearance</b>	<p>Absence of typical imaging features AND presence of:</p> <ul style="list-style-type: none"> <li>• Diffuse, multifocal, perihilar, or unilateral GGOs ± consolidation lacking specific distribution; that are non-peripheral or non-rounded and lack a specific distribution pattern; or that are non-peripheral or non-rounded</li> <li>• Few GGOs that are very small and non-rounded and lack peripheral distribution</li> </ul>
<b>Atypical appearance</b>	<p>Absence of typical/indeterminate COVID-19 features AND presence of:</p> <ul style="list-style-type: none"> <li>• Isolated segmental or lobar consolidation with the absence of GGOs</li> <li>• Discrete small nodular opacities (“tree-in-bud,” centrilobular)</li> <li>• Lung cavitation</li> <li>• Smooth interlobular septal thickening + pleural effusion</li> <li>• Pneumothorax</li> </ul>
<b>Negative for pneumonia</b>	No HRCT features suggestive of pneumonia.

A retrospective study in 2020 reported that the rate of barotrauma in COVID-19 patients who were mechanically ventilated was much higher (24%) compared to patients with other causes of ARDS (11%).<sup>97</sup>

Four stages of temporal HRCT imaging changes during active COVID-19 have been described.<sup>73,92,98</sup> In the early or initial stage (0-4 days), HRCT shows normal imaging findings or only GGOs. In the progressive stage (5-8 days), there is a progressive increase in GGOs and the appearance of a crazy paving pattern. Consolidation is seen in the peak stage (9-13 days). In the absorption stage (>14 days), as the disease course improves, “fibrous stripes” appear with the resolution of the abnormal imaging findings at one month or beyond.

**Ultrasound:** Lung ultrasonography has shown to have significant utility in the management of COVID-19 pneumonia due to its precision, low cost, safety, absence of radiation & point of care use. Ultrasonography can aid in:<sup>99</sup>

- rapid initial assessment of the severity of pneumonia/ARDS
- tracking the evolution of disease
- monitoring lung recruitment maneuvers
- guiding response to a prone position and extracorporeal membrane therapy
- making decisions regarding weaning the patient off of ventilatory support

Ultrasonographic findings noted in COVID-19 pneumonia are:<sup>99–103</sup>

- B lines (discrete, multifocal, or confluent)
  - These can be in focal, multifocal, or confluent patterns.
  - They represent thickened subpleural interlobular septa.
  - The thickened septa manifest as a vertical broad-based reverberation artifact known as a light beam sign.
- Thickened pleural line which is irregular and shows scattered discontinuities

- Consolidations can present in different patterns (multifocal small, non-translobar, or translobar consolidations with mobile air bronchograms)
  - Subpleural consolidations may be associated with a localized pleural effusion. On color Doppler study, these are relatively avascular. Pneumonic consolidations typically demonstrate preserved vascular flow or hyperemia.
  - Alveolar consolidations with static & dynamic air bronchograms are seen. These are usually associated with progressive, severe disease.
- Multilobar distribution of abnormalities
- Pleural effusion is a relatively rare finding.

In mild infections and early stages, focal *B* lines are usually the main features. Alveolar interstitial syndrome is usually the main feature in critically ill patients and in the progressive stages. In the convalescent stage, with restitution of aeration, there is reappearance of *A* lines. Patients who develop pulmonary fibrosis demonstrate pleural line thickening and uneven *B* lines.<sup>101,102</sup>

#### **NUCLEAR MEDICINE (PET-CT)**

There is increased FDG uptake in the GGOs in COVID-19 pneumonia. In a retrospective study comprising a small study sample conducted in Wuhan, it was noted that patients who demonstrated higher FDG uptake in the pulmonary lesions took longer to recover. The higher FDG uptake in these patients positively correlated with the ESR values.<sup>104–106</sup>

## **RADIOLOGY REPORTING OF COVID-19**

### **Plain radiograph reporting**

Various radiological societies have published recommendations for reporting radiographs of COVID-19 patients. The British Society of Thoracic Imaging (BSTI) published the following radiograph reporting proforma:<sup>107</sup>

#### **Findings:**

- **Normal**  
COVID-19 not excluded. Correlate with RT-PCR.
- **Classic/Probable COVID-19**  
Predominantly peripheral and usually bilateral multiple opacities in lower lobes
- **Indeterminate for COVID-19**  
Imaging findings do not fit the classic or non-COVID-19 descriptors.
- **Non-COVID-19**  
Lobar Pneumonia/ Pneumothorax/ Pleural effusion/ Pulmonary edema  
Other findings

#### **Quantifying disease:**

**Mild/ Moderate/ Severe**

BSTI has also published the following post-COVID-19 chest radiograph proforma:<sup>107</sup>

#### **COVID-19-related Findings:**

- **Resolved**  
Normal imaging findings/No significant persisting COVID-19 changes/Return to the pre-COVID-19 baseline

- **Significantly improved**  
≥ 50% abnormal imaging findings have resolved (extent ± density of opacification)
- **Not significantly improved/ unchanged**  
< 50% abnormal imaging findings have resolved (extent ± density of opacification)
- **Worsening**  
Development of fibrosis (even if alveolar opacities have improved)/  
Deteriorating alveolar opacities

**Other findings:**

- Lung malignancy; Pneumomediastinum; Pneumothorax; New non-COVID-19 infection(s) / Pleural effusion(s)

**HRCT Reporting**

In March 2020, a consensus statement was released by the Radiological Society of North America (RSNA) to standardize reporting of COVID-19 on HRCT. The American College of Radiology (ACR) and the Society of Thoracic Radiology endorsed the statement. It classifies the HRCT appearance of COVID-19 into the following four categories:<sup>108</sup>

<b>Reported Language for CT imaging findings related to COVID-19.</b>			
<b>COVID-19 pneumonia imaging classification</b>	<b>Rationale</b>	<b>CT Findings</b>	<b>Suggested Reporting Language</b>
<b>Typical appearance</b>	Commonly reported imaging features that are highly specific for COVID-19 pneumonia	Bilateral, peripheral GGOs ± consolidation or visible intralobular septal lines (i.e., crazy paving pattern) Multifocal rounded GGOs ± consolidation /visible intralobular septal lines (i.e., crazy paving pattern). Reverse halo sign or presence of other imaging features of organizing pneumonia	<i>“Commonly reported imaging features of COVID-19 pneumonia are present. Other processes such as influenza pneumonia &amp; organizing pneumonia, as can be seen with drug toxicity and connective tissue disease, can cause a similar imaging pattern.”</i>
<b>Indeterminate appearance</b>	Imaging features that are nonspecific for COVID-19 pneumonia	<b>Absence of typical features + Presence of:</b> Diffuse, multifocal, perihilar, or unilateral GGOs ± consolidation with nonspecific distribution and are non-peripheral or non-rounded Few very small GGOs with a non-peripheral and non-rounded distribution	<i>“Imaging features can be seen with COVID-19 pneumonia, though are non-specific and can occur with a variety of infectious and noninfectious processes.”</i>

<b>Overview of CO-RADS categories and the corresponding level of suspicion for pulmonary involvement in COVID-19</b>			
<b>Atypical appearance</b>	Uncommon imaging features or imaging features that are not reported for COVID-19 pneumonia	<b>Absence of typical or indeterminate imaging features AND Presence of:</b> - Isolated segmental or lobar consolidation without GGOs. - Discrete small centrilobular nodules (“tree-in-bud” appearance) - Lung cavitation - Smooth interlobular septal thickening + pleural effusion	<i>“Imaging features are atypical or uncommonly reported for COVID-19 pneumonia. Alternative diagnoses should be considered.”</i>
<b>Negative for pneumonia</b>	No features of pneumonia	No HRCT imaging features suggestive of pneumonia, in particular, absence of GGOs and consolidation	<i>“No CT findings present to indicate pneumonia. (Note: HRCT may be negative in the early stages of COVID-19).”</i>

### CO-RADS

The Dutch Association for Radiology proposed an HRCT scoring system for COVID-19 and called it CO-RADS (COVID-19 reporting and Data system). It aimed to ensure uniform & replicable CT reporting. It assigns a score of 0 to 6, depending on the HRCT findings. A score of 0 is given if the CT is uninterpretable. A score of 6 is given if there is a confirmed RT-PCR test.<sup>109</sup>

<b>CO-RADS Category</b>	<b>Level of suspicion for pulmonary involvement of COVID-19</b>	<b>Summary</b>
0	Not interpretable	Scan technically insufficient for assigning a score
1	Very low	Normal or noninfectious
2	Low	Typical for other infections but not COVID-19
3	Equivocal/unsure	Features compatible with COVID-19 but also others
4	High	Suspicious for COVID-19
5	Very high	Typical for COVID-19
6	Proven	RT-PCR positive for SARS-CoV-2

## **TREATMENT AND PROGNOSIS**

### **Treatment**

A multi-pronged approach focusing on public health measures to prevent interhuman transmission of SARS-CoV-2 is required, including measures such as usage of face masks, meticulous hand-washing, good personal hygiene, ventilation, social distancing, avoidance of crowded environments, & self-isolation.<sup>110</sup>

Research has shown that aerosol transmission has a more significant role to play in the spread of the virus than previously believed. Measures such as better

ventilation (which can be as simple as opening the windows) and control systems for aerosol infection (e.g., air filtration, UV lighting) help counter it.<sup>34,111</sup>

Rapid diagnosis, quarantine, and providing effective supportive therapy (antibiotics, antivirals, supportive measures) to the infected patients play an important role not just in the management of the patient but also in preventing further inter-human transmission of the virus.

Both non-invasive and invasive mechanical ventilation & extracorporeal membrane ventilation (ECMO) have also been utilized.

### **Prone positioning (“Proning”)**

Placing in a prone position has been shown to improve lung oxygenation in COVID-19 patients.<sup>112</sup>

### **Antiviral therapy**

Ronapreve, a formulation comprising of two potent monoclonal antibodies, imdevimab and casirivimab, was the first specific antiviral drug for adult COVID-19 patients.<sup>113</sup>

Molnupiravir, an analogue of cytidine originally developed for treating influenza, is currently in phase 3 trials for the treatment of COVID-19.<sup>114,115</sup>

Protease inhibitors, which showed success in treating SARS, have been utilized as combination therapy in the management of COVID-19.<sup>116,117</sup> However, a recent randomized controlled trial failed to show any added benefit of combination therapy of lopinavir-ritonavir.<sup>118</sup>

Remdesivir and baricitinib in combination against SARS-CoV-2, showed promising in vitro results.<sup>119,120</sup> A preliminary trial in May 2020 showed a slight reduction of time to recovery in patients who were administered remdesivir.<sup>121</sup> However, there were concerns about the credibility of this study, and remdesivir did not show evidence of a decrease in mortality or reduction in the duration of hospital stay.<sup>122</sup>

A few other antivirals that are in phase III trials include lopinavir, oseltamivir, ASC09F, ritonavir, cobicistat, and darunavir.<sup>123</sup>

In June 2020, RECOVERY (Randomized Evaluation of COVid-19 therapy) randomized controlled trial showed dexamethasone to decrease mortality by 33% in patients on mechanical ventilation and by 20% in non-ventilated patients who required oxygen. There was no evidence of benefit in patients who did not need respiratory support.<sup>124</sup>

In early 2020, a few in vitro studies reported that chloroquine & hydroxychloroquine, both antimalarial drugs, demonstrated strong anti-SARS-2-CoV activity. An initial RCT demonstrated that patients treated with hydroxychloroquine showed a significant reduction in viral carriage along with a lower carrying period. Furthermore, when used in combination with azithromycin, it showed a synergistic effect.<sup>125,126</sup> However, this trial was later strongly criticized because of gross flaws in its methodology and questionable conclusions. The positive effects of these drugs that were previously described have not been replicated in later research, and there may be side effects as well.<sup>127</sup>

Another drug that has been explored in the management of COVID-19 is ivermectin. The WHO recommends not using ivermectin for COVID-19 patients, regardless of the disease severity, except in a clinical trial setting.<sup>128</sup>

### **Early therapy**

A recent retrospective study showed evidence that early treatment of COVID-19 patients within 72 hours with low-dose aspirin, indomethacin, omeprazole, bioflavonoids, azithromycin, heparin, and betamethasone results in the reduction of the disease severity and the rate of hospitalizations.<sup>129</sup>

### **Passive Immunity**

Another treatment modality utilized in managing COVID-19 patients is the one based on passive immunity. This includes convalescent plasma and hyperimmune immunoglobulins.<sup>130–133</sup>

- Convalescent plasma is obtained from patients who have completely recovered from COVID-19 and therefore contains antibodies against the SARS-CoV-2.
- Hyperimmune immunoglobulins are the purified antibodies that are prepared from convalescent plasma.

These have shown some degree of success in critically ill patients. However, in May 2020, a Cochrane review failed to find any convincing evidence that these modalities were indeed an effective treatment.<sup>133</sup>

**Vaccines**

The spike (S) protein is the primary antigen target for developing vaccines against the coronavirus. The spike protein is located on the surface of the virion and is an important antigen playing a vital role in inducing an immune response in vivo.<sup>134-136</sup>

About 125 SARS-CoV-2 vaccines were originally in development. About ten of these vaccines are now being used globally, while the rest remain either in development or were abandoned because of lack of efficacy.<sup>134-136</sup>

Anti-SARS-CoV-2 vaccines may be classified based on their mechanisms of action:<sup>134,135</sup>

Genetic vaccines	Protein vaccines:
<ul style="list-style-type: none"> <li>• Adenoviral vector vaccines: e.g., Oxford-AstraZeneca, Covishield, Sputnik V</li> <li>• mRNA-based vaccines: e.g., Pfizer, Moderna</li> <li>• DNA-based vaccines: ZyCoV-D</li> </ul>	<ul style="list-style-type: none"> <li>• Protein subunit vaccines: e.g., Novavax, CorBEvax, Covovax</li> <li>• Inactivated virion: e.g., Covaxin, Sinopharm</li> </ul>

Of these, the vaccines available in India include the following:

- Covishield
- Covaxin
- Sputnik V
- CorBEvax
- AyCoV-D

## **REVIEW OF RELEVANT STUDIES**

HRCT thorax has played an indispensable role in the diagnosis, evaluation & management of COVID- 19 patients. Its role during acute COVID- 19 infection has been extensively documented; however, the data on the radiological features of sequelae and complications is still unfolding.

Lingering symptoms have been documented in a significant percentage of patients in the post-recovery phase, with cough and dyspnea being the most common respiratory symptoms. Therefore, awareness of the lung parenchymal changes that may persist in the recovered COVID- 19 pneumonia patients and their evolution or resolution patterns is essential. It's equally important to be aware of the radiologic imaging features of pulmonary complications not uncommonly seen as immediate or long-term consequences of COVID- 19.<sup>137</sup>

Since the outbreak in December 2020, studies have been conducted worldwide to study the long-term imaging features & sequelae of COVID-19. HRCT of the thorax has been the imaging modality of choice for the evaluation of post-COVID-19 patients.<sup>138</sup>

A prospective longitudinal study by Wang et al in January 2020 - February 2020 in Wuhan, China, described the temporal changes in HRCT thorax imaging findings in COVID-19 pneumonia. It showed that the HRCT imaging abnormalities progressed quickly after the onset of symptoms, peaking at day 6- day 11 of the illness. Following this period, the abnormalities persisted at a high level. The most common pattern of imaging findings was GGO. The second most common imaging finding seen in the initial period was consolidation. The mixed pattern (including GGO, architectural distortion, and consolidation) peaked between days 12 & 17 of

illness. 94% of discharged patients showed residual imaging findings on the final HRCT, with GGOs being the most common imaging pattern.<sup>139</sup>

Yu-Miao Zhao et al conducted a multi-center retrospective cohort study in January-February 2020 that included COVID-19 survivors who underwent HRCT thorax imaging, pulmonary function testing (PFT), and laboratory testing of serum levels of IgG antibodies against SARS-CoV-2 3 months after discharge. A considerable proportion of these subjects showed SARS-CoV-2 infection-related radiological findings, clinical symptoms, elevated D-dimer levels, and abnormal PFTs results even three months after discharge.<sup>140</sup>

A prospective study was conducted by Han et al consisting of 114 patients who had been treated for COVID-19 and discharged between December 2019 and February 2020. Initial & follow-up HRCT scans were done at 17 days ( $\pm 11$  days) and 175 days ( $\pm 20$  days), respectively, after the onset of symptoms. 35% of subjects showed fibrotic changes in the follow-up HRCT, 38% of cases showed complete radiologic resolution, and 27% showed GGO of interstitial septal thickening. The fibrotic changes were associated with the patients who were older, who had severe COVID-19 pneumonia initially, longer hospital stays, acute respiratory distress syndrome (ARDS), non-invasive mechanical ventilation, tachycardia, and higher initial CT severity score. The common persistent lung parenchymal abnormalities on HRCT Thorax scans at three months, six months, and one year after resolution of the primary disease included ground-glass opacities (GGOs), reticular opacities, interlobular septal thickening, crazy-paving pattern, parenchymal bands, and bronchiectatic changes (traction bronchiectasis/bronchiolectasis) and honeycombing.<sup>141</sup>

Xiaoyu et al conducted a year-long prospective study in 2020-2021 to study the fibrotic lung abnormalities one year later in patients with severe COVID-19. The study showed that fibrotic interstitial lung abnormalities were common & persistent at one-year follow-up HRCT in patients who had severe COVID-19, which indicates that these persistent fibrotic changes in later stages may be irreversible.<sup>142</sup>

Liu et al observed the pulmonary imaging sequelae in discharged COVID-19 patients. Their study showed that younger patients (<44 years) had a significantly higher chance of complete radiological resolution than older patients at as early as three weeks. There was a gradual reduction in the count of GGOs, fibrotic stripes, and adjacent pleural thickening. GGOs resolved completely within the 1st week after discharge, with the fibrotic stripes showing obvious resolution during 3rd week after discharge. Almost 50% of patients had complete radiological resolution of the disease. 40% of the patients had persistent residual findings on HRCT thorax, of which fibrotic bands and GGOs were the most common. Two unique features, the “tinted” sign (extension of the area of GGO with a reduction in density) and bronchovascular bundle distortion, were discovered during the evolution of imaging findings.<sup>143</sup>

In a prospective study to determine clinical/physiological features & imaging findings at three months follow-up, Zhao et al concluded that persistent HRCT abnormalities were present in almost 70% of patients. Ground-glass opacities, interstitial thickening, and crazy-paving pattern were the common imaging findings.<sup>140</sup>

Han et al conducted a prospective 6-month follow-up study on patients recovering from severe COVID-19 and found that 65% of patients showed complete

resolution of the disease on CT. 27% of patients showed residual GGOs / interstitial thickening at six months follow-up. Fibrotic changes were seen in 35% of patients and included bronchiectatic changes, parenchymal bands, and/or honeycombing. Patients with fibrotic lung disease at six months were found to have had a higher CT severity score at initial imaging. This patient group also had a higher incidence of ARDS in the initial acute phase with frequent mechanical ventilation than the group that demonstrated complete resolution or had GGOs only. The study also showed that 77% of patients with fibrotic interstitial lung abnormalities at six months follow-up had persistent fibrotic changes even after one year, while 63% of patients who had non-fibrotic interstitial lung abnormalities at 6-month follow-up showed complete resolution at one year.<sup>142</sup>

In a prospective study of 118 patients who had recovered from moderate-to-severe COVID-19, Caruso et al showed that at 6-month follow-up HRCT, 72% of the patients had fibrotic changes. A baseline CT severity score of >14 significantly predicted the development of fibrotic changes in the post-recovery phase. The most common imaging finding reported were persistent GGOs, septal thickening, and consolidation.<sup>144</sup>

Association between fungal infections and COVID-19 has been studied by many, including the WHO REACT (Rapid evidence appraisal for COVID-19 therapies) working group, which stated that immune dysregulation, underlying comorbidities (e.g., diabetes mellitus), usage of immunomodulatory drugs and corticosteroids likely increase the risk for superimposed fungal infections in post-COVID-19 patients.<sup>145,146</sup>

J. Jung et al conducted a study comparing HRCT findings in invasive pulmonary aspergillosis and pulmonary mucormycosis. The presence of imaging features like mass-like consolidation, cavitation, pleural effusion, “halo sign,” nodules, “air crescent” sign, and “reverse halo” sign in post-COVID-19 patients should raise suspicion of fungal infections. Some of the characteristic features of invasive fungal infections seen in patients without COVID-19 (such as GGOs, “halo sign,” consolidation) can overlap with the imaging sequelae of COVID-19 pneumonia. The presence of thickened bronchial walls with peribronchial consolidation and centrilobular nodules in clusters favor COVID-19 associated aspergillosis (CAPA). The presence of pleural effusion, “reverse halo” sign and concurrent sinusitis point towards COVID-19 associated pulmonary mucormycosis (CAPM). Often, laboratory/histopathological diagnosis is required in addition to imaging for confirmation.<sup>147</sup>

Soni et al reported the uncommon complication of pseudoaneurysms in post-covid19 fungal infections.<sup>148</sup>

Schulte-Schrepping et al’s study showed that immune dysregulation and immunosuppression make COVID-19 patients more susceptible to developing superadded bacterial infections. Few post-COVID-19 patients too remain vulnerable to developing infections due to *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Hemophilus influenzae*.<sup>149</sup>

A case report by Zahid et al highlighted the incidence of cases of pulmonary tuberculosis in post-COVID-19 patients (particularly in tuberculosis-endemic countries), with immunosuppression due to steroids playing an important role.<sup>150</sup>

A review article by Garg et al stated that the presence of underlying pulmonary parenchymal changes of sequelae due to primary COVID-19 infection might make it challenging to identify superimposed bacterial infections in patients of post-COVID-19 pneumonia. The presence of nodular airspace opacification, consolidation, and cavitation should raise suspicion of superadded infections in these patients. Radiological differentiation between fungal and bacterial pulmonary infections can be difficult. The presence of randomly distributed nodules, “reverse halo” sign, cavitation, and concurrent sinusitis favor the diagnosis of fungal infections, while the presence of lobar consolidations, centrilobular branching nodules, and pleural effusion favor the diagnosis of bacterial infections. Cavitating bacterial pneumonias (particularly those caused by *S. aureus*, *K. pneumoniae*, and *M. tuberculosis*) are often indistinguishable from fungal pneumonias. Histopathological evaluation in the form of sputum/endotracheal sample or bronchoalveolar lavage helps make the correct diagnosis.<sup>138</sup>

## MATERIALS AND METHODS

**Source of data:** Previously confirmed COVID-19 cases that are currently RT-PCR / RAT negative and have been referred to the Department of Radio-diagnosis, KLES Dr. Prabhakar Kore Hospital & MRC for HRCT thorax.

**Method of collection of data:**

- **Study design:** Cross-sectional study
- **Sample size:** Since this is a new study, the prevalence of the study population with the required attributes and, consequently, sample size cannot be predicted. Therefore, patients with the required attributes referred between 1st January 2021 and 31st December 2021 will be enrolled in the study.
- **Sampling method:** Universal sampling; patients in the age group of 18-80 years will be enrolled in the study.
- **Study duration:** January 2021 - December 2021
- **Inclusion criteria:**
  1. Previously RT-PCR / RAT confirmed COVID-19 cases who are now RT-PCR / RAT negative
  2. Patients who are currently symptomatic (cough, fever, breathlessness), or have developed new symptoms (cough, fever, breathlessness) after resolution of the initial illness, or have been referred to the Department of Radio-diagnosis, KLES Dr. Prabhakar Kore Hospital & MRC for HRCT thorax.
  3. Patients over 18 years and below 80 years of age

- **Exclusion criteria:**
  1. Patients who are currently RT-PCR / RAT positive
  2. Patients with a history of pulmonary diseases other than COVID-19
  3. Patients receiving any therapy that may cause any pathological change in pulmonary architecture
  4. Patients below 18 years and over 80 years of age
  
- **Methodology:** Previously confirmed and consenting COVID-19 patients who are currently RT-PCR / RAT negative and are either symptomatic or have developed new symptoms after resolution of the initial illness and have been referred to the Department of Radio-diagnosis, KLES Dr. Prabhakar Kore Hospital & MRC, Belagavi for HRCT thorax will be enrolled in this study. Patients will undergo an HRCT thorax scan in the General Electronics (GE) Revolution CT (128 slice, single tube machine) to detect and evaluate the lung findings. Once the HRCT thorax is done, imaging findings will be noted and analyzed. The data will be collected using a standard questionnaire.

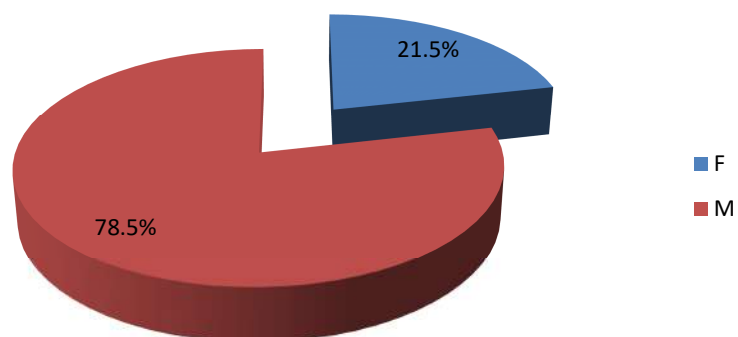
## RESULTS

A total of 223 post-COVID-19 patients observing the inclusion & exclusion criteria were included in this study.

*Table 1. Gender-wise distribution of cases*

SEX	No. of cases	Percentage
F	48	21.5%
M	175	78.5%
Total	223	100.0%

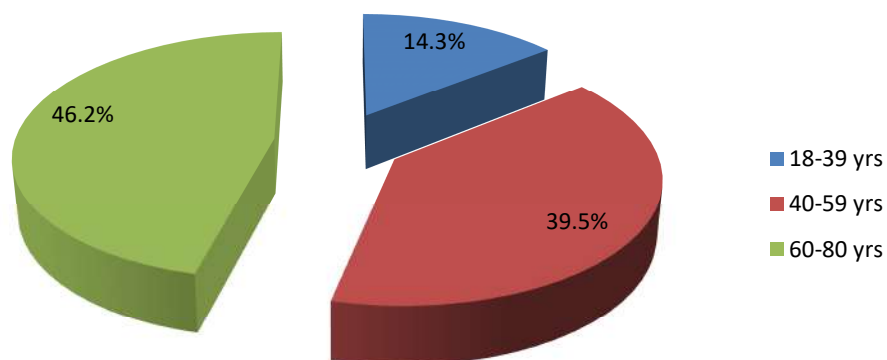
*Graph 1. Pie chart showing the gender-wise distribution of cases*



Of the total 223 cases, 48 were females (21.5%), and 175 were males (78.5%).

*Table 2. Age-wise distribution of cases*

AGE GROUP	Frequency	Percent
18-39 yrs	32	14.3%
40-59 yrs	88	39.5%
60-80 yrs	103	46.2%
Total	223	100.0%

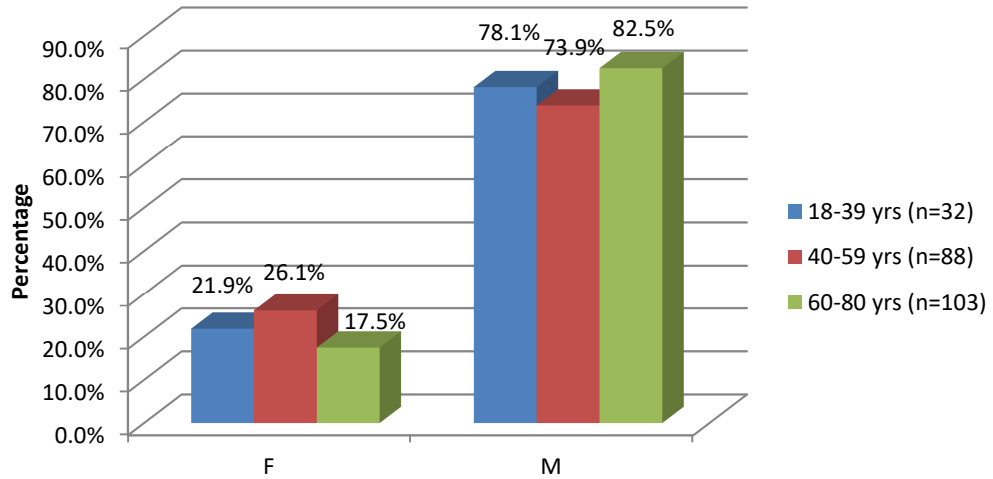
*Graph 2. Pie chart showing the age-wise distribution of cases*

Of the 223 cases, 32 cases were between 18-39 years age group (14.3%), 88 were between 40-59 years (39.5%), and 103 were between 60-80 years (46.2%).

Table 3. Age-wise frequency distribution of male & female patients

AGE GROUP	18-39 yrs (n=32)		40-59 yrs (n=88)		60-80 yrs (n=103)		Total	Chi-square value	p-value
	Frequency	Percent	Frequency	Percent	Frequency	Percent			
SEX	F	7	21.9 %	23	26.1 %	18	17.5 %	2.110	0.348
	M	25	78.1 %	65	73.9 %	85	82.5 %		
TOTAL		32	100.0 %	88	100.0 %	103	100.0 %		

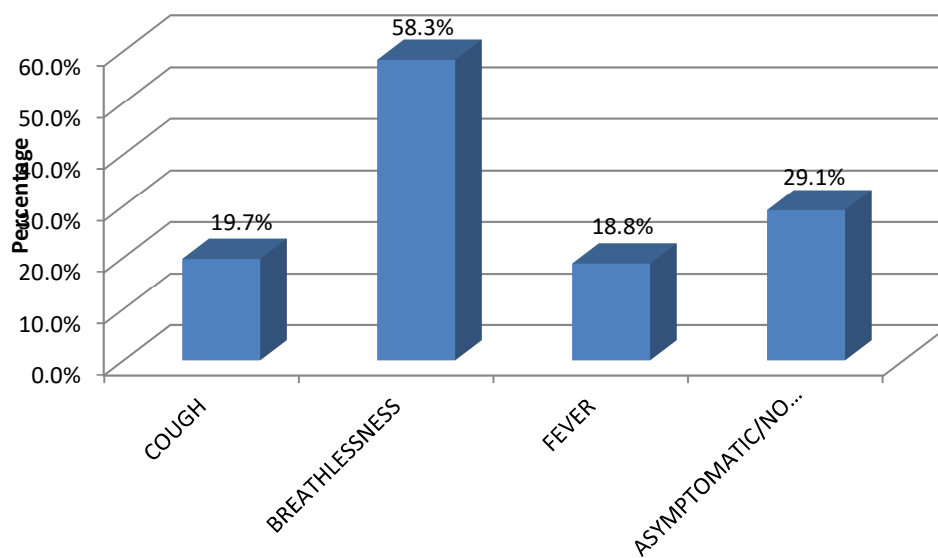
*Graph 3. Bar graph representing age-wise frequency distribution of male & female patients.*



In the 18-39 years age group, there were 7 females (21.9%) and 25 males (78.1%). In the 40-59 years age group, there were 23 females (26.1%) and 65 males (73.9%). In the 60-80 years age group, there were 18 females (17.5%) and 85 males (82.5%).

**Table 4. Frequency distribution of symptoms**

<b>SYMPTOMS</b>	<b>Frequency</b>	<b>Percent</b>
Cough	44	19.7%
Breathlessness	130	58.3%
Fever	42	18.8%
Asymptomatic/Non-respiratory symptoms	65	29.1%

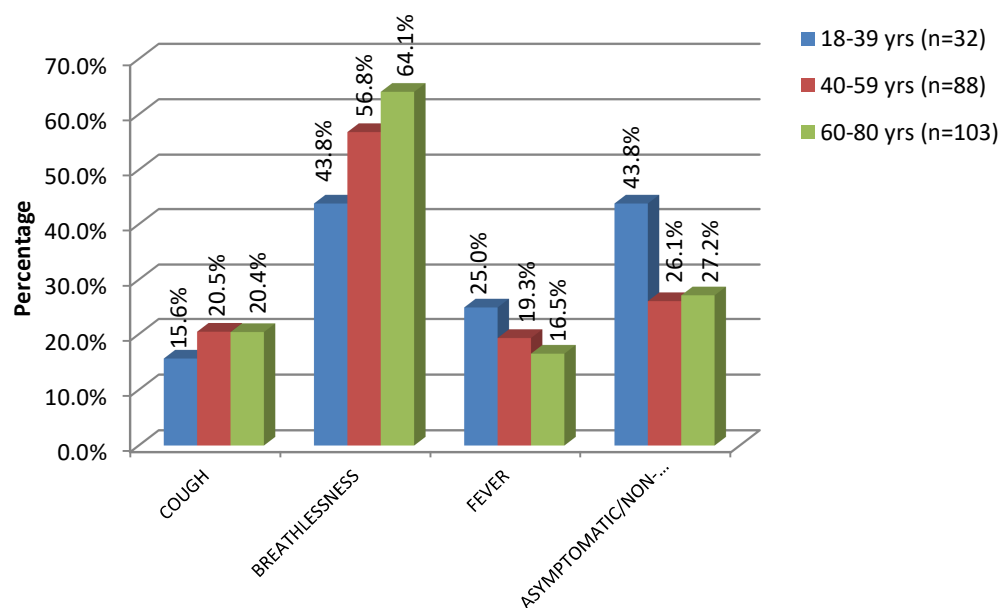
**Graph 4. Bar chart showing the frequency distribution of symptoms**

Cough was present in 44 cases (19.7%), breathlessness in 130 cases (58.3%), and fever in 42 cases (18.8%). There was either absence of symptoms or the presence of non-respiratory symptoms in 65 cases (29.1%).

Table 5. Age-wise frequency distribution of clinical symptoms

SYMPTOM	18-39 yrs (n=32)		40-59 yrs (n=88)		60-80 yrs (n=103)		Total
	Frequency	Percent	Frequency	Percent	Frequency	Percent	
Cough	5	15.6 %	18	20.5 %	21	20.4 %	44
Breathlessness	14	43.8 %	50	56.8 %	66	64.1 %	130
Fever	8	25.0 %	17	19.3 %	17	16.5 %	42
Asymptomatic / non-respiratory symptoms	14	43.8%	23	26.1%	28	27.2%	65

**Graph 5. Bar chart showing the age-wise frequency distribution of clinical symptoms**



Of the total 32 cases in the 18-39 years age group, 5 cases (15.6%) presented with cough, 14 cases (43.8%) with breathlessness, 8 cases (25.0%) with fever, whereas 14 cases (43.8%) were either asymptomatic or had non-respiratory symptoms.

Of the total 88 cases in the 40-59 years age group, 18 cases (20.5%) presented with cough, 50 cases (56.8%) with breathlessness, 17 cases (19.3%) with fever, whereas 23 cases (26.1%) were either asymptomatic or had non-respiratory symptoms.

Of the total 103 cases in the 60-80 years age group, 21 cases (20.4%) presented with cough, 66 cases (64.1%) with breathlessness, 17 cases (16.5%) with fever, whereas 28 cases (27.2%) were either asymptomatic or had non-respiratory symptoms.

Table 6. Frequency-distribution of HRCT imaging findings

HRCT IMAGING FINDINGS	FREQUENCY	PERCENT
Ground glass opacification	103	46.2%
Reticular opacities	112	50.2%
Septal thickening	54	24.2%
Consolidation	59	26.5%
Cavity	24	10.8%
Abscess	3	1.3%
Nodule	28	12.6%
Emphysematous changes	12	5.4%
Bronchiolar dilatation	14	6.3%
Bronchiectasis	42	18.8%
Mosaic attenuation	13	5.8%
Pleural thickening	21	9.4%
Pleural effusion	51	22.9%
Hydropneumothorax	5	2.2%
Pneumothorax	7	3.1%
Pneumomediastinum	4	1.8%
Collapse	5	2.2%
Fibrosis	101	45.3%
Atelectasis	43	19.3%
Architectural distortion	18	8.1%
Pulmonary hypertension	15	6.7%
Cardiomegaly	28	12.6%

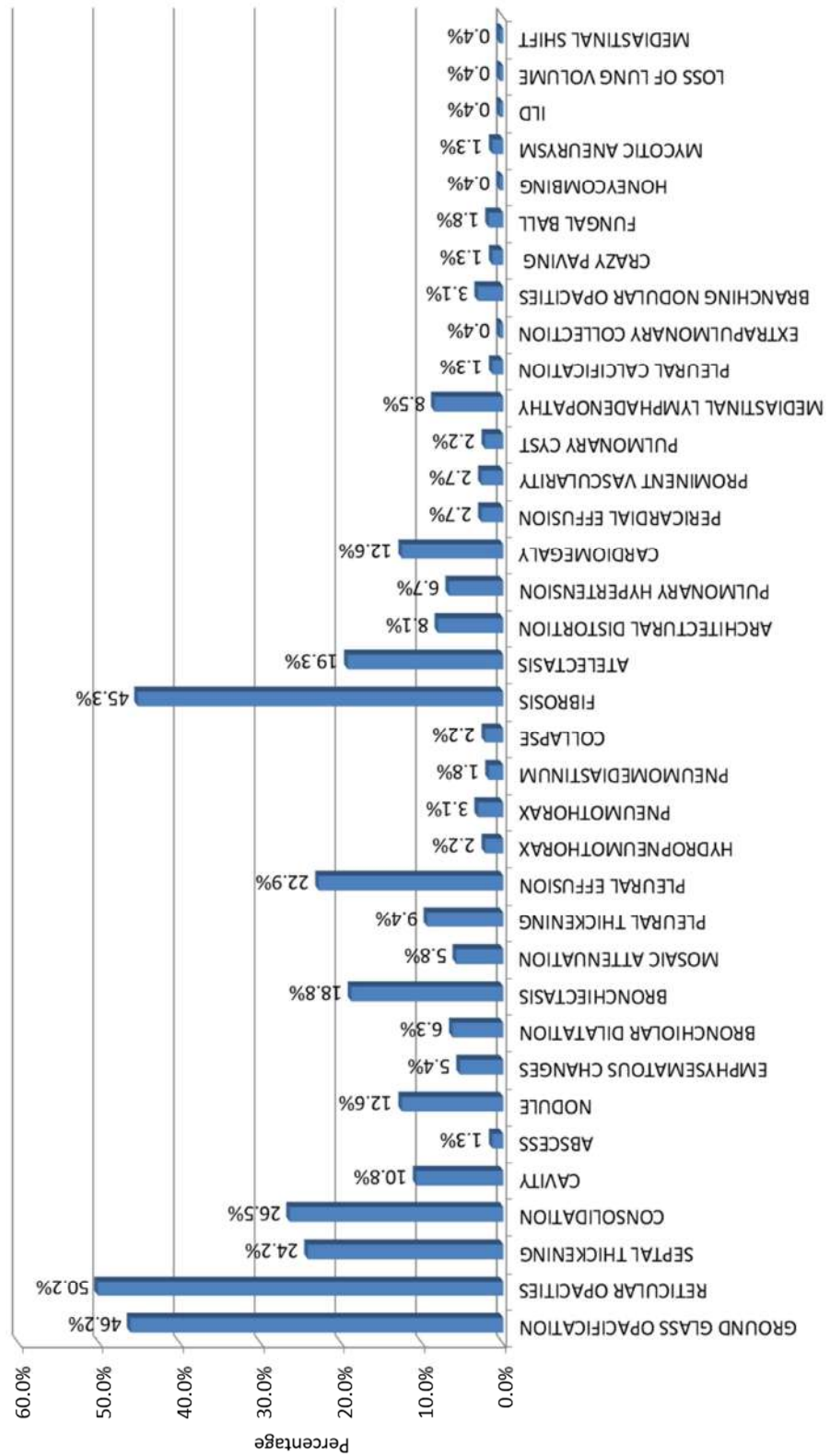
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**Results**

Pericardial effusion	6	2.7%
Prominent vascularity	6	2.7%
Pulmonary cyst	5	2.2%
Mediastinal lymphadenopathy	19	8.5%
Pleural calcification	3	1.3%
Extrapulmonary collection	1	0.4%
Branching nodular opacities	7	3.1%
Crazy paving pattern	3	1.3%
Fungal ball	4	1.8%
Honeycombing	1	0.4%
Mycotic aneurysm	3	1.3%
Interstitial lung disease (ILD) pattern	1	0.4%
Loss of lung volume	1	0.4%
Mediastinal shift	1	0.4%

Graph 6. Bar chart representing frequency distribution of HRCT imaging findings



In the 223 patients that were part of this study, the most common HRCT imaging finding was reticular opacities seen in 112 patients (50%).

The second most common imaging finding was ground glass opacification, seen in 103 patients (46.2%).

The third most common imaging finding on HRCT in this study was fibrosis, seen in 101 patients (45.3%).

59 patients (26.5%) had consolidation, 54 patients had septal thickening (24.2%), and 51% had pleural effusion (22.9%).

Following these, the next most common imaging findings were atelectasis and bronchiectasis, with 43 patients (19.3%) showing evidence of atelectasis and 42 patients (18.8%) showing evidence of bronchiectasis.

28 patients showed soft tissue density nodules (12.6%). The same number of patients also showed evidence of cardiomegaly.

24 patients (10.8%) showed evidence of cavities of varying morphology (thick- vs thin-walled, multiple vs solitary, internal air-fluid levels).

21 cases (9.4%) showed evidence of pleural thickening, 19 cases (8.5%) had mediastinal lymphadenopathy, and 18 cases (8.1%) showed architectural distortion.

The rest of the imaging findings which were relatively low in frequency included abscess {3 cases (1.3%)}, emphysematous changes {12 cases (5.4 %)}, bronchiolar dilatation {14 cases (6.3%)}, mosaic attenuation {13 cases (5.8%)}, hydropneumothorax {5 cases (2.2)}, pneumothorax {7 cases (3.1%)},

pneumomediastinum {4 cases (1.8%)}, lung collapse {5 cases (2.2%)}, pulmonary hypertension {15 cases (6.7%)}, pericardial effusion {6 cases (2.7%)}, prominent vascularity {6 cases (2.7%)}, pulmonary cysts {5 cases (2.2%)}, pleural calcification {3 cases (1.3%)}, extrapulmonary collection {1 case (0.4%)}, branching nodular opacities {7 cases (3.1%)}, crazy paving pattern {3 cases (1.3%)}, fungal ball {4 cases (1.8%)}, honeycombing {1 case (0.4%)}, mycotic aneurysm {3 cases (1.3%)}, interstitial lung disease pattern {1 case (0.4%)}, loss of lung volume {1 case (0.4%)}, and mediastinal shift {1 case (0.4%)}.

Table 7. Age-wise frequency distribution of HRCT imaging findings

IMAGING FINDING		18-39 yrs (n=32)		40-59 yrs (n=88)		60-80 yrs (n=103)		Total	Chi-square value	p-value
		No. of cases	Percent	No. of cases	Percent	No. of cases	Percent			
Ground glass opacification	N	24	75.0%	49	55.7%	47	45.6%	120	8.677	0.013
	Y	8	25.0%	39	44.3%	56	54.4%	103		
Reticular opacities	N	23	71.9%	39	44.3%	49	47.6%	111	7.500	0.024
	Y	9	28.1%	49	55.7%	54	52.4%	112		
Septal thickening	N	24	75.0%	73	83.0%	72	69.9%	169	4.418	0.110
	Y	8	25.0%	15	17.0%	31	30.1%	54		
Consolidation	N	22	68.8%	62	70.5%	80	77.7%	164	1.711	0.425
	Y	10	31.3%	26	29.5%	23	22.3%	59		

IMAGING FINDING		18-39 yrs (n=32)		40-59 yrs (n=88)		60-80 yrs (n=103)		Total	Chi-square value	p-value
		No. of cases	Percent	No. of cases	Percent	No. of cases	Percent			
Cavity	N	30	93.8%	74	84.1%	95	92.2%	199	4.068	0.131
	Y	2	6.3%	14	15.9%	8	7.8%	24		
Abscess	N	32	100.0%	87	98.9%	101	98.1%	220	0.711	0.690
	Y	0	0.0%	1	1.1%	2	1.9%	3		
Nodule	N	30	93.8%	80	90.9%	85	82.5%	195	4.392	0.111
	Y	2	6.3%	8	9.1%	18	17.5%	28		
Emphysematous changes	N	31	96.9%	84	95.5%	96	93.2%	211	0.846	0.655
	Y	1	3.1%	4	4.5%	7	6.8%	12		

IMAGING FINDING	18-39 yrs (n=32)		40-59 yrs (n=88)		60-80 yrs (n=103)		Total	Chi-square value	p-value
	No. of cases	Percent	No. of cases	Percentage	No. of cases	Percent			
Bronchiolar dilatation	N	32	100.0%	82	93.2%	95	92.2%	2.575	0.276
	Y	0	0.0%	6	6.8%	8	7.8%		
Bronchiectasis	N	29	90.6%	67	76.1%	85	82.5%	3.453	0.178
	Y	3	9.4%	21	23.9%	18	17.5%		
Mosaic attenuation	N	31	96.9%	81	92.0%	980	95.1%	1.329	0.515
	Y	1	3.1%	7	8.0%	5	4.9%		
Pleural thickening	N	28	87.5%	81	92.0%	93	90.3%	0.587	0.745
	Y	4	12.5%	7	8.0%	10	9.7%		

IMAGING FINDING		18-39 yrs (n=32)		40-59 yrs (n=88)		60-80 yrs (n=103)		Total	Chi-square value	p-value
		No. of cases	Percent	No. of cases	Percent	No. of cases	Percent			
Pleural effusion	N	25	78.1%	70	79.5%	77	74.8%	172	0.638	0.727
	Y	7	21.9%	18	20.5%	26	25.2%	51		
Hydropneumothorax	N	31	96.9%	87	98.9%	100	97.1%	218	0.638	0.727
	Y	1	3.1%	1	1.1%	3	2.9%	5		
Pneumothorax	N	29	90.6%	84	95.5%	103	100.0%	216	8.003	0.018
	Y	3	9.4%	4	4.5%	0	0.0%	7		
Pneumomediastinum	N	31	96.9%	87	98.9%	102	99.0%	219	0.832	0.660
	Y	1	2.3%	2	2.3%	1	1.0%	4		

IMAGING FINDING		18-39 yrs (n=32)		40-59 yrs (n=88)		60-80 yrs (n=103)		Total	Chi-square value	p-value
		No. of cases	Percent	No. of cases	Percent	No. of cases	Percent			
Collapse	N	30	93.8%	87	98.9%	101	98.1%	218	2.878	0.237
	Y	2	6.3%	1	1.1%	2	1.9%	5		
Fibrosis	N	20	62.5%	55	62.5%	47	45.6%	122	6.365	0.041
	Y	12	37.5%	33	37.5%	56	54.5%	101		
Atelectasis	N	26	81.3%	71	80.7%	83	80.6%	180	0.007	0.996
	Y	6	18.8%	17	19.3%	20	19.4%	43		
Architectural distortion	N	29	90.6%	77	87.5%	99	96.1%	205	4.834	0.089
	Y	3	9.4%	11	12.5%	4	3.9%	18		

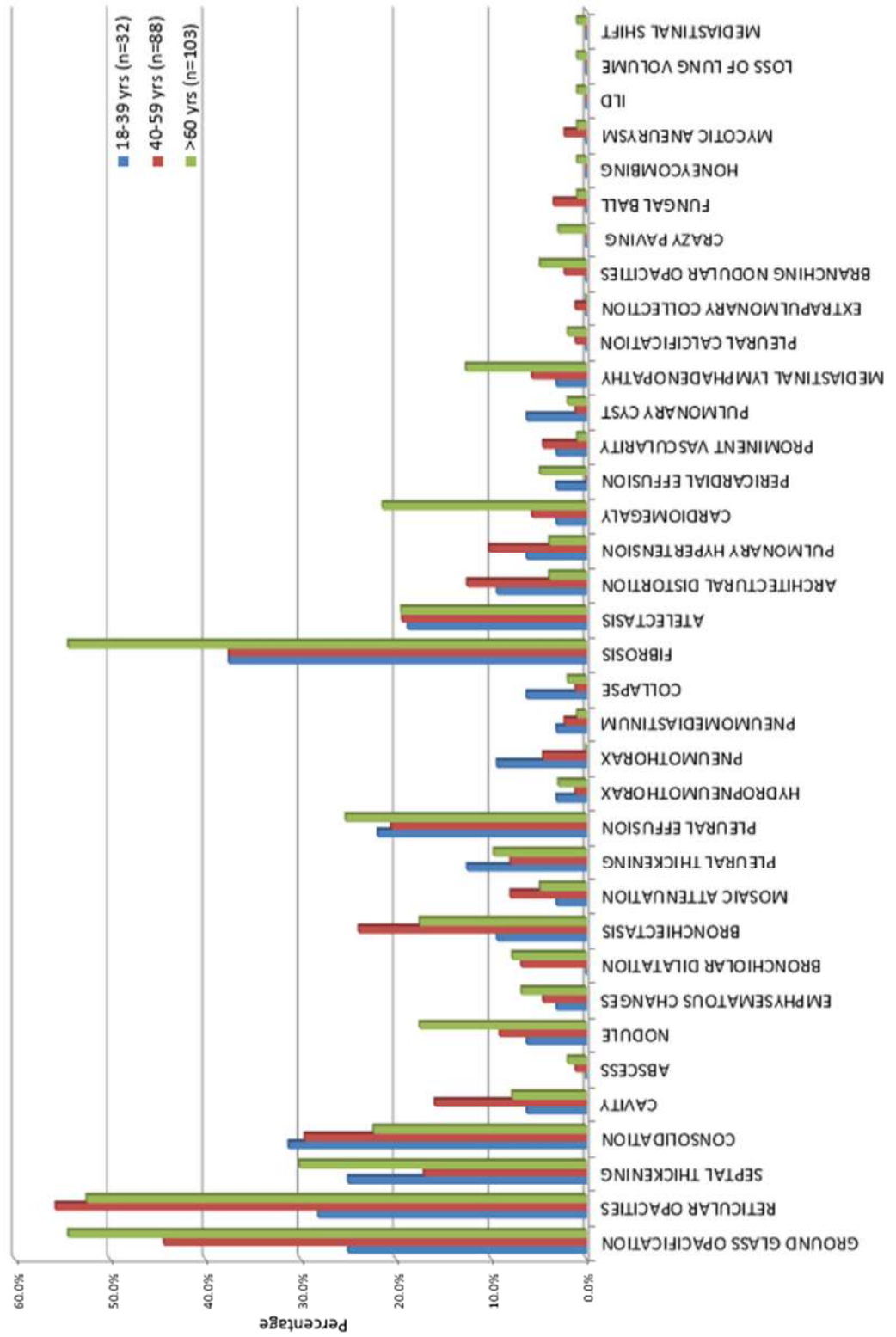
IMAGING FINDING		18-39 yrs (n=32)		40-59 yrs (n=88)		60-80 yrs (n=103)		Total	Chi-square value	p-value
		No. of cases	Percent	No. of cases	Percent	No. of cases	Percent			
Pulmonary hypertension	N	30	93.8%	79	89.8%	99	96.1%	208	3.057	0.217
	Y	2	6.3%	9	10.2%	4	3.9%	15		
Cardiomegaly	N	31	96.9%	83	94.3%	81	78.6%	195	13.650	0.001
	Y	1	3.1%	5	5.7%	22	21.4%	28		
Pericardial effusion	N	31	96.9%	88	100.0%	98	95.1%	217	4.298	0.117
	Y	1	3.1%	0	0.0%	5	4.9%	6		
Prominent vascularity	N	31	96.9%	84	95.5%	102	99.0%	217	2.343	0.310
	Y	1	3.1%	4	4.5%	1	1.0%	6		

IMAGING FINDING		18-39 yrs (n=32)		40-59 yrs (n=88)		60-80 yrs (n=103)		Total	Chi-square value	p-value
		No. of cases	Percent	No. of cases	Percent	No. of cases	Percent			
Pulmonary cyst	N	30	93.8%	87	98.9%	101	98.1%	218	2.878	0.237
	Y	2	6.3%	1	1.1%	2	1.9%	5		
Mediastinal lymphadenopathy	N	31	96.9%	83	94.3%	90	87.4%	204	4.327	0.115
	Y	1	3.1%	5	5.7%	13	12.6%	19		
Pleural calcification	N	32	100.0%	87	98.9%	101	98.1%	220	0.741	0.690
	Y	1	3.1%	0	0.0%	5	4.9%	6		
Extrapulmonary collection	N	32	100.0%	87	98.9%	103	100.0%	222	1.541	0.463
	Y	0	0.0%	1	1.1%	0	0.0%	1		

IMAGING FINDING		18-39 yrs (n=32)		40-59 yrs (n=88)		60-80 yrs (n=103)		Total	Chi-square value	p-value
		No. of cases	Percent	No. of cases	Percent	No. of cases	Percent			
Branching nodular opacities	N	32	100.0%	86	97.7%	98	95.1%	216	2.251	0.324
	Y	0	0.0%	2	2.3%	5	4.9%	7		
Crazy paving	N	32	100.0%	86	97.7%	98	95.1%	216	3.543	0.170
	Y	0	0.0%	0	0.0%	3	2.9%	3		
Fungal ball	N	32	100.0%	85	96.6%	102	99.0%	219	2.284	0.319
	Y	0	0.0%	3	3.4%	1	1.0%	4		
Honeycombing	N	32	100.0%	88	100.0%	1	99.0%	222	1.170	0.557
	Y	0	0.0%	0	0.0%	0	1.0%	1		

IMAGING FINDING		18-39 yrs (n=32)		40-59 yrs (n=88)		60-80 yrs (n=103)		Total	Chi-square value	p-value
		No. of cases	Percent	No. of cases	Percent	No. of cases	Percent			
Mycotic aneurysm	N	32	100.0%	86	97.7%	102	99.0%	220	1.115	0.573
	Y	0	0.0%	2	2.3%	1	1.0%	3		
Interstitial lung disease	N	32	100.0%	88	100.0%	102	99.0%	222	1.170	0.557
	Y	0	0.0%	0	0.0%	1	1.0%	1		
Loss of lung volume	N	32	100.0%	88	100.0%	102	99.0%	222	1.170	0.557
	Y	0	0.0%	0	0.0%	1	1.0%	1		
Mediastinal shift	N	32	100.0%	88	100.0%	1	99.0%	222	1.170	0.557
	Y	0	0.0%	0	0.0%	0	1.0%	1		

Graph 7. Bar chart representing age-wise frequency distribution of HRCT imaging findings



In the total 223 patients, ground-glass opacification, reticular opacities, fibrosis, pneumothorax, and cardiomegaly were found to be statistically significant.

GGOs were seen in 25% of cases in the age group of 18-39 years, 44.3% in the age group of 40-59 years, and 54.5% in the age group of 60-80 years.

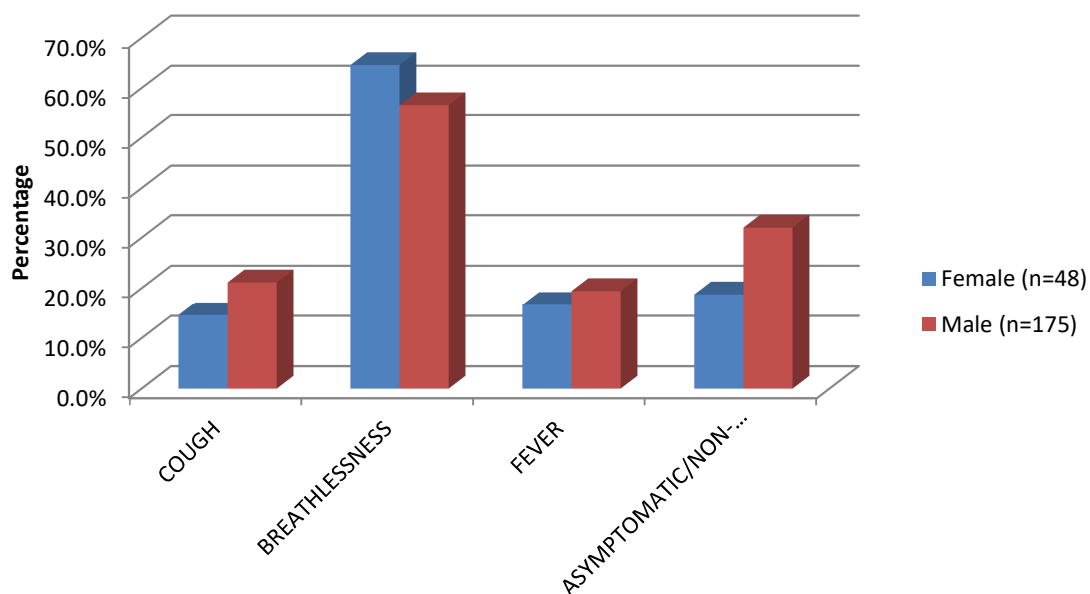
Reticular opacities were seen in 28.1% of cases in the age group of 18-39 years, 55.7% in the age group of 40-59 years, and 52.4% in the age group of 60-80 years.

Fibrosis was seen in 37.5% of cases in the age group of 18-39 years, 37.5% in the age group of 40-59 years, and 54.4% in the age group of 60-80 years.

Table 8. Gender-wise distribution of clinical symptoms

CLINICAL SYMPTOMS		Female (n=48)		Male (n = 175)		Total	Chi-square value	P-value
		No. of cases	Percent	No. of cases	Percent			
Cough	N	41	85.4%	138	78.9%	179	1.023	0.312
	Y	7	14.6%	37	21.1%	44		
Breathlessness	N	17	54.4%	76	43.4%	93	0.995	0.319
	Y	31	64.6%	99	56.6%	130		
Fever	N	40	83.3%	141	80.6%	181	0.188	0.655
	Y	8	16.7%	34	19.4%	42		
Asymptomatic/Non-respiratory	N	39	81.3%	119	68.0%	158	3.202	0.074
	Y	9	18.8%	56	32.0%	65		

**Graph 8. Bar-graph representing gender-wise distribution of clinical symptoms**



Breathlessness was the most common symptom at presentation in females & males. It was a presenting symptom in 64.6% (31 cases) of the total 48 females and 21.1% (37 cases) of the 175 males.

Cough was a presenting symptom in 14.6% (7 cases) of the total 48 females and 21.1% (37 cases) of the 175 males.

Fever was the presenting symptom in 16.7% (8 cases) of the total 48 females and 19.4% (34 cases) of the 175 males.

9 females (18.8%) of the total 48 females and 56 males (32%) of the total 175 males were either asymptomatic or had non-respiratory symptoms.

Table 9. Gender-wise distribution of HRCT imaging findings

IMAGING FINDING		Female (n=48)		Male (n = 175)		Total	Chi-square value	p-value
		No. of cases	Percent	No. of cases	Percent			
Ground glass opacification	N	27	56.3%	93	53.1%	120	0.146	0.702
	Y	21	43.8%	82	46.9%	103		
Reticular opacities	N	23	47.9%	88	50.3%	111	0.085	0.771
	Y	25	52.1%	87	49.7%	112		
Septal thickening	N	39	81.3%	130	74.3%	169	0.996	0.318
	Y	9	18.8%	45	25.7%	54		
Consolidation	N	35	72.9%	129	73.7%	164	0.012	0.912
	Y	13	27.1%	46	26.3%	59		

IMAGING FINDING		Female (n=48)		Male (n = 175)		Total	Chi-square value	p-value
		No. of cases	Percent	No. of cases	Percent			
Cavity	N	42	87.5%	157	89.7%	199	0.192	0.661
	Y	6	12.5%	18	10.3%	24		
Abscess	N	48	100.0%	172	98.3%	220	0.834	0.361
	Y	0	0.0%	3	1.7%	3		
Nodule	N	41	85.4%	154	88.0%	195	0.229	0.632
	Y	7	14.6%	21	12.0%	28		
Emphysematous changes	N	47	97.9%	164	93.7%	211	1.307	0.253
	Y	1	2.1%	11	6.3%	12		

IMAGING FINDING		Female (n=48)		Male (n = 175)		Total	Chi-square value	p-value
		No. of cases	Percent	No. of cases	Percent			
Bronchiolar dilatation	N	48	100.0%	161	92.0%	209	4.097	0.044
	Y	0	0.0%	14	8.0%	14		
Bronchiectasis	N	36	75.0%	145	82.9%	181	1.521	0.217
	Y	12	25.0%	30	17.1%	42		
Pleural thickening	N	41	85.4%	161	92.0%	202	1.914	0.167
	Y	7	14.6%	14	8.0%	21		
Pleural effusion	N	40	83.3%	132	75.4%	172	1.334	0.248
	Y	8	16.7%	43	24.6%	51		

IMAGING FINDING		Female (n=48)		Male (n = 175)		Total	Chi-square value	p-value
		No. of cases	Percent	No. of cases	Percent			
Hydropneumothorax	N	47	97.9%	171	97.7%	218	0.007	0.933
	Y	1	2.1%	4	2.3%	5		
Pneumothorax	N	47	97.9%	169	96.6%	216	0.224	0.636
	Y	1	2.1%	6	3.4%	7		
Pneumomediastinum	N	48	100.0%	171	97.7%	219	1.117	0.291
	Y	0	0.0%	4	2.3%	4		
Lung collapse	N	48	100.0%	170	97.1%	219	1.403	0.236
	Y	0	0.0%	5	2.9%	5		

IMAGING FINDING		Female (n=48)		Male (n = 175)		Total	Chi-square value	p-value
		No. of cases	Percent	No. of cases	Percent			
Fibrosis	N	26	54.2%	96	54.9%	122	0.007	0.932
	Y	22	45.8%	79	45.1%	101		
Atelectasis	N	35	72.9%	145	82.9%	122	2.391	0.122
	Y	13	27.1%	30	17.1%	43		
Architectural distortion	N	47	97.9%	158	90.3%	205	2.956	0.131
	Y	1	2.1%	17	9.7%	18		
Pulmonary hypertension	N	42	87.5%	166	94.9%	208	3.250	0.099
	Y	6	12.5%	9	5.1%	15		

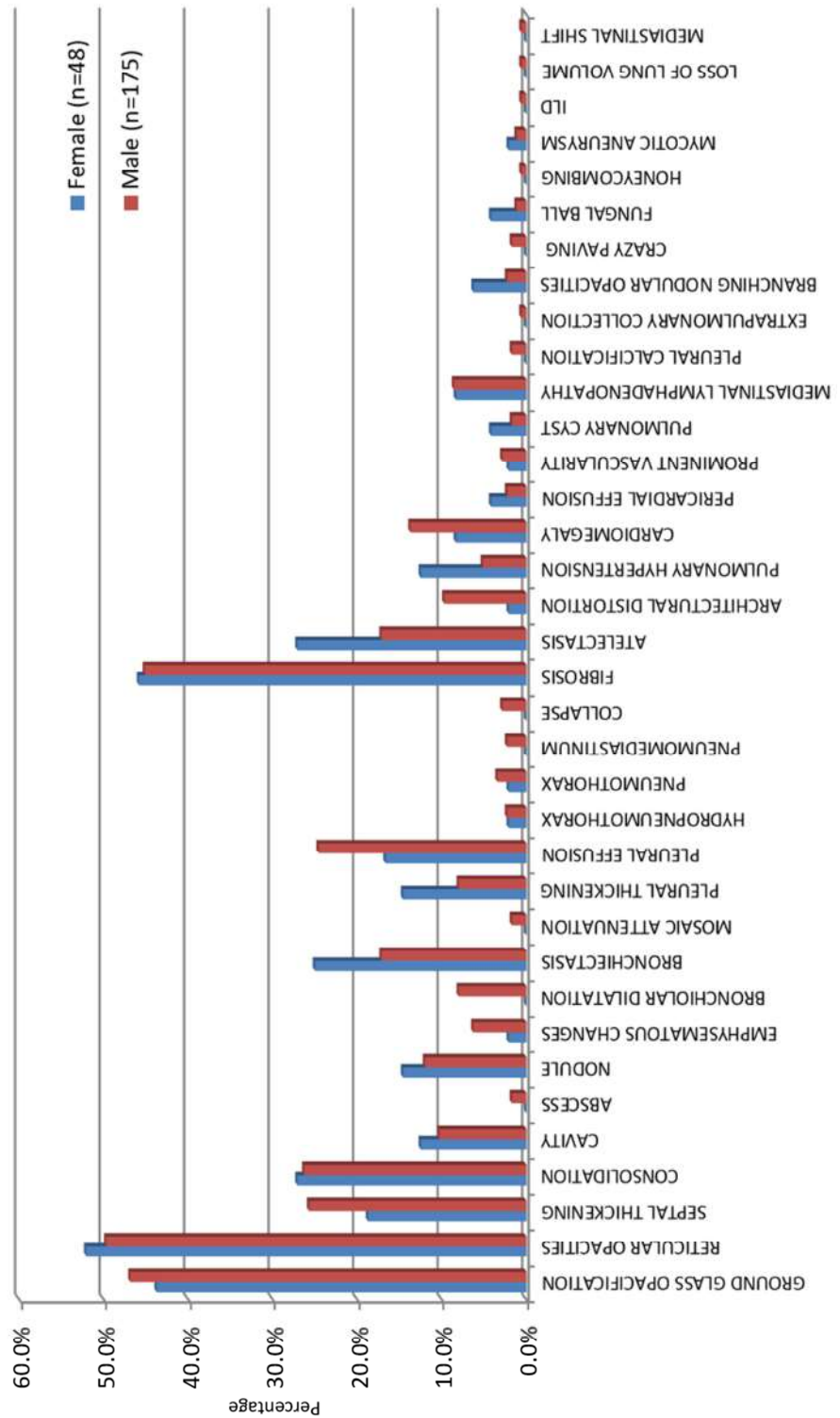
IMAGING FINDING		Female (n=48)		Male (n = 175)		Total	Chi-square value	p-value
		No. of cases	Percent	No. of cases	Percent			
Cardiomegaly	N	44	91.7%	151	86.3%	195	0.993	0.319
	Y	4	8.3%	24	13.7%	28		
Pericardial effusion	N	46	95.8%	171	97.7%	217	0.509	0.476
	Y	2	4.2%	4	2.3%	6		
Prominent vascularity	N	47	97.9%	170	97.1%	217	0.086	0.769
	Y	1	2.1%	5	2.9%	6		
Pulmonary cyst	N	46	95.8%	172	98.3%	218	1.034	0.309
	Y	2	4.2%	3	1.7%	5		

IMAGING FINDING		Female (n=48)		Male (n = 175)		Total	Chi-square value	p-value
		No. of cases	Percent	No. of cases	Percent			
Mediastinal lymphadenopathy	N	44	91.7%	160	91.4%	204	0.003	0.958
	Y	4	8.3%	15	8.6%	19		
Pleural calcification	N	48	100.0%	172	98.3%	220	0.834	0.361
	Y	0	0.0%	3	1.7%	3		
Extrapulmonary collection	N	48	100.0%	174	99.4%	222	0.276	0.600
	Y	0	0.0%	1	0.6%	1		
Branching nodular opacities	N	45	93.8%	171	97.7%	216	1.947	0.162
	Y	3	6.3%	4	2.3%	7		

IMAGING FINDING		Female (n=48)		Male (n = 175)		Total	Chi-square value	p-value
		No. of cases	Percent	No. of cases	Percent			
Crazy paving	N	48	100.0%	172	98.3%	220	0.834	0.361
	Y	0	0.0%	3	1.7%	3		
Fungal ball	N	46	95.8%	173	98.9%	219	1.955	0.162
	Y	2	4.2%	2	1.1%	4		
Honeycombing	N	48	100.0%	174	99.4%	222	0.276	0.600
	Y	0	0.0%	1	0.6%	1		
Mycotic aneurysm	N	47	97.9%	173	98.9%	220	0.251	0.616
	Y	1	2.1%	2	1.1%	3		

IMAGING FINDING		Female (n=48)		Male (n = 175)		Total	Chi-square value	p-value
		No. of cases	Percent	No. of cases	Percent			
ILD	N	27	56.3%	93	53.1%	120	0.146	0.702
	Y	21	43.8%	82	46.9%	103		
Loss of lung volume	N	23	47.9%	88	50.3%	111	0.085	0.771
	Y	25	52.1%	87	49.7%	112		
Mediastinal shift	N	39	81.3%	130	74.3%	169	0.996	0.318
	Y	9	18.8%	45	25.7%	54		
Mosaic attenuation	N	48	100.0%	172	98.3%	220	0.834	0.361
	Y	0	0.0%	3	1.7%	3		

Graph 9. Bar chart representing gender-wise distribution of HRCT imaging findings



## **DISCUSSION**

Since the outbreak of COVID-19, multiple studies have documented the lung imaging findings in patients who tested positive for RT-PCR or RAT, with HRCT being the primary imaging modality in the evaluation of these patients.<sup>87,88,93</sup>

We conducted this study to observe the spectrum of lung imaging findings on HRCT thorax scans of post-COVID-19 patients and evaluate the role of HRCT in the follow-up of these patients.

### **AGE & SEX DISTRIBUTION**

In our study of 223 cases, there were significantly more male than female cases; 175 males (78.5%) compared to 48 females (21.5%).

The majority of the cases were middle-aged & elderly, with 46.2 % of cases belonging to the age group 60-80 years and 39.5% belonging to the age group of 40-59 years; together, these groups formed about 85% of the total sample size. The younger cases, between 18-39 years, formed the smallest group with only 32 cases (14.3%).

These findings were similar to the past studies conducted by Han X et al and Vijayakumar B et al in which the data showed that the majority of cases were males and had a mean age exceeding 55 years.<sup>151,152</sup>

### **CLINICAL PRESENTATION**

Like the studies conducted by Vijayakumar et al and J. Alarcón-Rodríguez et al, breathlessness was the most common presenting symptom in this study. The other common symptoms were cough and fever, with most cases showing a combination of

these symptoms at presentation. Only 29% of patients were either asymptomatic or had non-respiratory symptoms.<sup>151,153</sup>

## **IMAGING FINDINGS**

The most common imaging findings were reticular opacities, followed by ground-glass opacities and fibrosis. These three imaging findings, along with pneumothorax and cardiomegaly, were statistically significant ( $p<0.05$ ).

Overall, reticular opacities were seen in up to 50% of cases. These were more commonly seen in patients >40 years old, with more than half of the patients belonging to age groups 40-59 years and 60-80 years showing evidence of reticular opacities ( $p=0.024$ ). The percentage was lower in younger patients. Sex distribution of reticular opacities as an imaging finding was equivocal, with 52.1% of female cases and 49.7% of male cases showing their presence on HRCT.

Ground glass opacities were the second most common imaging findings in about 46% of the study sample. Similar to the reticular opacities, the GGOs were also more common in the 40-59 years & 60-80 years age groups ( $p=0.024$ ). In the age group 18-39 years, the percentage of cases showing evidence of GGOs was 25.0%. Again, no obvious sex predilection was noted with GGOs.

Fibrotic changes constituted the 3<sup>rd</sup> most common imaging finding. These were most commonly seen in the elderly (60–89-year age group), with about 54.4% of cases in that age group showing fibrotic changes. The percentage of cases showing fibrosis was lower in age groups 18-39 and 40-59 years, about 37.5% in each. There

was no evident sex predilection, with about 45% each of males & females showing fibrotic changes.

The above-mentioned imaging findings in our study were in accordance with the findings of Liu et al's, which documented that 40% of patients had residual persistent imaging abnormalities on HRCT, with GGOs and fibrous stripes being the most common.<sup>143</sup> Another study by Zhao et al also concluded that GGOs and reticulation (in the form of intralobular septal thickening) were seen in a significant (about 70%) of patients after three months of follow-up. However, it also found that interlobular interstitial thickening and crazy paving were additionally common at three months follow-up.<sup>140</sup> Similarly, Han et al's study demonstrated that at six months follow-up, 35% of patients demonstrated fibrotic-like changes, 27% showed residual GGOs or intralobular reticular opacities., and the remaining 38% showed complete radiologic resolution. At the end of one year, the only positive imaging finding in these patients who had shown sequelae at six months, was fibrotic changes, with the remaining showing complete resolution.<sup>141</sup> Caruso et al's study demonstrated that at 6-month follow-up, most patients showed fibrotic-like changes, followed by persistent GGOs & intralobular reticular opacities.<sup>144</sup>

Two other imaging findings with statistically significant age-wise distribution were pneumothorax ( $p= 0.018$ ) and cardiomegaly ( $p=0.001$ ). 3.1% of patients (1 out of 31 patients) in the age group 18-30 years, 4.5% of patients (4 out 95 patients) in the age group 40-59 years, and 0.0% of patients in the age group 60-80 years showed pneumothorax. 9.4% of patients (3 out of 29 patients) in the age group 18-30 years, 4.5% of patients (4 out 95 patients) in the age group 40-59 years, and 0.0% of patients in the age group 60-80 years showed pneumothorax. Literature regarding the

occurrence of spontaneous pneumothorax in post-COVID pneumonia patients is rare. Matthijs L. Janssen et al, Hollingshead & Hanrahan, and others have each reported single patient studies with pneumothorax after completely recovering from initial COVID-19 disease. The proposed factors responsible for this include previous lung bullae/cysts and inflammatory/ischemic lung parenchymal damage, likely caused by the SARS-CoV-2.<sup>154,155</sup> Cardiomegaly was seen in 28 cases (12.6%). The majority of cases were in the 60-80years age group (22 cases). While cardiac complications have been described due to COVID-19 and COVID-19 vaccines, there is a lack of existing literature regarding any association between isolated cardiomegaly & post-COVID-19 patients.<sup>156</sup>

## **CONCLUSION**

- ❖ HRCT thorax imaging has been extensively used in the diagnosis & management of patients with acute COVID-19.
- ❖ After recovery from the acute disease, post-COVID-19 patients may continue to present with a myriad spectrum of clinical features or complications.
- ❖ HRCT is an essential diagnostic tool in the evaluation of patients in the post-COVID-19 recovery period to look for the resolution/evolution of the lung disease, detect its sequelae and identify complications.
- ❖ The most common & statistically significant imaging findings were reticular opacities followed by ground-glass opacities & fibrosis.
- ❖ These imaging findings are more commonly seen in middle-aged and older age groups
- ❖ Pneumothorax and cardiomegaly were also found to be statistically significant.

## LIMITATIONS

There are a few limitations of this study.

- The study duration and sample size might limit the interpretation of the imaging findings. The long-term evolution of these findings needs to be studied for a more extended period and in a larger group to understand better the clinical & prognostic significance, which will aid in better management of post-COVID-19 patients.
- Variability in reported sensitivity & specificity of the RT-PCR / RAT is a limiting factor that affects the selected sample.
- Subgroup analysis of cases based on the severity of symptoms and/or signs was not performed. Such an analysis would help determine potential prognostic factors.
- A lack of a singular HRCT imaging feature unique to COVID-19 and objective criteria defining the disease may overestimate the specificities of these imaging findings.
- This study did not focus on the confounding factors that may have impacted the incidence of these imaging findings in post-COVID-19 patients, e.g., smoking and previous undiagnosed pulmonary pathologies.
- HRCT thorax imaging findings at baseline followed by follow-up imaging would serve well in better understanding the evolution of the imaging findings in these patients.

## **SUMMARY**

- ❖ The study was a cross-sectional study conducted over a period of one year from 1<sup>st</sup> January 2021 to 31<sup>st</sup> December 2021.
- ❖ 223 patients were studied after observing the various inclusion and exclusion criteria.
- ❖ After taking written informed consent, the patients underwent an HRCT thorax scan to detect and evaluate the lung findings.
- ❖ The most common & statistically significant imaging findings were reticular opacities, ground-glass opacities, fibrosis, pneumothorax, and cardiomegaly.
- ❖ The results obtained during this study correlated well with studies conducted by other authors previously

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**ANNEXURE - I**

**WRITTEN INFORMED CONSENT**

**TITLE OF THE STUDY: “Role of High Resolution Computed Tomography Thorax Imaging in Follow-up of COVID-19 Patients – A One-year Hospital Based Cross-sectional Study”**

**PRINCIPAL INVESTIGATOR: Dr.**

**GUIDE: Dr.**

**INTRODUCTION AND PURPOSE:** By providing accurate & detailed information about lung anatomy, HRCT thorax serves as a valuable imaging modality in the detection of lung lesions.

The purpose of this study is to analyze HRCT thorax imaging findings and evaluate the role of HRCT thorax in the follow-up of COVID-19 in the study population.

**PROCEDURE:** I request you to kindly participate in the study titled study “ROLE OF HIGH RESOLUTION COMPUTED TOMOGRAPHY THORAX IMAGING IN FOLLOW-UP OF COVID-19 PATIENTS - A ONE YEAR HOSPITAL BASED CROSS-SECTIONAL STUDY” being conducted at KLES Dr. Prabhakar Kore Hospital & Medical Research Centre, Belagavi by Dr. \_\_\_\_\_, Post-graduate in Radio-diagnosis at J.N. Medical College, Belagavi, Karnataka, under the guidance of Dr. \_\_\_\_\_, Professor & Head, Dept. of Radio-diagnosis, J.N. Medical College, Belagavi.

The purpose of the study will be explained and written informed consent will be obtained from you prior to participation. Your eligibility for participation in the study will be decided based on the inclusion and exclusion criteria. The study will be conducted over a period of one year. During the study, you will be asked questions regarding your present & past medical history and you will be required to answer to the best of your knowledge. You will also be clinically examined as per the protocol drawn. As part of the study, you will be subjected to High resolution computed tomography (HRCT) scan of the chest. Please wear loose-fitting and comfortable clothing to your scan. Remove any metal objects, including jewellery, eyeglasses, and mobile phones prior to the scan. The technologist will ask you a few questions regarding your medical history and explain the steps involved in the scan in detail. You will then be asked to lie flat on your back on the CT table with arms over your head. The CT table will then slide into the gantry. The technologist will convey further instructions in your desired language over the intercom. You will be asked to lie very still and hold breath for a few seconds. The entire scan will be completed within five minutes.

If you agree to participate in the study, please furnish the details pertaining to the study.

**BENEFITS:** HRCT thorax will provide detailed information about lung anatomy and detect any pathological changes in lung architecture.

**RISKS/ COMPLICATIONS:** The risk for radiation exposure with HRCT is low as the amount of radiation used during HRCT is considered minimal.

Notify your doctor if you are pregnant or suspect that you may be pregnant.

Very rarely, HRCT may cause induction of cancer.

**ALTERNATIVES:** If you are not willing to take part in the study, your treatment or any other further investigations you want to undergo in the future in KLE will not be affected by your decision.

**VOLUNTARY PARTICIPATION / WITHDRAWAL:** Taking part in this study is voluntary. You may choose not to take part in this study, or if you decide to take part, you can later change your mind and withdraw from the study. Your decision will not change the present or future health care or other services that you receive. The study doctor or the sponsor may stop your participation in this study. You will tell if any important new findings that may change your willingness to continue to take part. If you choose not to take part in the study, you will receive the standard treatment for patients with your condition.

**COSTS:** NIL (The study is to be conducted on the participants who are advised HIGH RESOLUTION COMPUTED TOMOGRAPHY as an investigation by the referring consultant and the participants will bear the charges for it.)

**PAYMENT FOR PARTICIPATION:** No incentive will be paid to you for participating in this study.

**COMPENSATION:** In the event that you become injured as a result of taking part in this study, treatment, whatever is available at KLE Charitable hospital, Belagavi, will be offered to you. No reimbursement, compensation, or free medical care is given.

**CONFIDENTIALITY:** All information collected about you during the course of the study will be kept confidential to the extent permitted by the law. The code numbers will identify you in this research record. Information from this study may be published but your identity will be kept confidential in any publication/ presentation.

**QUESTION:** If you have any inquiries in the future or in case of research-related injury or illness, you may contact the following persons:

**Name: Dr.**

**Mobile No:**

Email ID:

		<b>Dr. ROOPA BELLAD</b>
		Chairperson, JNMC, IEC & Scientist D, ICMR, National Institute Of Traditional Medicine, Belagavi
		Ph. 0831-2473777 Ext. 1529 Mob. 9480422500

**CONSENT TO PARTICIPATE IN THE RESEARCH STUDY:**

“I understand that I am participating in the study, which includes high resolution computed tomography thorax.

I confirm that I have read and understood the information in the patient information sheet. The procedure is explained to me in detail, along with information about the advantages and disadvantages of taking part in the study. I have been given the opportunity to discuss all aspects of the trial, to ask questions and hereby consent to participation in the trial outlined above.

I understand that the decision to take part in this study is completely voluntary and I am aware that I can choose to withdraw from the study at any point of time.

I consent to the photographing or recording of the procedure to be performed, including appropriate portions of my body, for medical, scientific, or educational purposes, provided my identity is not revealed in the pictures or by the descriptive texts accompanying them.

I understand that there is no significant risk involved in the test that would be done in this study.

No guarantee or assurance has been given by anyone as to the results that may be obtained.

My signature on this form signifies that I have willingly decided to participate after understanding the above information.”

Participant's Name/ legally authorized \_\_\_\_\_

representative

Signature \_\_\_\_\_

Name and signature of witness \_\_\_\_\_

Name and signature of interviewer \_\_\_\_\_

Date: \_\_\_\_\_

Place: \_\_\_\_\_

**ANNEXURE – II**

**PROFORMA**

**KAHER**

**J. N. MEDICAL COLLEGE, BELAGAVI**

**DEPARTMENT OF RADIO-DIAGNOSIS**

**TITLE:** “ROLE OF HIGH RESOLUTION COMPUTED TOMOGRAPHY THORAX IMAGING IN FOLLOW-UP OF COVID-19 PATIENTS - A ONE YEAR HOSPITAL BASED CROSS-SECTIONAL STUDY”

**RESEARCH INVESTIGATOR:** Dr.

**GUIDE:** Dr.

**PROFORMA FOR DATA COLLECTION**

**DATE OF INTERVIEW:** \_\_\_\_\_

**NAME OF THE PATIENT:** \_\_\_\_\_

**AGE (in years):** \_\_\_\_\_ **SEX:** \_\_\_\_\_ **OP/IP NO:** \_\_\_\_\_

**MOBILE NUMBER:** \_\_\_\_\_

**ADDRESS: House No** \_\_\_\_\_ **Galli** \_\_\_\_\_ **Ward/Village** \_\_\_\_\_

**City** \_\_\_\_\_ **District** \_\_\_\_\_ **PIN CODE:** \_\_\_\_\_

**CT NUMBER:** \_\_\_\_\_

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	<b>CURRENT (DATE   RESULT)</b>	<b>PREVIOUS (DATE   RESULT)</b>
<b>RT-PCR</b>		
<b>RAT</b>		

<b>CHIEF COMPLAINTS:</b>	<b>DURATION</b>

**PAST HISTORY:**

**HRCT FINDINGS:**

**ANNEXURE – III**

**PHOTOGRAPHS**

Photograph of General Electronics (GE) Revolution CT (128 slice, single tube machine) at KLES Dr. Prabhakar Kore Hospital & MRC, Belagavi

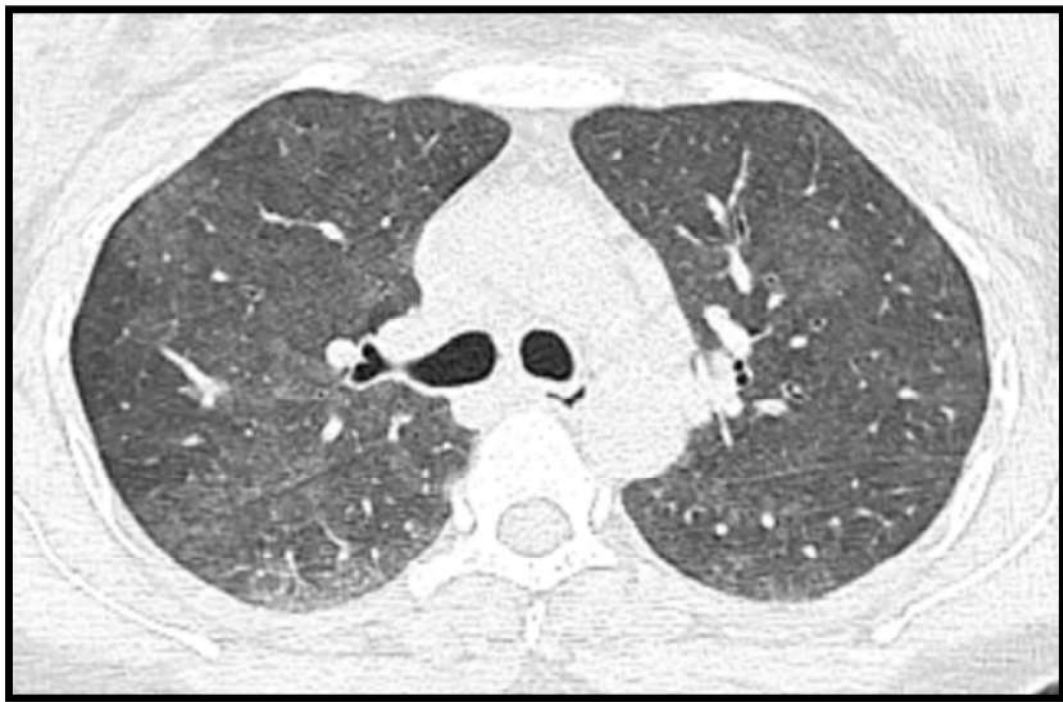


**PHOTOGRAPH OF CASES**

**CASE 1**

A 61-year-old male patient with past history of COVID (4 months ago) presented with complaints of breathlessness and cough for 2 months.

HRCT thorax scan showed ground glass opacities diffusely involving bilateral lungs.



**CASE 2**

A 72-year-old male patient with past history of COVID (6 months ago) presented with severe breathlessness on exertion since 5 months.

HRCT thorax scan shows fibrotic areas with adjacent traction bronchiectatic changes involving bilateral lungs.



**CASE 3**

A 75-year-old male patient with past history of COVID (2 months ago) presented with breathlessness & cough for 2 months.

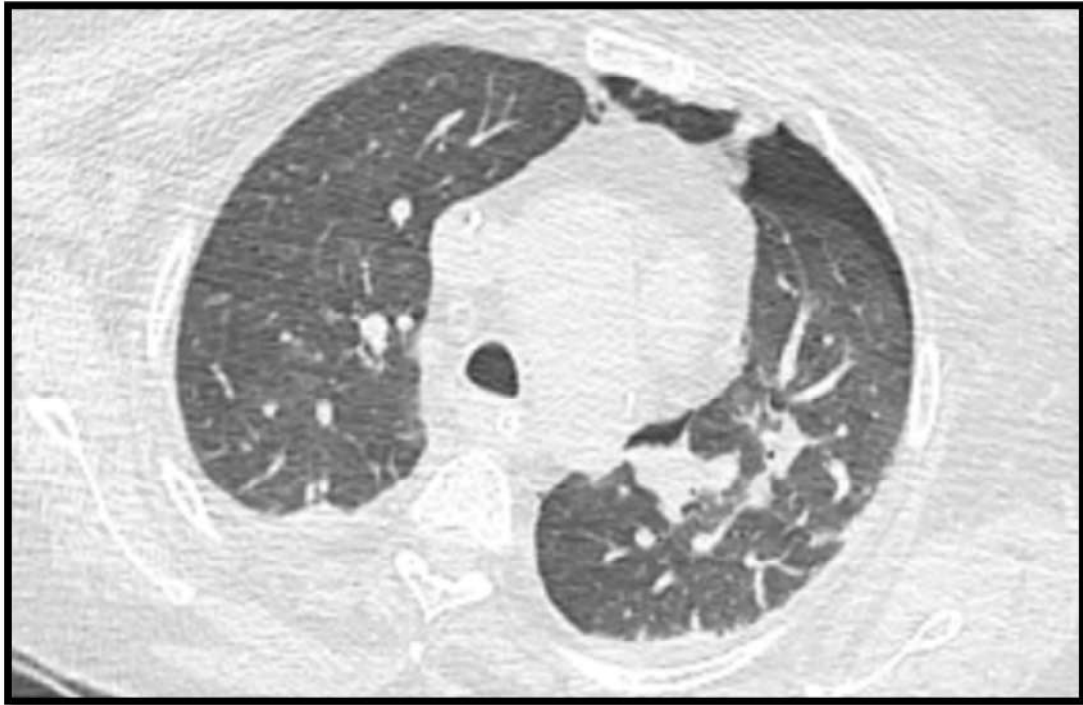
HRCT thorax scan shows reticular opacities with intralobular septal thickening and architectural distortion diffusely involving bilateral lungs predominantly on the right side.



**CASE 4**

A 22-year-old female with past history of COVID-19 (2 months ago) presented with sudden onset breathlessness for 2 days.

HRCT thorax scan shows mild left-sided pneumothorax.



**CASE 5**

A 55-year-old male with past history of COVID-19 (1 month ago) presented with fever & cough for 1 month.

HRCT thorax scan shows consolidation involving basal segments of bilateral lower lobes, predominantly on the right side, with mild bilateral pleural effusion.



**ANNEXURE – IV**

**KEY TO MASTER CHART**

1	PRESENT
0	ABSENT

**ANNEXURE – V**  
**MASTER CHART**









