Ministry of higher education and scientific research

Thi-Qar university \ college of medicine

Department of surgery

# ATYPICAL RADIOLOGICAL FINDINGS IN PATIENTS WITH COVID-19 ON COMPUTED TOMOGRAPHY

*Ahmed Akeel Saad, Hussam Aldeen Muhammed Abd, Haider Anwar Ghaleb, Ali Abd-Alrazzaq Abd-Alhussain, Muhammed Omran Jafar, Noor Al-huda Razzaq Jameel.*

***Supervised by**:*

*Dr. Firas Abdullah Noori*

## Contents

# Abstract

### *Background*

The typical CT manifestations of COVID-19 pneumonia include ground-glass opacity (GGO) with or without consolidation and superimposed interlobular septal thickening. These are often rounded in morphology and frequently bilateral, multilobar, posterior, peripheral, and basilar in distribution. The various atypical CT features of COVID-19 are seldom described in the literature. The study aims to enumerate the atypical pulmonary CT features in patients with COVID-19 pneumonia and their distribution among different age groups.

### *Results*

A total of 298 confirmed cases of COVID-19 pneumonia with positive reverse transcription polymerase chain reaction (RT-PCR) who underwent chest CT scans were retrospectively evaluated. The cohort included 298 cases of COVID-19 pneumonia and the mean age was 53.48. Out of the 298 cases, 218 cases (73.1%) showed typical CT features while 63 cases (21.1%) showed atypical CT features with concurrent classical findings and the remaining 17 cases (5.8%) were normal. Among the atypical CT features, the most common was pleural effusion [n = 30 (10.0%)]. The other features in the order of frequency included nodules [n = 19 (6.3%)], pulmonary cysts [n = 16 (5.3%)], cavitation [n = 4 (1.3%)], spontaneous pneumothorax [n = 2 (0.6%)], spontaneous pneumo-mediastinum with subcutaneous emphysema [n = 1 (0.3%)].

### *Conclusion*

CT imaging features of COVID-19 pneumonia while in a vast majority of cases is classical, atypical diverse patterns are also encountered. A comprehensive knowledge of various atypical presentations on imaging plays an important role in the early diagnosis and management of COVID-19.


# Introduction

In December 2019, a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified as the cause of a cluster of pneumonia cases in Wuhan, a city in the Hubei province of China **(1)**.

Although SARS-CoV-2 disease (or coronavirus disease 2019 [COVID-19]) primarily manifests as a lung infection, with symptoms ranging from those of a mild upper respiratory infection to severe pneumonia and acute respiratory distress syndrome

(ARDS), other multisystemic manifestations of this disease and related complications are becoming more commonly recognized **(2).**

## Literature review

### *Virology*

Coronaviruses are large, enveloped RNA viruses that contain an unsegmented genome of single-stranded RNA **(3).**

Phylogenic analysis revealed that SARS-CoV-2 is closely related to the beta-coronaviruses. Similar to other coronaviruses, the genome of SARS-CoV-2 is positive-sense single-stranded RNA [(+) ssRNA] with a 5′-cap, 3'-UTR poly(A) tail. The length of the SARS-CoV-2 genome is less than 30 kb, in which there are 14 open reading frames (ORFs), encoding non-structural proteins (NSPs) for virus replication and assembly processes, structural proteins including spike (S), envelope (E), membrane/matrix (M) and nucleocapsid (N), and accessory proteins **(4, 5).** The first ORF contains approximately 65% of the viral genome and translates into either polyprotein pp1a (nsp1–11) or pp1ab (nsp1–16). Among them, six NSPs (NSP3, NSP9, NSP10, NSP12, NSP15 and NSP16) play critical roles in viral replication. Other ORFs encode structural and accessory proteins **(6, 7**).

The **S protein** is a transmembrane protein that facilitates the binding of viral envelop to angiotensin-converting enzyme 2 (ACE2) receptors expressed on host cell surfaces **(8)**. The **N protein attaches** to the viral genome and is involved in RNA replication, virion formation and immune evasion **(9).** The **M protein** is one of the most abundant and well-conserved proteins in the virion structure. This protein promotes the assembly and budding of viral particles through interaction with N and accessory proteins 3a and 7a **(10).** The **E protein** is the smallest component in the SARS-CoV-2 structure that facilitates the production, maturation and release of virions **(6).**

### *Pathophysiology*

The entry of the SARS-CoV-2 into host cells and release their genomes into target cells is dependent on a sequence of steps. The virus uses the protein spike, which is important for assessing tropism and virus transmissibility. Additionally, SARS-CoV-2 even targets human respiratory epithelial cells with ACE2 receptors, indicating a structure of RBD similar to SARS-CoV **(11).**

Following virus entry, the uncoated genomic RNA is translated into polyproteins (pp1a and pp1ab) and then assembled into replication/transcription complexes with virus-induced double-membrane vesicles (DMVs). Subsequently, this complex replicates and synthesizes a nested set of subgenomic RNA by genome transcription, encoding structural proteins and some accessory proteins. Newly formed virus particles are assembled by mediating the endoplasmic reticulum and the Golgi complex. Finally, virus particles are budded and released into the extracellular milieu compartment. Thus, both the viral replication cycle and progression begin **(12).**

Inside the host cells, survival of SARS CoVs is maintained by multiple strategies to evade the host immune mechanism, which can also be generalized to SARS-CoV-2. As a result of the lack of pathogen-associated molecular patterns on DMVs originating from the first step of SARS-CoVs infection, they are not recognized by pattern recognition receptors of the host immune system **(13).**

Nsp1 can impede the interferon (IFN)-I responses through several mechanisms, such as a silencing of the host translational system, the induction of host mRNA degradation and the repression of transcription factor signal transducer and activator of transcription (STAT)1 phosphorylation. Nsp3 antagonizes interferon and cytokine production by blocking the phosphorylation of interferon regulation factor 3 (IRF3) and interrupting the nuclear factor-kappa B (NF-KB) signaling pathway. NSPs 14 and 16 cooperate to form a viral 5′ cap similar to that of the host. Thus, the viral RNA genome is not recognized by immune system cells **(14).**

### *Clinical features*

COVID-19 manifests with a wide clinical spectrum ranging from asymptomatic patients to septic shock and multiorgan dysfunction (**15**). COVID-19 is classified based on the severity of the presentation (**15**).

The disease may be classified into mild, moderate, severe, and critical (**16**). The most common symptoms of patients include fever (98.6%), fatigue (69.6%), dry cough, and diarrhea (**16**)

**Mild Disease**

Patients with mild illness may present with symptoms of an upper respiratory tract viral infection (**15)**. These include dry cough, mild fever, nasal congestion, sore throat, headache, muscle pain, and malaise (**15)**. It is also characterized by the absence of serious

symptoms such as dyspnea. The majority (81%) of COVID-19 cases are mild in severity. Furthermore, radiograph features are also absent in such cases. Patients with mild disease can quickly deteriorate into severe or critical cases **(15)**.

**Moderate Disease**

These patients present with respiratory symptoms of cough, shortness of breath, and tachypnea (**15)**. However, no signs and symptoms of severe disease are present.

**Severe Disease**

Patients with severe disease present with severe pneumonia. acute respiratory distress syndrome (ARDS), sepsis, or septic shock. Diagnosis is clinical, and complications can be excluded with the help of radiographic studies. Clinical presentations include the presence of severe dyspnea, tachypnea (respiratory rate > 30/minute), respiratory distress, SpO2 ≤ 93%, PaO2/FiO2 < 300, and/or greater than 50% lung infiltrates within 24 to 48 hours. Even in severe forms of the disease, fever can be absent or moderate [**15**].

In addition, 5% of patients can develop a critical disease with features of respiratory failure, RNAaemia, cardiac injury, septic shock, or multiple organ dysfunction [**15, 16**]. Data from the Chinese Centers for Disease Control and Prevention (CDC) suggest that the case fatality rate for critical patients is 49% (**15)**. Patients with preexisting comorbidities have a higher case fatality rate. These comorbidities include diabetes (7.3%), respiratory disease (6.5%), cardiovascular disease (10.5%), hypertension (6%), and oncological complications (5.6%) [**16**]. Patients without comorbidities have a lower case fatality rate (0.9%) [**16**]

**Acute Respiratory Distress Syndrome**

The development of ARDS indicates new-onset or worsening respiratory failure. It occurs as a complication within one week of known clinical insult. The values of PaO2/FiO2 are used to distinguish ARDS based on varying degrees of hypoxia. PaO2/FiO2 ≤ 100 mm Hg is indicative of severe ARDS [**15**]. PaO2/FiO2 values between 100 mm Hg and 200 mm Hg are diagnostic for moderate ARDS [**15**]. PaO2/FiO2 values between 200 mmHg and 300 mmHg support the diagnosis of mild ARDS (**15)**. Levels of AST (aspartate transaminase) and ALT (alanine transaminase) at the time of admission correlate with clinical deterioration to ARDS. Therefore, higher levels at admission result in rapid clinical deterioration to ARDS.

In addition to the clinical and ventilatory criteria, chest imaging modalities such as chest X-ray, computed tomography (CT) scan, and lung ultrasound can be used to support the diagnosis. The most frequent finding on CT scan includes ground-glass opacity (86%), consolidation (29%), crazy paving (19%), bilateral disease distribution (76%), and peripheral disease distribution (33%) [**17**]. It is important to note that a chest X-ray has a lower sensitivity (59%) to detect subtle opacities. A CT scan can further detect mediastinal lymphadenopathy, nodules, cystic changes, and pleural effusion. The aforementioned abnormalities might be detectable before the onset of symptoms.

**Sepsis and Septic Shock**

Patients with COVID-19 and sepsis are deemed the most critical of them all. The accompanying multiorgan dysfunction results as a consequence of dysregulated host response to infection. Signs of organ dysfunction include severe dyspnea, low oxygen saturation, reduced urine output, tachycardia, hypotension, cold extremities, skin mottling, and altered mentation [**15**]. Laboratory evidence of other homeostatic dysregulation includes acidosis, high lactate, hyperbilirubinemia, thrombocytopenia, and evidence of coagulopathy [**15**].

Patients with septic shock are persistently hypotensive despite volume resuscitation. They may also have an accompanying serum lactate level of >2 mmol/L.

*Laboratory investigations*

Nucleic acid testing

RNA testing is done with polymerase chain reaction (PCR) is cost-effective, easy to perform, and available **(18)**. However, the PCR test has accuracy issues. Sensitivity of FDA-approved viral RNA tests range from 63%–95% **(19**, **20**, **21, 22)**. Sensitivity of RNA tests is dependent on the site of specimen collection. Sensitivity was highest in bronchioalveolar lavage (93%), then sputum (73%), nasal swab (63%), feces (29%) and blood (1%) **(19)**. Another study found that patients with pneumonia often have negative nasopharyngeal samples, but positive lower airway samples **(23)**. The sensitivity of PCR tests have been estimated at 71%, resulting in ~30% of infected patients having a negative finding. Another drawback is the presence of viral RNA does not mean the virus is live, therefore, detection does not necessarily mean the virus can be transmitted **(23)**. RNA-based tests are limited to the setting of acute illness. Saliva-based tests offer promising results as a non-invasive and non-aerosol generating method of specimen collection **(24)**. Compared to nasopharyngeal tests, saliva specimens have high sensitivity

(84.2%) **(24)**. and can be self-administered **(24)**. Another study reported that SARS-CoV-2 viral load in posterior oropharyngeal saliva samples was higher at initial presentation of COVID-19 symptomatic patients, increased with age, presence of comorbidities, and severity of the COVID-19 disease **(25)**. Reduced variability in samples taken from self-administered tests is helpful for mass testing because it preserves collection reliability and allows patients to send in their own samples from the comfort of their home.

## SEROLOGICAL TEST

The second type of test is serologic, which detects immunoglobulins (IgG and IgM) specific for SARS-CoV-2 and provides an estimation of population virus exposure **(18).** One drawback of serologic testing is the lag period between symptoms and antibody formation-one analysis found patients do not begin to seroconvert until 11–12 days post-symptom onset **(26)**. The sensitivity and specificity of FDA-approved serologic tests ranges from 61.1%–98% and 90%–100% **(27)**. Many FDA-approved serologic tests have high sensitivity and specificity. For example, Cellex Inc. developed a rapid diagnostic test with 93.8% sensitivity and 95.6% specificity. Bio-Rad manufactured an ELISA test with sensitivity and specificity of 98% and 99%, respectively **(27)**.

## BIOCHEMICAL TEST

Biochemical findings specific to COVID-19 include elevated prothrombin time, LDH (lactate dehydrogenase), D-dimer, ALT, C-reactive protein (CRP), and creatine kinase [**16**]. In the early stages of the disease, a marked reduction in CD4 and CD8 lymphocytes can also be noted [**16**]. Patients in the intensive care unit have shown higher levels of interleukin (IL) 2, IL-7, IL-10, GCSF (granulocyte colony-stimulating factor), IP10 (interferon gamma-induced protein 10), MCP1 (monocyte chemotactic protein 1), MIP1A (macrophage inflammatory protein alpha), and TNF-α (tumor necrosis factor-α) **(28)**. They also displayed other abnormal findings indicative of coagulation activation, cellular immune deficiency, myocardial injury, renal injury, and hepatic injury [**16**]. In critical patients, amylase and D-dimer levels are significantly elevated (**15**, **28)**. However, blood lymphocyte counts progressively decreased (**15**, **28)**. Common to non-survivors are the elevations in ferritin, neutrophil count, D-dimer, blood urea, and creatinine levels **(29)**. Elevations in procalcitonin levels are not a feature of COVID-19. Therefore, an elevated level of procalcitonin may suggest an alternative diagnosis such as bacterial pneumonia. Levels of CRP correlate directly with disease severity and progression.

*Imaging in COVID-19*

## Imaging indications

The threshold for the imaging of patients with potential/confirmed COVID-19 demonstrates a degree of variation globally due to local resources, the published guidelines of individual learned bodies and sociocultural approaches to imaging.

The use of CT as a primary screening tool is discouraged, not least because these studies tended to suffer from selection bias **(30, 31).**

With a meta-analysis in April 2020, reporting a pooled sensitivity of 94% and specificity 37%. In low prevalence (<10%) countries, the positive predictive value of RT-PCR was ten-fold that of CT chest

According to a **Fleischner Society consensus** statement published on 7 April 2020 **(32)**

- imaging is indicated in a patient with COVID-19 and worsening respiratory status
- imaging is indicated for medical triage of patients with suspected COVID-19 who present with moderate-severe clinical features and a high pretest probability of disease
- imaging is not indicated in patients with suspected COVID-19 and mild clinical features unless they are at risk for disease progression

Moreover, performing CT routinely for large cohorts of patients carries additional risks **(33)**

- additional ionizing radiation exposures
- increased risk of viral transmission (to staff, patients and carers) as COVID-19 positive and negative patients come into close proximity in the radiology department

## Radiographic features

The primary findings of COVID-19 on chest radiograph and CT are those of atypical pneumonia or organizing pneumonia **(34)**

However, imaging has limited sensitivity for COVID-19, as up to 18% demonstrate normal chest radiographs or CT when mild or early in the disease course, but this decreases to 3% in severe disease. Bilateral and/or multilobar involvement is common

The current recommendation of the vast majority of learned societies and professional radiological associations is that imaging should not be employed as a screening/diagnostic tool for COVID-19, but reserved for the evaluation of complications

## Chest X-ray Findings

Although chest x-ray has a lower sensitivity than chest CT in detection of COVID-19, findings on chest x-ray correlate with chest CT. Bilateral, lower lobe, and peripheral distribution of opacities are the most common expected findings on chest x-ray of COVID-19 cases .In contrast to parenchymal abnormalities, pleural effusion is rare (3%) **(30, 35)**

Chest radiographs may be normal in early/mild disease. In those COVID-19 cases requiring hospitalization, 69% had an abnormal chest radiograph at the initial time of admission, and 80% had radiographic abnormalities sometime during hospitalization. Findings are most extensive about 10-12 days after symptom onset **(35)**

## CT scan

**The typical findings on CT** in adults have been reported as **(36):**

- ground-glass opacities (GGO): bilateral, subpleural, peripheral
- crazy paving appearance (GGOs and inter-/intra-lobular septal thickening)
- air space consolidation
- bronchovascular thickening in the lesion
- traction bronchiectasis

The ground-glass and/or consolidative opacities are usually bilateral, peripheral, and basal in distribution

A small number of patients have shown a pulmonary target sign, which has only been reported in COVID-19 patients so far. At present it is unclear if this new sign is pathognomonic or simply newly recognized. **(37)**

**Atypical CT findings**

These findings only seen in a small minority of patients should raise concern for superadded bacterial pneumonia or other diagnoses **(34, 38):**

- mediastinal lymphadenopathy
- pleural effusions: may occur as a complication of COVID-19

- multiple tiny pulmonary nodules (unlike many other types of viral pneumonia)
- tree-in-bud
- pneumothorax
- cavitation
- atoll sign
- pneumomediastinum

**Four stages on CT have been described (34)**

1. early/initial stage (0-4 days): normal CT or GGO only up to half of patients have normal CT scans within two days of symptom onset
2. progressive stage (5-8 days): increased GGO and crazy paving appearance
3. peak stage (9-13 days): consolidation
4. absorption stage (>14 days): with an improvement in the disease course, "fibrous stripes" appear and the abnormalities resolve at one month and beyond.

## Ultrasound

The following patterns have been observed, tending to have a bilateral and posterobasal predominance **(39):**

- multiple B-lines
    - -ranging from focal to diffuse with spared areas
    - -representing thickened subpleural interlobular septa
- may also manifest as a light beam sign, an evanescent, broad-based vertical reverberation artifact arising from a regular pleural line
- irregular, thickened pleural line with scattered discontinuities
- subpleural consolidations
    - can be associated with a discrete, localized pleural effusion
    - relatively avascular with color flow Doppler interrogation
    - pneumonic consolidation typically associated with preservation of flow or hyperemia
- alveolar consolidation

tissue-like appearance with dynamic and static air bronchograms associated with severe, progressive disease

Nuclear medicine

*PET-CT*

FDG uptake is increased in ground-glass opacities in those with presumed/confirmed COVID-19. It has been hypothesized that those with higher SUVs in lung lesions take longer to heal (34).

## Method

This was a retrospective study using data collected from the database in Al-Hussain teaching hospital in Thi-Qar, Iraq. During the period from June 2020 to November 2020

**Inclusion criteria:** Reverse-transcriptase polymerase chain reaction (RT-PCR) confirmed COVID-19 pneumonia patients who underwent chest CT scans were considered.

**Exclusion criteria**: Patients with negative RT-PCR results.

## Results

A total of 298 reverse-transcriptase polymerase chain reaction (RT-PCR) confirmed COVID-19 pneumonia patients admitted between 1 June and 31 November 2020 were retrospectively evaluated. The demographics pertaining to age, gender, presenting symptoms, presence of comorbidities/risk factors.

The mean age in our cohort was 53.48 years. The age was further classified into 3 groups: (20-40), (11–40), (41–60), (61-90) as depicted in the Table 1. The age group (41–60) had highest atypical cases with total of 28 cases (44.44%).

| Age groups | Total of 63 | percentage |
|---|---|---|
| 20 – 40 | 14 | 22.2% |
| 41 – 60 | 28 | 44.4% |
| 61 – 90 | 21 | 33.4% |

Out of 298 cases of COVID-19 pneumonia, 218 cases (73.1%) showed typical CT features while 63 cases (21.1%) showed atypical CT features with concurrent classical findings and the remaining 17 cases (5.8%) were normal. Among the atypical CT imaging features, pleural effusions were the most common feature in our study. Other various atypical imaging features with their incidences in our study.

| Atypical presentations | Number of cases | Percentage per 298 cases |
|---|---|---|
| Pleural effusion | 30 | 10% |

| | | |
|---|---|---|
| Nodules | 19 | 6.3 |
| Pulmonary cysts | 16 | 5.3 |
| Cavitations | 4 | 1.3 |
| Spontaneous pneumothorax | 2 | 0.6 |
| Spontaneous pneumomediastinum with subcutaneous emphysema | 1 | 0.3 |

## Discussion

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This has rapidly resulted in a worldwide pandemic with significant increase in morbidity and mortality **(40)**. The imaging changes in COVID-19 pneumonia are diverse with the various atypical CT features being less clearly described. The study conducted herein explains the atypical CT features in COVID-19 pneumonia.

based on current literature, the typical imaging features of COVID-19 pneumonia on CT include bilateral, multilobar GGOs with/without consolidation, and superimposed interlobar septal thickening **(41, 42)** They show a peripheral, posterior, and basilar distribution **(41)** In our study, majority of the patients (73.1%) showed typical CT features and only 21.1% patients showed atypical CT features with concurrent above classical findings. Among the atypical CT features, the most common was pleural effusion. The other features in the order of frequency included pleural effusion, nodules, cavitation, spontaneous pneumothorax, hilar lymphadenopathy, spontaneous pneumo-mediastinum with subcutaneous emphysema, halo sign, empyema, and necrotizing pneumonia with abscess.

The incidence of pleural effusion in our study was 10%. However, the incidence of pleural effusion in COVID-19 has been reported to be varying as per the available literature**,** for instance the study of Woon H.Chong et al **(43)** showed an incidence of 7.3%, meanwhile, according to the study by Shi et al., the prevalence of pleural effusion varies depending on the stage of the disease, with a reported prevalence of 13% in the third week after onset of symptoms **(44).** Pleural effusion may also be predictive of worse prognosis (**45**).

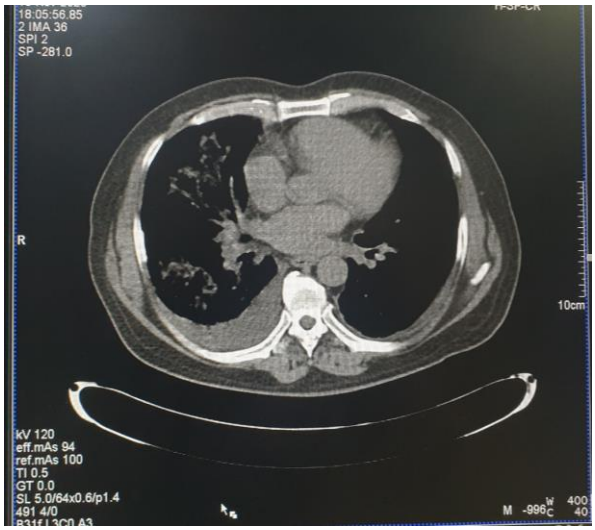


**Figure 1:** CT scan showing effusion of the right lung with a small amount of effusion on the left side

In our study, the incidence of pulmonary nodules was 6.3%. The reported incidence of nodules in COVID-19 has been found to be varying, 3 ~ 13% as per the available literature **(46, 47).**

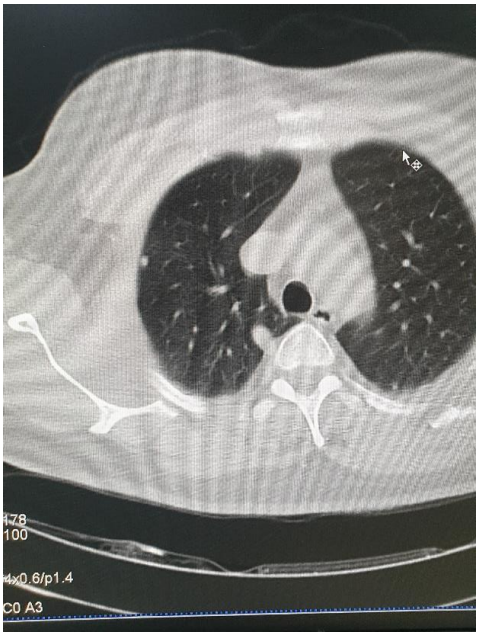

**Figure 2:** CT scan showing pulmonary nodule of the right lung.

The incidence of pulmonary cysts in our study was 5.3% while the study by Shi H et al **(44)** showed an incidence of 10%. Recent studies speculate that the pulmonary cystic change in COVID-19 might be secondary to ischemic parenchymal damage, lung fibrosis and low lung compliance (**48**). Another explanation is blockage of the bronchioles by

mucus and mucus plugs followed by the over-inflation of the alveoli and resultant rupturing of the alveolar septum with subsequent formation of small cysts (**49**).

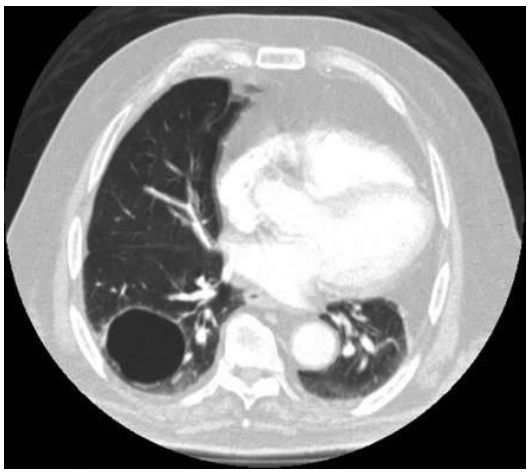

Figure 3: CT scan showing cystic lesion in the right lung.

Lung cavitation due to COVID-19 pneumonia is an uncommon finding which usually is seen in the late stage **(50, 51),** The incidence in our study was 1.3%. There are few reports of intrapulmonary cavities of COVID-19-infection (45, 50, 52, 53).

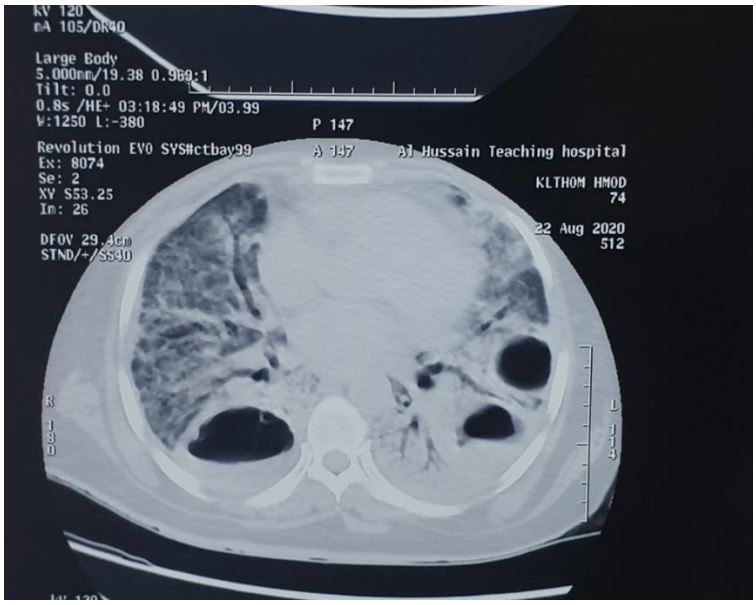


Figure 4: CT scan sowing multiple cavitations on both sides of the lung.

Spontaneous pneumomediastinum refers to the presence of air in the mediastinum occurring in the absence of traumatic or an iatrogenic origin **(41, 54),** In current limited research, only few case reports of SPM in COVID-19 have been made **(41. 55, 56, 57).** The incidence of SPM in our study was 0.3% and isolated spontaneous pneumothorax

was 0.6%. Chen N et al. showed incidence of isolated spontaneous pneumothorax of 1% in COVID-19 patients **(58).**

It is believed that the possible causes of SPM in COVID-19 were similar to those in SARS showing severe diffuse alveolar damage. This diffuse alveolar damage results in alveolar rupture which can be further precipitated by high interalveolar pressure caused by factors like artificial ventilation, coughing or straining. This results in air migration into the mediastinum through the Macklin effect **(41, 59, 60, 61)**. he SPM can lead to other complications such as pneumothorax, extensive subcutaneous emphysema, and an uncommon complication of lung infections **(41)**.

## Conclusion

During the course of the pandemic, much of the literature published describes the classical imaging features encountered in COVID-19, with anecdotal references made to the atypical CT imaging features. A small subset of cases with COVID-19 pneumonia show diverse imaging manifestations, which if ignorant can confound the clinical approach to the patient leading to misdiagnosis. The present study aimed not only to illustrate the various atypical CT features in COVID-19 pneumonia but also correlated with age groups. The atypical features observed includes pleural effusion, nodules, pulmonary cystic changes, cavitation, hilar lymphadenopathy, spontaneous pneumothorax, spontaneous pneumo-mediastinum, empyema and abscess. There was a significant increase in the percentage of atypical findings in middle and old age groups (age >40) in comparison to young age group (age <40). Thus, older patients may represent a radiological diagnostic challenge and higher index of suspicion with prompt clinical correlation is needed.

## Acknowledgements

We would like to thank the esteemed radiology specialist at Thi-Qar college of medicine Dr. Firas Abdullah Noori who gave us the continuous support and valuable recommendations. We’d also like to wholeheartedly express our gratitude to the chief of department of surgery DR. Muhannad Alshureifi for giving us a golden opportunity to work on this project.

## References:


1. Cantwell R, Clutton-Brock T, Cooper G et al. Saving Mothers' Lives: Reviewing maternal deaths to make motherhood safer: 2006-2008—The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. BJOG 2011;118(suppl 1):1–203 [Published correction appears in BJOG 2015;122(5):e1.]
2. Wang T, Du Z, Zhu F et al. Comorbidities and multi-organ injuries in the treatment of COVID-19. Lancet 2020;395(10228):e52. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30558-4/fulltext
3. Stefan Riedel, Jeffery A. Hobden: Jawetz, Melnick, & Adelberg's Medical microbiology, 28th edition, Chapter 41: corona viruses, P.P. 617-618
4. *Abduljali J, Abduljali B. Epidemiology, genome and clinical features of the pandemic SARS-CoV-2: a recent view. New Micr New Infect. 2020;35:100672.*
5. *Parsamanesh N, Pezeshgi A, Hemmati M, Jameshorani M, Saboory E. Neurological manifestations of coronavirus infections: role of angiotensin-converting enzyme 2 in COVID-19. Int J Neurosci. 2020.*
6. *Naqvi AAT, Fatima K, Mohammad T, et al. Insights into SARS-CoV-2 genome, structure, evolution, pathogenesis and therapies: structural genomics approach. Biochim Biophys Acta Mol Basis Dis. 2020;1866(10):165878.*
7. *Krichel B, Falke S, Hilgenfeld R, Redecke L, Uetrecht C. Processing of the SARS-CoV pp1a/ab nsp7-10 region. Biochem J. 2020;477:1009-1019.*
8. *Khailany RA, Safdar M, Ozaslan M. Genomic characterization of a novel SARS-CoV-2. Gene Rep. 2020;19:100682.*
9. *Mu J, Xu J, Zhang L, et al. SARS-CoV-2-encoded nucleocapsid protein acts as a viral suppressor of RNA interference in cells. Sci China Life Sci. 2020;63:1-4.*
10. *Astuti I. Ysrafil. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): an overview of viral structure and host response. Diab Metab Syndr. 2020;14:407-412.*
11. *Voto C, Berkner P, Brenner C. Overview of the pathogenesis and treatment of SARS-CoV-2 for clinicians: a comprehensive literature review. Cureus. 2020;12(9):e10357.*
12. *Ashour HM, Elkhatib WF, Rahman M, Elshabrawy HA. Insights into the recent 2019 novel coronavirus (SARS-CoV-2) in light of past human coronavirus outbreaks. Pathogens. 2020;9:1-5.*

13. *Shang J, Wan Y, Luo C, et al. Cell entry mechanisms of SARS-CoV-2. Proc Natl Acad Sci. 2020;117:11727-11734.*
14. *Totura AL, Baric RS. SARS coronavirus pathogenesis: host innate immune responses and viral antagonism of interferon. Curr Opin Virol. 2012;2:264-275.*
15. Cascella M, Rajnik M, Cuomo A, Dulebohn SC, Napoli RD. Treasure Island, FL: StatPearls Publishing; [Mar;2020 ]. 2020. Features, Evaluation and Treatment Coronavirus (COVID-19).
16. Unique epidemiological and clinical features of the emerging 2019 novel coronavirus pneumonia (COVID-19) implicate special control measures [Epub ahead of print] [Mar;2020 ];Wang Y, Wang Y, Chen Y, Qin Q. J Med Virol. 2020.
17. Chest CT findings in 2019 novel coronavirus (2019-nCoV) infections from Wuhan, China: Key points for the radiologist. Kanne JP. Radiology. 2020;295:16–17.
18. Walensky RP, del Rio C. From mitigation to containment of the COVID-19 pandemic: putting the SARS-CoV-2 genie back in the bottle. JAMA. Published online April 17, 2020.
19. Detection of SARS-COV-2 in different types of clinical specimens. JAMA. 2020; 323: 1843-1844
20. Smart detect SARS-CoV-2 rRT-PCR kit. InBios. Accessed May 19th, 2020.
21. COVID-19 RT-digital PCR detection kit. Gnomegen. Accessed May 19th, 2020.
22. QIAstat-Dx respiratory SARS-CoV-2 panel instructions for use (handbook). Qiagen. Accessed May 19th, 2020.
23. Report from the American Society for Microbiology COVID-19 International Summit, 23 March 2020: value of diagnostic testing for SARS-CoV-2/COVID-19. *mBio*. 2020; **11** (Published 2020 Mar 26) ([Accessed May 19th, 2020])e00722-20
24. Saliva sample as a non-invasive specimen for the diagnosis of coronavirus disease-2019 (COVID-19): a cross-sectional study. *Clin Microbiol Infect.* 2020; (published online ahead of print, 2020 May 15) ([S1198-743X(20)30278-0. Accessed May 19th, 2020])
25. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study.Lancet Infect Dis. 2020 Mar 23; ([Epub ahead of print]. PMID: 32213337)
26. Abbasi J. The promise and peril of antibody testing for COVID-19. JAMA. Published online April 17, 2020. [Accessed May 19th, 2020].
27. Serology-based tests for COVID-19. Johns Hopkins – Center for Health Security.Accessed May 19th, 2020.

28. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Huang C, Wang Y, Li X, et al. Lancet. 2020;395:497–506.
29. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. [Mar;2020 ];Wang D, Hu B, Hu C, et al. JAMA. 2020 323:1061–1069.
30. ACR Recommendations for the Use of Chest Radiography and Computed Tomography (CT) for Suspected COVID-19 Infection." American College of Radiology.
31. COVID-19 Updates". Ranzcr.com, 2020.
32. Rubin Geoffrey D., Linda B. Haramati. "The Role of Chest Imaging in Patient Management during the COVID-19 Pandemic: A Multinational Consensus Statement from the Fleischner Society". Radiology (2020)
33. Constantine A. Raptis, Mark M. Hammer, Chest CT and Coronavirus Disease (COVID-19): A Critical Review of the Literature to Date. (2020) American Journal of Roentgenology
34. Essentials for Radiologists on COVID-19: An Update—Radiology Scientific Expert Panel. (2020) Radiology. [ Pubmed]
35. Frequency and Distribution of Chest Radiographic Findings in COVID-19 Positive Patients. (2019) Radiology. – [Pubmed]
36. Wang D, Hu B, Hu C et-al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. (2020) JAMA.
37. Jafari R, Jafari MH, J. A Unique Feature of COVID-19 Infection in Chest CT; "Pulmonary Target" Appearance. (2021) Academic radiology. – [Pubmed]
38. Another Decade, Another Coronavirus. (2020) New England Journal of Medicine
39. Qian-Yi Peng, Xiao-Ting Wang. Findings of lung ultrasonography of novel corona virus pneumonia during the 2019–2020 epidemic. (2020) Intensive Care Medicine.
40. Revzin MV, Raza S, Warshawsky R, D'Agostino C, Srivastava NC, Bader AS et al (2020) Multisystem imaging manifestations of COVID-19, part 1: viral pathogenesis and pulmonary and vascular system complications. Radiographics. 40(6):1574–1599. https://doi.org/10.1148/rg.2020200149
41. Brogna B, Bignardi E, Salvatore P, Alberigo M, Brogna C, Megliola A et al (2020) Unusual presentations of COVID-19 pneumonia on CT scans with spontaneous pneumomediastinum and loculated pneumothorax: a report of two cases and a

review of the literature. Heart Lung. 49(6):864–868. https://doi.org/10.1016/j.hrtlng.2020.06.005
42. Yadav R, Sahoo D, Graham R (2020) Thoracic imaging in COVID-19. Cleve Clin J Med. 87(8):469–476. https://doi.org/10.3949/ccjm.87a.ccc032
43. Woon H.Chong, Biplab K. Sahaa: The incidence of pleural effusion in COVID-19 pneumonia: State-of-the-art review, Heart and lung: Volume 50, Issue 4, July–August 2021, Pages 481-490.
44. Shi H, Han X, Jiang N, Cao Y, Alwalid O, Gu J et al (2020) Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. Lancet Infect Dis. https://doi.org/10.1016/S1473-3099(20)30086-4
45. Ye Z, Zhang Y, Wang Y, Huang Z, Song B (2020) Chest CT manifestations of new coronavirus disease 2019 (COVID-19): a pictorial review. Eur Radiol:4381–4389. https://doi.org/10.1007/s00330-020-06801-0
46. Ai T, Yang Z, Hou H, Zhan C, Chen C, Lv W et al (2020) Correlation of chest CT and RT-PCR testing for coronavirus disease 2019 (COVID-19) in China: A Report of 1014 Cases. Radiology. 296(2):E32–E40. https://doi.org/10.1148/radiol.2020200642
47. Xiong Y, Sun D, Liu Y, Fan Y, Zhao L, Li X et al (2020) Clinical and high-resolution CT features of the COVID-19 infection: comparison of the initial and follow-up changes. Invest Radiol. 55(6):332–339. https://doi.org/10.1097/RLI.0000000000000674
48. Liu K, Zeng Y, Xie P, Ye X, Xu G, Liu J et al (2020) COVID-19 with cystic features on computed tomography: a case report. Medicine 99, 18(e20175). https://doi.org/10.1097/MD.0000000000020175
49. Chen J, Peng S, Zhang B, Liu Z, Liu L, Zhang W (2020) An uncommon manifestation of COVID-19 pneumonia on CT scan with small cavities in the lungs: a case report. Medicine 99, 28(e21240). https://doi.org/10.1097/MD.0000000000021240
50. Muheim M, Weber FJ, Muggensturm P, Seiler E (2020) An unusual course of disease in two patients with COVID-19: pulmonary cavitation. BMJ Case Rep 13(9). https://doi.org/10.1136/bcr-2020-237967
51. Chen Y, Chen W, Zhou J, Sun C, Lei Y (2020) Large pulmonary cavity in COVID-19 cured patient case report. Ann Palliat Med. https://doi.org/10.21037/apm-20-452

52. Kong W, Agarwal PP (2020) Chest imaging appearance of COVID-19 infection. Radiol Cardiothoracic Imaging. 2(1):e200028. https://doi.org/10.1148/ryct.2020200028
53. Xu Z, Pan A, Zhou H et al (2020) Rare CT feature in a COVID-19 patient: cavitation. Diagn Interv Radiol. 26(4):380–381. https://doi.org/10.5152/dir.2020.20181
54. Sahni S, Verma S, Grullon J, Esquire A, Patel P, Talwar A (2013) Spontaneous pneumomediastinum: time for consensus. N Am J Med Sci. 5:460–464. https://doi.org/10.4103/1947-2714.117296
55. Zhou C, Gao C, Xie Y, Xu M (2020) COVID-19 with spontaneous pneumomediastinum. Lancet Infect Dis. 20(4):510. https://doi.org/10.1016/S1473-3099(20)30156-0
56. Wang W, Gao R, Zheng Y, Jiang L (2020) COVID-19 with spontaneous pneumothorax, pneumomediastinum and subcutaneous emphysema. J Travel Med 27(5). https://doi.org/10.1093/jtm/taaa062
57. Sun R, Liu H, Wang X (2020) Mediastinal emphysema, giant bulla, and pneumothorax developed during the course of COVID-19 pneumonia. Korean J Radiol. 21(5):541–544. https://doi.org/10.3348/kjr.2020.0180
58. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y et al (2020) Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 395(10223):507–513. https://doi.org/10.1016/S0140-6736(20)30211-7
59. Shan S, Guangming L, Wei L, Xuedong Y (2020) Spontaneous pneumomediastinum, pneumothorax and subcutaneous emphysema in COVID-19: case report and literature review. Rev Inst Med Trop Sao Paulo. 62:e76. https://doi.org/10.1590/S1678-9946202062076
60. Wintermark M, Schnyder P (2001) The Macklin effect: a frequent etiology for pneumomediastinum in severe blunt chest trauma. Chest. 120(2):543–547. https://doi.org/10.1378/chest.120.2.543
61. Chu CM, Leung YY, Hui JY, Hung IF, Chan VL, Leung WS et al (2004) Spontaneous pneumomediastinum in patients with severe acute respiratory syndrome. Eur Respir J. 23(6):802–804. https://doi.org/10.1183/09031936.04.00096404