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Review of chest CT manifestations of COVID-19 infection

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ABSTRACT

Coronavirus disease-19 (COVID-19) is a viral pandemic that started in China and has rapidly expanded worldwide. Typical clinical manifestations include fever, cough and dyspnea after an incubation period of 2–14 days. The diagnosis is based on RT-PCR test through a nasopharyngeal swab. Because of the pulmonary tropism of the virus, pneumonia is often encountered in symptomatic patients. Here, we review the pertinent clinical findings and the current published data describing chest CT findings in COVID-19 pneumonia, the diagnostic performance of CT for diagnosis, including differential diagnosis, as well the evolving role of imaging in this disease.

1. Introduction

COVID-19 is caused by an RNA virus, SARS CoV-2 (severe acute respiratory syndrome coronavirus 2) which is part of the *Coronaviridae* family (which includes SARS-CoV and MERS(Middle East respiratory syndrome)-CoV) [1,2]. The virus infects the upper respiratory tract, can cause pneumonia, and is easily transmitted from human to human. The initial epicenter was in Wuhan, the capital city of China's Hubei province, back in December 2019. The disease has rapidly spread to the rest of the world, particularly in Europe and the US, which are now harboring the largest number of cases in the world. COVID-19 was declared a pandemic by the World Health Organization (WHO) on 11 March 2020 [3]. As of 01 June 2020, there were over 6.15 million cases diagnosed worldwide, including more than 1.4 million in Europe and 1.82 million in the US, with over 372,000 deaths worldwide [4]. The greater New York City (NYC) region is among the epicenters of the pandemic, with more than 200 000 cases and over 16,410 deaths [5]. Here, we review pertinent clinical findings of COVID-19 and imaging manifestations most frequently encountered based on the literature compiled by early investigators, and illustrative cases from a major hospital system in NYC.

2. Clinical presentation of COVID-19

COVID-19 can affect all ages; however, the reported median age is lower in the largest Chinese series (47y) [6] compared to the largest American series (63y) [7], with less propensity to affect children (2% of patients were below age 19 in the largest series of 44,672 confirmed cases in China [8]). Asymptomatic cases represent approximately 1% of cases, and can contaminate people around them [8]. Men are overrepresented in COVID-19 cohorts, including in severe cases in series from China (58 %–73 % of the cohorts, 58 %–85 % of severe cases) [6,9] and the US (60.3 % of the largest US cohort, 66.5 % of patients admitted in ICU) [7]. Most people who contract COVID-19 experience mild symptoms and recover without specific treatment. The typical incubation period ranges between 2–7 days, but can be as long as two weeks. The most common symptoms include fever (reported between 43.8 %–98 %), cough (67.8 %–76 %), headache, malaise, myalgia, and dyspnea [6,9,10]. Gastrointestinal symptoms such as abdominal pain and diarrhea have been less frequently reported [6,10–13]. Anosmia and ageusia have also been recently described [14,15].

Several biologic findings have been reported: lymphopenia, elevated inflammatory indices such as C-reactive protein (CRP), D-dimer, procalcitonin and ferritin, lactate dehydrogenase (LDH) and interleukin-6 (IL-6); IL-6 in particular may identify cases with poor

Abbreviations: ARDS, acute respiratory distress syndrome; CAP, community-acquired pneumonia; COVID-19, coronavirus disease 2019; CRP, C-Reactive Protein; GGO, ground-glass opacity; MERS, Middle East respiratory syndrome; PUI, patient under investigation; RT-PCR, reverse transcription polymerase chain reaction; SARS, severe acute respiratory syndrome; SARSCoV-2, severe acute respiratory syndrome coronavirus 2

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prognosis and prompt intervention in order to improve outcomes [6,9]. Blood hypercoagulability and disseminated intravascular coagulation (DIC) have been described in severe cases of COVID-19 [16,17].

The course of disease can be described as nonsevere or severe, based on the need for hospitalization for dyspnea, hypoxia, and the possible need for mechanical ventilation. In two Chinese series, most cases were classified as mild (81 %–84.3 %), with16.7 %–19 % of cases being severe (including critical cases) [6,8]. A proportion of 2.3%–12.2% of patients require mechanical ventilation [7,8]. The reported mortality rates vary between 1.4 % and 28 %, depending on the series [6–8,18].

3. Diagnostic confirmation of COVID-19

The two commonly used detection methods for SARS-CoV-2 are real-time reverse transcription polymerase chain reaction (RT-PCR) and high-throughput sequencing. High-throughput sequencing of the whole genome has a limited role clinically because of its high cost [19]. RT-PCR (which detects the viral nucleic acids when present in sufficient quantity) is the most commonly used method for diagnosis in respiratory secretions [20,21]. The largest study published on RT-PCR detection in various samples demonstrated positive rates between 32 %–93 % in the nasopharynx and upper respiratory tract (lowest in the pharynx, and highest in bronchoalveolar lavage fluid specimen), while nasal swabs had a 63 % positive rate [22]. The variation in positive rates may be explained by date of sampling (too early or too late), improper sampling, low viral load and difference of detection rate from different manufacturers [23].

Serum immunoglobulins (IgM and IgG) can be used to diagnose recent infection to COVID-19 [24]. For example, a study demonstrated that the positive detection rate is increased (98.6 %) when combining IgM assay with RT-PCR compared to RT-PCR alone (51.9 %) [25].

4. Imaging findings of COVID-19

A total of 30 original papers published in English totaling over 4000 patients were reviewed [23,26–54]. Reviews and case reports were excluded. Most reviewed papers originate from China [23,26–35,37–40,44–48,50–53] and the remainder from Japan [43,49], Korea [41], Italy [42,54] and the US add Ref [59]. Three papers were in collaboration between Chinese and US institutions [27,29,45].

4.1. Chest radiography findings

Chest radiography (CXR) findings in patients with COVID-19 have been described in small case series [41,46]. CXR is negative in 40 %–66.7 % of cases despite positive findings on chest CT (Fig. 1) [41,46]. The most common radiographic finding is opacification, often with a peripheral and lower lung distribution [41,46] (Fig. 2). Thus, CXR is not recommended for routine diagnosis of COVID-19, but may be helpful for follow-up.

4.2. Chest CT findings

A low dose, chest CT without intravenous contrast is generally used for evaluation [55]. Typically, COVID-19 pneumonia presents with bilateral peripheral patchy ground-glass opacities (GGO) with or without consolidation [40,44,56] (Figs. 2 and 3). GGOs may have a rounded morphology [27,29,33,39,42] in up to 54 % of the cases (Fig. 4). Superimposed interlobular septal thickening can also be present, resulting in a crazy-paving pattern (Fig. 2). Vascular enlargement, air bronchograms, and a halo sign have also been described (Fig. 2). The GGOs and consolidative lesions are larger than 1cm in 91 % of cases [40]. The lower lobes and posterior portions are more frequently involved [39]. Mediastinal and hilar lymphadenopathy, pleural effusions or thickening, discrete pulmonary nodules, and pulmonary cavitation have been rarely described in the Chinese series [27,29,40]. An Italian study described lymphadenopathy in up to 58 % of cases [42]. Table 1 shows the prevalence of various imaging findings on chest CT at initial presentation.

A Japanese study described that asymptomatic patients tend to have more GGO (80 %) and less consolidation (20 %) compared with symptomatic patients (63 % and 38 %) [43]. CXR and chest CT can be negative in up to 17.9 % of patients, especially in early and/or non severe disease [6]. In mild cases, CT findings consist more frequently of GGO alone (65 %), followed by GGO with consolidation (44 %) [40]. Severe cases with a clinical acute respiratory distress syndrome (ARDS) picture present with widespread dense consolidative opacification on CT (see below).

4.3. Stages of COVID-19 on chest CT

Several studies categorized COVID-19 CT findings into several stages based on time since the onset of symptoms [10,26,27,33,39]. These were classified into 4 main successive stages: early, intermediate and late [27] and a fourth resorptive stage [50].

- Early stage (≤2 days): More than half of the patients have negative chest CT (56 %). The remaining patients have predominantly GGO (44 %) and consolidation (17 %). Imaging findings when present were often unilateral [27]. Similar findings were described in another study [39], which demonstrated that in early disease 16.1 % of cases present with a solitary lesion seen in 70 % of cases in the right lower lobe.
- Intermediate stage (3–5 days): As the disease progresses, more GGO (88 %) and consolidation (55 %) are noted bilaterally (76 %) and with a peripheral lung distribution (64 %). Only 9% of patients have negative chest CT [27].
- Late phase (6–12 days): Most of the patients in this phase have positive chest CT findings. 88 % and 60 % of patients have GGO and consolidation, respectively. The imaging findings are bilateral in 88 % and peripheral-predominant in 72 % of cases [27].
- Absorption stage/fourth stage (> 14 days): 65 % and 75 % of patients have GGO and consolidation, respectively. The imaging findings are bilateral in 88 % and peripheral-predominant in 72 % of cases [50].

When patients improve, the lung disease evolves and organizes, and fibrous bands may appear [35,38,47,57]. A “reverse-halo sign” is occasionally observed and can be an indication of organizing pneumonia [46,58]. In severe cases, the consolidation and GGO increase and involve all five lung lobes, resulting in a dense consolidative appearance and characterized by diffuse alveolar damage, usually with a poor prognosis [47] (Fig. 5)

4.4. Prediction of severity with imaging

It has been suggested that imaging can help predict severity of COVID-19 disease. For example, a study showed that a severity score based on CXR at initial presentation in non-elderly patients (21 − 50y) predicts outcome (hospital admission and intubation) [59]. Another study suggested that severe/fatal cases were more likely to have more extensive and diffuse disease with more frequent architectural distortion and bronchiectasis compared to mild/common cases [37]. However, more data is needed particularly in comparison with blood tests, such as cytokine levels.

4.5. COVID-19 in special populations

Oncology patients: A retrospective study in 28 oncologic patients showed similar findings of GGO (75 %) and patchy consolidation (46.3 %). The presence of the latter at admission was associated with worse outcome [60].

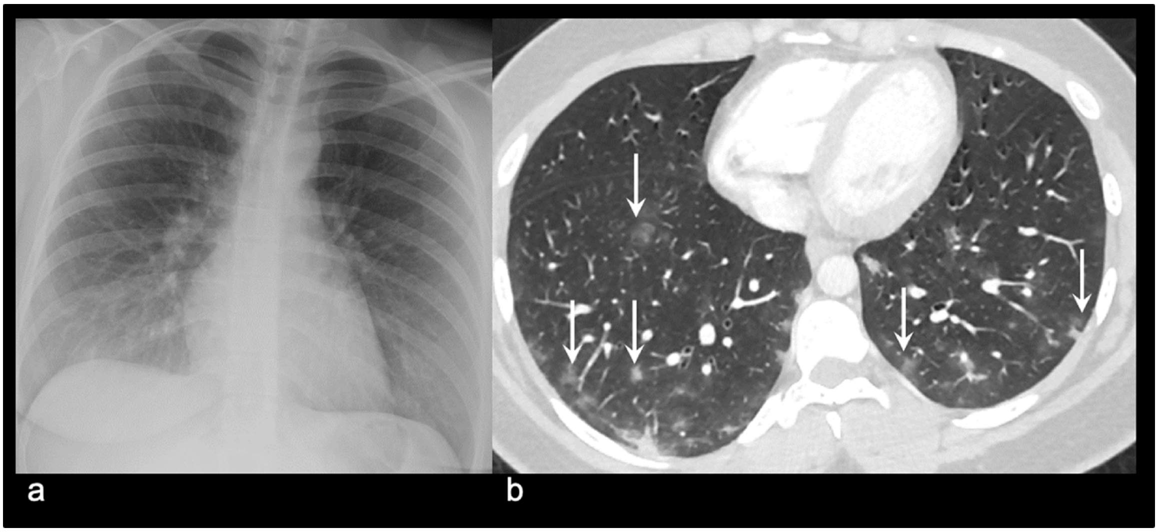

Fig. 1. 25-year-old female presenting to the emergency department (ED) with 7 days of fever and shortness of breath, with portable chest radiography (a) showing no abnormality. A subsequent CT angiogram of the chest (b) shows multifocal lower lobe rounded opacities, predominately ground-glass in attenuation (arrows). Patient tested positive for COVID-19.

Pediatric and pregnant patients: Few studies have described chest CT findings in children [61–64] who tend to have milder findings. The largest study included 13 patients [64], 20 % of whom had normal chest CT, 60 % had GGO, and 50 % had consolidation with a surrounding halo (which was considered a typical finding in this population). Bilateral disease was observed in 50 % of cases. Co-infection with another pathogen was identified in 2 %–40 % of the cases [63,64]. Another study [65] found that pregnant women have more consolidation (up to 56 %) as compared with the non-pregnant population (21 %). Pregnant woman also manifested with bilateral and peripheral-predominant GGO. Pleural effusions were more commonly encountered in pregnant than in non-pregnant women, up to 38 % versus 7%.

Elderly population: Older patients (> 60y) have similar (classic) chest CT findings [53]. However, they tend to have more areas of lung involvement with more lobes affected and more pleural thickening [53]. Similar findings were obtained in another study [32], where patients older than 50 years had more extensive disease with more consolidation as compared with patients younger than 50. They tended to have more architectural distortion, bronchiectasis, mediastinal and hilar lymphadenopathy and pleural effusions and worse outcomes than younger patients [37].

COVID-19 and pulmonary embolism: An increased incidence of acute pulmonary embolism in hospitalized COVID-19 patients has been reported [66]. Out of 25 patients, 40 % had an acute pulmonary embolism and it was associated with elevated D-dimer (up to 11.07 ug/mL). Thus, COVID-19 can be associated with pulmonary embolism especially when D-dimer is elevated (Fig. 6), and preventive anticoagulation has been recommended in severely ill hospitalized patients [67].

5. Differential diagnosis

COVID-19 pneumonias demonstrate a wide range of imaging findings, with variability based on disease severity and time course, and can overlap with a variety of infectious and non-infectious pulmonary pathologies. Overlap in imaging appearance occurs with other viral infections [i.e. severe acute respiratory syndrome (SARS), MERS, influenza, parainfluenza, adenovirus, respiratory syncytial virus (RSV), rhinovirus, human metapneumovirus, cytomegalovirus and others)], as well as community-acquired pneumonias (CAP) caused by *Streptococcus pneumonia* or mycoplasma infection [36,68]. A study performed by Bai et al. found that 6 of 7 radiologists had high specificity (93–100 %) and moderate sensitivity (67 − 93%) in distinguishing COVID-19 pneumonia from other viral pneumonias, although there was variability in radiologist performance [45]. Compared to viral pneumonia, COVID-19 tends to have a more peripheral distribution, greater GGO, increased

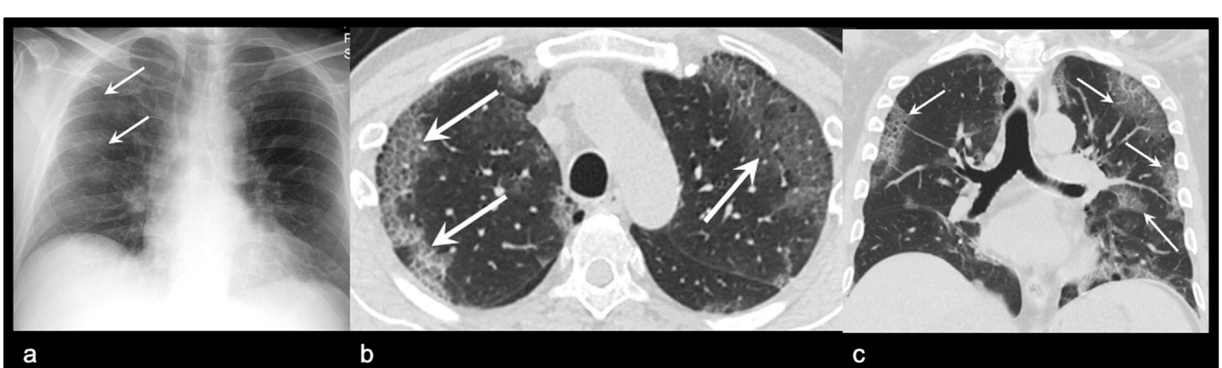

Fig. 2. 60-year-old male with fever and cough for 7 days due to COVID-19. (a) Antero-posterior chest radiography shows ill-defined opacities in the lateral aspect of the right lung (arrows). (b) Axial noncontrast chest CT shows GGOs with a peripheral distribution in both upper lobes (arrows). There is superimposed interlobular and intralobular septal thickening (crazy-paving pattern). (c) Reconstructed coronal chest CT image shows corresponding multifocal bilateral ground-glass opacities with a peripheral distribution (arrows).

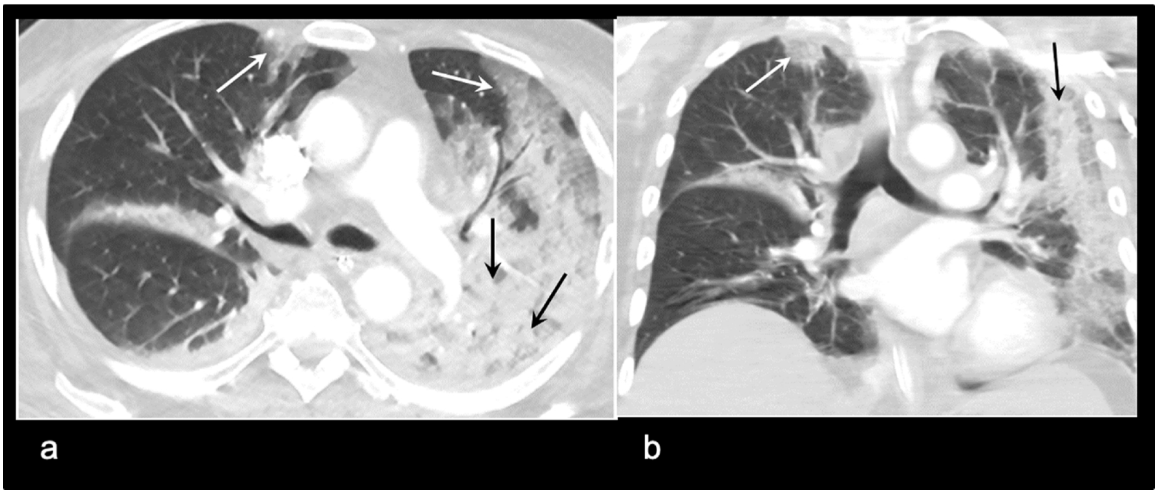

Fig. 3. 74 year-old male with fever and cough due to COVID-19. (a) Axial and (b) coronal CT angiography of the chest shows multifocal bilateral ground-glass (white arrow) and consolidative (black arrow) opacities.

vascular enlargement and a “reverse-halo sign”. Zhao et al. also demonstrated that COVID-19 had more frequent bilateral GGOs compared to non−COVID-19 viral infections [11]. Key findings less frequent in COVID-19 pneumonia compared to non−COVID pneumonia included air bronchograms, centrilobular nodules, tree-in-bud opacities, bronchial wall thickening and a reticular pattern [28,36].

Other coronavirus organisms with genetic resemblance to COVID-19 can produce similarly devastating pulmonary syndromes, including SARS (9.4 % mortality rate) and MERS (34.4 % mortality rate) [69,70]. While there have been no documented cases of SARS since 2003, MERS cases are still reported sporadically. All three of these infections cause peripheral multifocal airspace opacities (GGO and/or consolidation), without pneumothorax, cavitation or lymphadenopathy. Differences in the imaging appearances have been reported, as SARS tends to be unilateral and focal in distribution (50 %) and MERS patients can develop pleural effusion (33 %) [71,72]. Both SARS and MERS are associated with constriction of the pulmonary vasculature, whereas enlargement of the vasculature has been reported in COVID-19 [73]. Pulmonary fibrosis was reported as a late manifestation in MERS, but not in SARS. The long-term sequelae of COVID-19 remain to be determined; however, early publications indicate a fibrotic phase characterized by reticulation, interlobular septal thickening and traction bronchiectasis [47,69].

Finally, a variety of other noninfectious pulmonary diseases can produce imaging findings on CT that may overlap with COVID-19 pneumonia, including pulmonary edema, ARDS, organizing pneumonia, prior treatment (i.e. drug toxicity or radiation pneumonitis/fibrosis), pulmonary infarction, alveolar hemorrhage, and interstitial lung diseases [74]. Both ARDS and bacterial superinfection can complicate COVID-19 pneumonia. While there is an abundance of literature being published at a rapid rate, results of these studies must be scrutinized and interpreted with caution as a variety of sources of bias may produce artificially high performance characteristics of CT and certain imaging findings for COVID-19 pneumonia [74]. Ultimately, given the variable and non-specific nature of the imaging findings in COVID-19, integration of clinical history, laboratory tests, in addition to quantitative approaches including machine learning or artificial intelligence (AI, see below), are needed for accurate assessment.

6. Diagnostic performance of chest CT

Several studies compared the accuracy of chest CT against RT-PCR [23,31,42,44,48]. Abnormal chest CT findings can be present despite a negative RT-PCT with a sensitivity ranging between 72 %–97 %

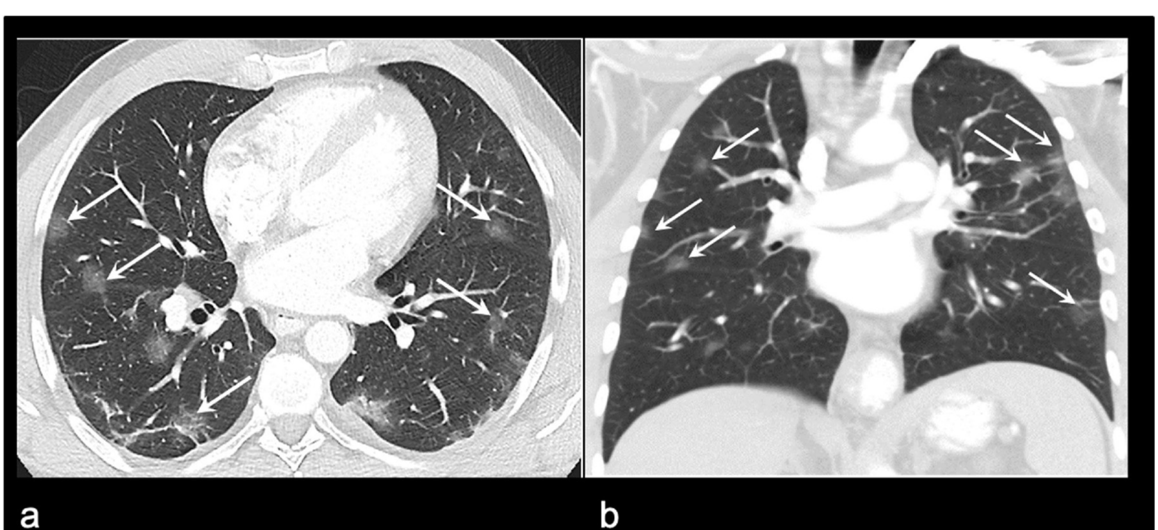

Fig. 4. 37-year-old male presenting with fever, cough and dyspnea for 7 days due to COVID-19. (a) Axial chest CT image shows multifocal bilateral GGOs with a rounded morphology (arrows). (b) Corresponding coronal CT shows the bilateral ground-glass lesions, many of which are peripheral in distribution as well.

Table 1
Reported prevalence of imaging findings of COVID-19 on chest CT.

Imaging findings	Mean (Range in %)	References
Common features		
Ground glass opacities (GGO)	71.7 (27.3 – 100)	[26,27,28,29,30,32,33,34,35,37,38,39,40,42,44,45,46,47,51,53]
Crazy-paving	26.7 (5 – 89.4)	[27,29,30,34,35,38,40,42,45,53]
Enlarged subsegmental vessels	80.9 (71.3 – 89)	[31,37,42]
Rounded morphology	34 (11 – 59.6)	[27,29,30,33,38,40,42]
Consolidation	41.2 (6 – 69)	[6,27,28,29,32,33,34,35,37,39,40,42,44,45,46,47,53]
GGO and consolidation	46.6 (29 – 64.4)	[27,28,29,31,32,33,37,38,40,43]
Interlobular septal thickening	50.9 (13 – 75)	[31,32,34,35,42]
Halo sign	34.3 (12 – 69)	[40,42,45]
Air bronchogram	50 (8 – 80)	[28,30,31,32,35,38,39,40,42,45]
Distribution		
Posterior	80 (67 – 93)	[32,41,42]
Bilateral	79.2 (51 – 93)	[26,27,29,30,32,35,37,42,43,44,45,51,53]
Peripheral	73 (43.6 – 100)	[26,27,28,29,30,31,32,33,35,37,39,40,41,42,43,45,46,51]
More than 2 lobes affected	62.5 (51 – 93)	[27,29,35,40,42,43]
Central and peripheral distribution	19.9 (2 – 56.4)	[32,33,39,40,43,45]
Uncommon Findings		
Centrilobular nodules	15.7 (0 – 32)	[27,28,29,30,37,45,47]
Tree-in-bud nodularity	9.1	[28]
Bronchiectasis	30.9 (1 – 52.5)	[27,28,37,39,42]
Bronchial wall thickening	10.5 (0 – 28.7)	[27,34,37,38,42,45]
Cystic changes	9.1	[28]
Pleural thickening	30 (0 – 56)	[35,39,40,45]
Subpleural linear opacity	18.2 (17.5 – 33.9)	[28,37,39,47,50]
Reverse halo sign	5.1 (3.9 – 17)	[27,31,45,46]
Pleural effusion	3.7 (0 – 13.9)	[27,28,29,30,31,32,33,34,35,37,39,40,42,45,46,51]
Pericardial effusion	3.4 (1 – 6)	[32,34,35,42,46,51]
Lymphadenopathy	5.8 (0 – 58)	[27,28,29,30,31,32,34,35,37,40,42,45,46,51,53]
Lung Cavitation	0	[27,29,35,38,42,46,51]

[23,42,44,45]. However, according to Raptis et al. this high sensitivity can be explained by a selection bias of the studied population and low threshold for positive disease on chest CT [75]. Using RT-PCR as a reference, specificity of chest CT ranges between 25 %–56 % and accuracy between 68 %–72 % [42,44]. The positive predictive value and accuracy of chest CT were higher in patients older than 60 years. 42 % of cases had improvement of imaging findings before negative conversion of RT-PCR [44]. The positive rate of RT-PCR was 32 %–93 % [22,23,44]. This can be explained by the fact that RT-PCR was obtained through throat swabs which have low positive rates [36,52] as viral pneumonia does not usually produce purulent sputum [48].

7. Guidelines and scientific societies from imaging societies

With the rapid evolution of this outbreak, the global community of radiologists has convened to construct guidelines and position statements regarding the appropriate use of imaging during this pandemic. Early in the outbreak, hospitals in China were using chest CT in many suspected patients, as well as to follow-up the progression of lung disease. In the US, the Centers for Disease Control and Prevention (CDC), the American College of Radiology (ACR), the Society of Thoracic Radiology (STR), and the American Society of Emergency Radiology (ASER) issued their position statements recommending against the use of CT for widespread screening and diagnosis of COVID-19, instead reserving CT for those cases with clinical suspicion for complications like abscess or empyema [76–78]. This was largely spurred by the early research on Chinese patients which showed that imaging, specifically CT, has a wide range in sensitivity for detecting COVID-19 pneumonia [27,44]. In addition, the CT imaging features of COVID-19 are sometimes nonspecific and can overlap with other infections as discussed above. The positive predictive value of CT is low in locations where COVID-19 prevalence is low [79].

The multinational consensus statement of the Fleischner society [80] recommended chest CT for patients with moderate to severe symptoms or with mild disease with associated co-morbidities or with worsening respiratory symptoms. The European Society of Radiology (ESR) and the European Society of Thoracic Imaging (ESTI) outlined their recommendations in a consensus document, stating that chest CT should not be performed as a screening tool in patients with “mild or no symptoms” [81]. However, they add on that chest CT may play a useful role in patients with milder symptoms who have co-morbidities (e.g. diabetes, obesity, chronic respiratory disease, etc.). In their statement, they also note that with further research, information gained from a baseline CT in COVID-19 patients may play an important role in predicting who will have poor outcomes or need ventilation.

8. Structured reporting and standardized language

With the spread of COVID-19 globally and the increasing number of CTs performed in patients under investigation (PUIs), there have been frequent questions in the radiology community regarding the optimal way to report CT findings potentially attributable to COVID-19 pneumonia. A national expert panel of thoracic radiologists gathered to produce a consensus statement on this topic, subsequently endorsed by the Radiological Society of North America (RSNA), the STR, and the ACR [82].

Chest CT findings were classified for COVID-19 pneumonia into four groups: typical appearance, indeterminate appearance, atypical appearance, and negative for pneumonia. Standardized language templates are provided in [82] with the goal of decreasing reporting variability and increasing clarity by using consistent language. The question of whether to include terminology such as “coronavirus” or “COVID-19” in reports remains an area of debate. The authors acknowledge that for patients with unexpected findings that could be attributable to COVID-19, the matter is complex and consultation with local clinical colleagues is needed to establish an approach. The term “viral pneumonia” is considered a reasonable alternative.

9. Future directions

Given the variable sensitivity in RT-PCR for the diagnosis of early COVID-19 and the overlap in the imaging appearances with other

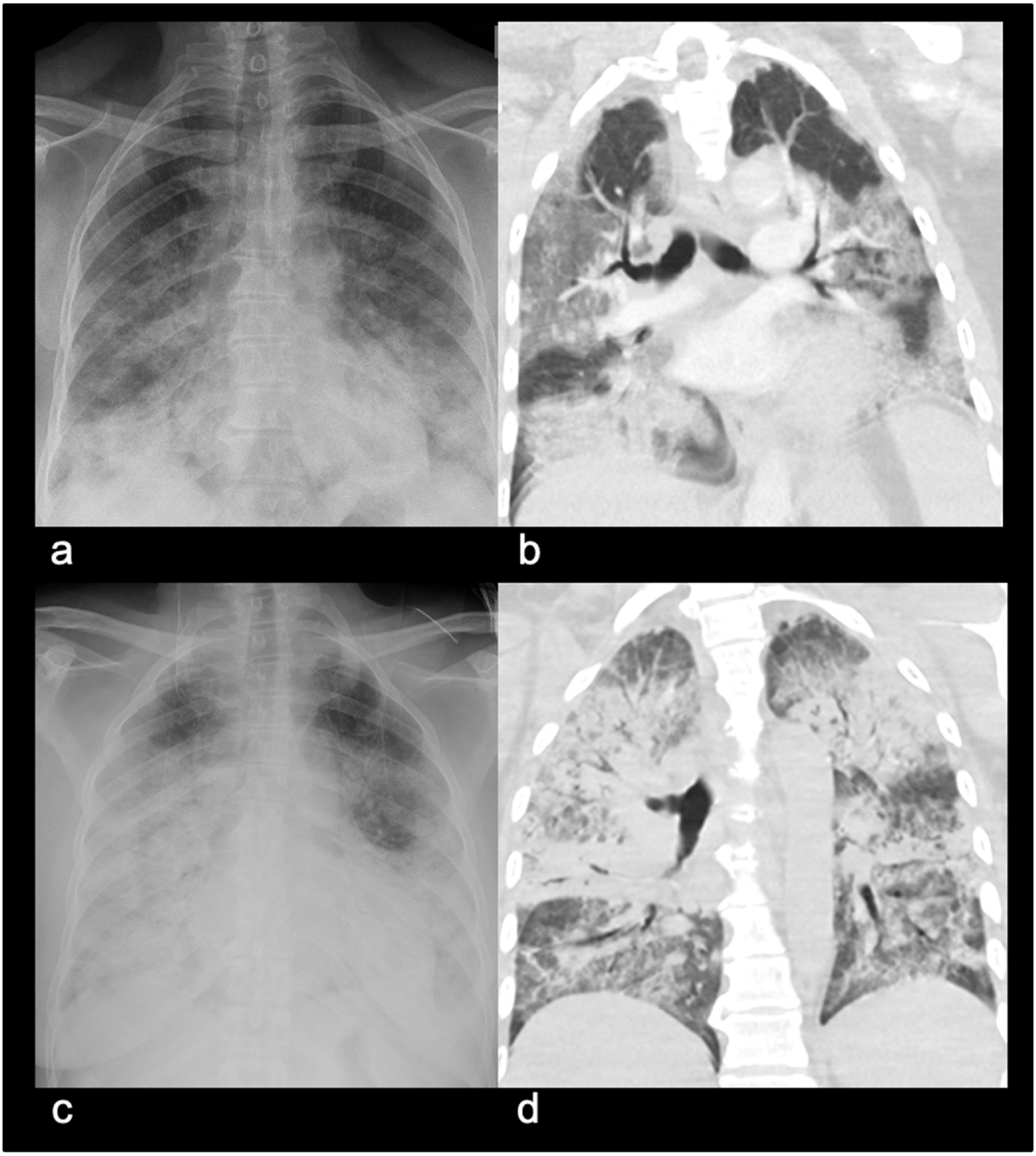

Fig. 5. 65-year-old female presenting with fever and dyspnea due to COVID-19. (a) Initial ED anteroposterior chest radiography with corresponding (b) coronal chest CT reformatted image show multifocal mid to lower lung predominant ground-glass and consolidative opacities. (c) Follow-up (c) anteroposterior chest radiography and (d) coronal CT reformatted image on day 14 of admission show progressive pulmonary opacities, now more consolidative and involving more of the upper lobes bilaterally.

pulmonary diseases, AI approaches have been applied in an effort to improve the diagnostic accuracy of CT. In a recent retrospective multicenter study of 4356 chest CTs from 3322 patients, a deep learning model detection neural network (COVNet) in an independent test set demonstrated excellent per-exam AUC, sensitivity and specificity of 0.96, 90 % and 96 %, respectively for detecting COVID-19 compared to CAP and other non-pneumonias [83]. Other studies using deep learning approaches have found similar results with reported AUCs up to 0.996 [84,85] and accuracy up to 86.7 % [86] for the classification of COVID-19 from non−COVID-19 pulmonary infection. A recently published algorithm integrating chest CT and clinical history in patients presenting early in the course of the disease reached an AUC of 0.92 and had higher sensitivity (84.3 %) when compared to a senior thoracic radiologist (74.6 %) and a thoracic radiology fellow (56 %). The algorithm was able to identify 68 % of cases presenting with positive RT-PCR but normal chest CT. This method may have a role for a quick diagnosis of COVID-19 pneumonia with CT [87]. More work in terms of performance and clinical implementation/acceptance is needed.

10. Conclusion

COVID-19 is a new rapidly spreading pandemic. It has typical CT

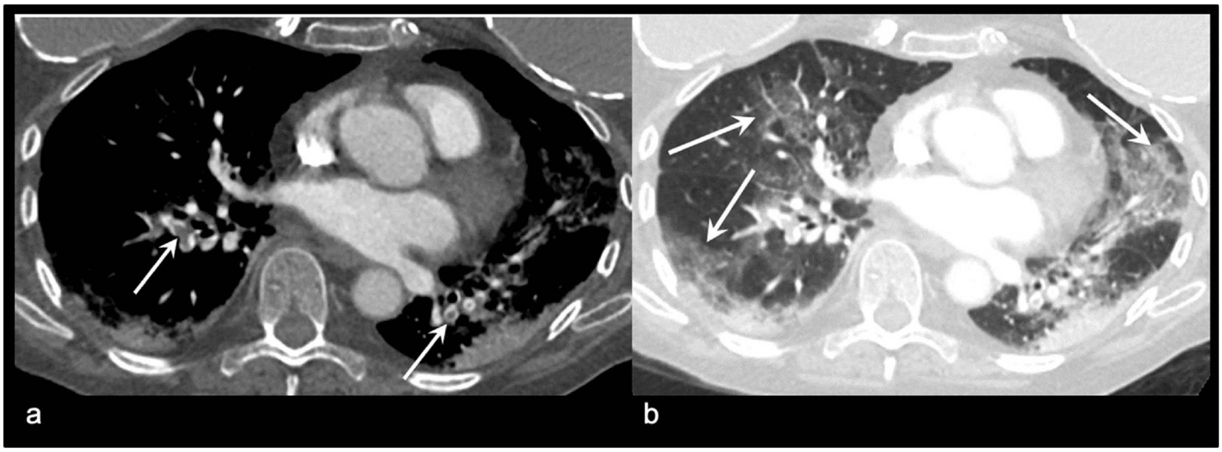

Fig. 6. 76-year-old female presenting with 3 weeks of cough, dyspnea and palpitations. CT angiography of the chest (a) shows bilateral lower lobe segmental and subsegmental pulmonary emboli (arrows). Corresponding image in lung windows (b) shows multifocal bilateral ground-glass and consolidative opacities consistent with the patient's diagnosed COVID-19 pneumonia.

findings with GGOs and consolidation often with a peripheral and lower lung distribution. In early disease, imaging findings can be absent; therefore, CT chest cannot be used as a screening method, and RT-PCR remains the reference diagnostic test. AI may play a role in the rapid diagnosis of COVID-19, but more data is needed to assess its added value.

Declaration of Competing Interest

There is no conflict of interest associated with this publication and there has been no financial support for this work

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