

# Diagnostic accuracy of chest computed tomography in improving the false negative rate as compared to reverse transcriptase polymerase chain reaction in coronavirus disease 2019 pneumonia: A cross sectional analysis of 348 cases from India

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## ABSTRACT

**Background:** Early differentiation between emergency department (ED) patients with and without coronavirus disease 2019 (COVID-19) is very important. The diagnosis of COVID-19 depends on real-time reverse transcriptase polymerase chain reaction (RT-PCR). On imaging, computed tomography (CT) manifestations resemble those seen in viral pneumonias, with multifocal ground-glass opacities and consolidation in a peripheral distribution being the most common findings. Although these findings lack specificity for COVID-19 diagnosis on imaging grounds, CT could be used to provide objective assessment about the extension of the lung opacities, which could be used as an imaging surrogate for disease burden. We set out to investigate the diagnostic accuracy of chest CT scanning in detecting COVID-19 in a population with suspected COVID-19 patients. **Materials and Methods:** In this cross-sectional single-center study performed on 348 cases with clinical suspicion of COVID-19, all adult symptomatic ED patients had both a CT scan and a PCR upon arrival at. CT results were compared with PCR test (s) and diagnostic accuracy was calculated. **Results:** Between February 15, 2020, and June 30, 2020, 348 symptomatic patients were included. In total, 62.3% of patients had a positive PCR and 69.8% had a positive CT, resulting in a sensitivity of 94.2%, specificity of 76.7%, likelihood ratio (LR) of +2.94 and (LR) -0.18. The sensitivity of the CT tended to be higher in those with acute respiratory distress syndrome (100.0%,  $P = 0.017$ ) and severe COVID-19 (98.5%,  $P = 0.027$ ) than in patients with mild (82.5%,  $P = 0.047$ ) and moderate COVID-19 (89.3%,  $P = 0.039$ ). The diagnostic ability of chest CT was found to be high with 86.3% concordance between findings of CT and PCR. In 48 (13.7%) patients, discordant findings between CT and PCR were observed. In most cases, the CT scan was considered suspicious for COVID-19, while the PCR was negative (37/48, 77.0%). In the majority of these, the diagnosis at discharge was pulmonary infection ( $n = 26$ ; 54.1%). **Conclusion:** The accuracy of chest CT in symptomatic COVID suspect patients is high, but when used as a single diagnostic test, CT cannot accurately diagnose or exclude COVID-19. Therefore, we recommend a combination of both CT and RT-PCR for future follow-up, management, and medical surveillance.

**KEY WORDS:** Coronavirus disease 2019, RT PCR, CT, sensitivity, specificity

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**Submitted:** 24-May-2020    **Revised:** 28-Jul-2020    **Accepted:** 16-Aug-2020    **Published:** 06-Mar-2021

Access this article online	
Quick Response Code:	Website:
	www.lungindia.com
	DOI:
	10.4103/lungindia.lungindia_410_20

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**How to cite this article:** Ravikanth R. Diagnostic accuracy of chest computed tomography in improving the false negative rate as compared to reverse transcriptase polymerase chain reaction in coronavirus disease 2019 pneumonia: A cross sectional analysis of 348 cases from India. Lung India 2021;38:S11-21.

## INTRODUCTION

In late December 2019, a lower respiratory tract febrile illness was reported in a cluster of patients from Wuhan City, Hubei Province, China, and a novel strain of coronavirus was isolated from the bronchoalveolar lavage of infected patients.<sup>[1]</sup> The World Health Organization on January 09, 2020, named the pulmonary syndrome as coronavirus disease 2019 (COVID-19).<sup>[2]</sup> At the time of writing this article on July 29, 2020, the number of confirmed cases stand at 16,901,802 with 663,570 reported deaths;<sup>[3]</sup> As of late June 2020, the number of cases of confirmed COVID-19 globally is over 10 million, affecting virtually every territory, other than isolated South Pacific island states and Antarctica. The United States has more than two million cases, Russia more than one million, and India and four other countries has >250,000 cases.<sup>[3]</sup> COVID-19 is a droplet infection primarily transmitted person to person by coughing or sneezing or close contact with infected individuals' upper respiratory tract secretions. A study that examined the first 425 infected cases in Wuhan estimated that the  $R_0$  (basic reproduction number) of novel coronavirus to be 2.2, that is, each infected individual on average causes 2.2 new cases of the disease.<sup>[4]</sup> The study also calculated the incubation period in the group to be 5.2 days on average.<sup>[4]</sup>

COVID-19 is a highly contagious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).<sup>[5]</sup> Early differentiation between patients with and without the disease is extremely important, particularly in patients who visit the emergency department (ED) and patients who are admitted to the hospital. This differentiation is necessary to be able to select patients who need to be isolated to protect other patients and health-care personnel.<sup>[6]</sup>

Currently, reverse transcriptase polymerase chain reaction (RT-PCR) is the reference standard in diagnosing COVID-19. However, PCR may have suboptimal sensitivity, for instance because in early stages of COVID-19, the viral load is below detection limit or because of technical issues, i.e., sampling errors.<sup>[7]</sup> In addition, in practice, it may take up to 24 h to get a test result, although same day results are achieved most of the times.<sup>[8]</sup>

As most COVID-19 patients present with pneumonia, computed tomography (CT) scanning of the thorax could be helpful in screening and diagnosing. In addition, CT has the advantage that the results can be available almost directly.<sup>[9]</sup> Chest CT can show characteristic findings including areas of ground-glass, with or without signs of reticulation (so called "crazy paving pattern"), consolidative pulmonary opacities in advanced stages, and the "reverse halo" sign.<sup>[10]</sup> Since peripheral areas of ground glass are a hallmark of early COVID-19, which can easily be missed at chest X-rays, CT scanning has an advantage over chest X-rays in the early stages of COVID-19.<sup>[11]</sup> Because COVID-19-related changes can indeed be found

on CT scans, some studies suggest that CT scanning could be helpful in discriminating between COVID-19-positive and COVID-19-negative patients at the ED.<sup>[12]</sup> The value of CT is, however, debated because of suspected lack of discriminatory value.<sup>[13]</sup> The sensitivity of PCR may also be suboptimal, which makes it difficult to compare RT-PCR and CT.<sup>[7]</sup> Furthermore, the added value of a diagnostic test is affected by the prevalence of disease, and the data on the performance of CT in a population with a moderate prevalence of COVID-19 are scarce.

## Objective of the study

The current cross-sectional study investigated the diagnostic accuracy of CT scanning in detecting COVID-19 in a population with suspected COVID-19 presenting at the ED using RT-PCR testing as reference standard.

## MATERIALS AND METHODS

### Setting

This study was performed on 348 cases with clinical suspicion of COVID-19 referred to a tertiary care hospital in South India between February 15, 2020, and June 30, 2020. This study is reported in line with the STARD guidelines for diagnostic accuracy studies.<sup>[14]</sup>

### Patients and design

All adult (18 years or older) patients who visited the ED between February 15, 2020, and June 30, 2020, with respiratory symptoms including dyspnea, coughing, sore throat, and fever were scanned in a CT scan unit. Of these patients, a nasopharyngeal and/or oropharyngeal swab was taken and tested for presence of SARS-CoV-2. If the first PCR was negative, a second PCR was performed within 48 h after the first test in patients who were still admitted in the hospital, if deemed indicated by the clinicians. The current study included all symptomatic patients who received a chest CT and at least one PCR test for the detection of COVID-19.

### Reverse transcriptase polymerase chain reaction

Laboratory confirmation of SARS-CoV-2 was performed with RT-PCR assay. The SARS-CoV-2 laboratory test was based on the detection of unique sequences of virus RNA by nucleic acid amplification test such as real-time RT-PCR and targeted the SARS-CoV-2 *E* (envelope protein) and *RdRp* (RNA-dependent RNA polymerase) genes. All swabs were also tested for influenza A, B, respiratory syncytial virus, and *Human metapneumovirus*. For the diagnosis of *Mycoplasma pneumoniae* infection, PCR and the immunoglobulin M immunofluorescence assay, with culture and the complement fixation (CF) test, were used. For the diagnosis of *Chlamydia pneumoniae*, CF test, the microimmunofluorescence test, and the enzyme-linked immunosorbent assay were used.

### Chest computed tomography

The chest CT was obtained in a GE (General Electric

Medical Systems, Milwaukee, WI, USA) 16-slice MDCT machine upon arrival at the ED. CT scans were performed in caudocranial scanning direction without intravenous contrast injection, at 120 kVp and 50–210 mA, depending on their weight, using  $16 \times 1.25$  collimation, 0.5 s rotation time reconstructed at 1.25 mm slices with 1.25 mm increment. Patients were instructed to hold their breath if clinically possible. Images were reconstructed using a moderately soft reconstruction filter (“DETAIL”) at mediastinal window and a sharp reconstruction filter (“LUNG”) at lung window settings. Initial judgment of the CT scan was performed by a senior resident with scans being assessed as a dichotomous outcome: being either suspicious or not suspicious for COVID-19-related pneumonia. In case of pneumonia, in which COVID-19 was unlikely but could not be excluded, the scan was judged positive. The final reading and reporting were performed by an experienced chest radiologist within 12 h of scanning. Since the PCR results were available after 12–24 h, both readers were unaware of the PCR test results.

### Data collection

From electronic medical records, the following data were retrieved: demographic data (age and sex); comorbidity; duration and severity of current disease; PCR results and other microbiological data; CT scan reports; and discharge diagnosis. Severity of disease categorization of COVID-19 suspected/confirmed patients into mild, moderate, and severe disease and acute respiratory distress syndrome (ARDS) was done as per the WHO guidelines and as per the Government of India guidelines:<sup>[15]</sup> mild COVID-19 disease, symptomatic patients meeting the case definition for COVID-19 without evidence of viral pneumonia or hypoxia; moderate COVID-19 disease, adolescents or adults with clinical signs of pneumonia (fever, cough, dyspnea, and fast breathing) but no signs of severe pneumonia, including  $\text{SpO}_2 \geq 90\%$  on room air; severe COVID-19 disease, adolescents or adults with clinical signs of pneumonia (fever, cough, dyspnea, and fast breathing) plus one of the following (respiratory rate  $>30$  breaths/min; severe respiratory distress; or  $\text{SpO}_2 < 90\%$  on room air); and ARDS, adolescents or adults with onset of clinical signs within 1 week of a known clinical insult (i.e., pneumonia) or new or worsening respiratory symptoms. Oxygenation impairment in adults is categorized as mild ARDS when  $\text{PaO}_2/\text{FiO}_2$  is  $\leq 200$ –300 mmHg (with PEEP or CPAP  $\geq 5$   $\text{cmH}_2\text{O}$ ), as moderate ARDS when  $\text{PaO}_2/\text{FiO}_2$  is  $\leq 100$ –200 mmHg (with PEEP  $\geq 5$   $\text{cmH}_2\text{O}$ ) and as severe ARDS when  $\text{PaO}_2/\text{FiO}_2$  is  $\leq 100$  mmHg (with PEEP  $\geq 5$   $\text{cmH}_2\text{O}$ ).<sup>[16]</sup>

### Data analysis and statistics

The current study performed a descriptive analysis of baseline characteristics of included patients. The collected data were tabulated using Microsoft Excel 2010 Microsoft Corp., Redmond, WA, USA, and statistical analyses were conducted using SPSS Statistical Package (version 20.0), IBM SPSS Statistics for Windows, V.20.0, IBM Corp., Armonk, New York, USA. Continuous variables were reported as

medians with interquartile ranges and categorical variables as proportions. In case of missing values, valid percentages were used. The current study compared the CT scan results with the PCR testing results. Diagnostic accuracy of the CT scan in terms of sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), and likelihood ratios (LRs) was assessed. Next, the diagnostic accuracy (sensitivity, specificity, PPV, NPV, and LR) with respect to the severity of disease and the absence/presence of sepsis was calculated. The Chi-square test was used to compare the sensitivity and specificity between patients with low and high severity of disease. Discordances between CT results and PCR testing results were further investigated by retrieving data on alternative diagnoses and, if possible, duration of symptoms (using ancillary viral/bacterial test results and discharge diagnoses in medical charts (e.g., pneumonia caused by influenza)). These data were analyzed in a descriptive way. In all cases,  $P \leq 0.05$  was considered significant.

### Ethical considerations

All examinations performed in studies involving human participants were in accordance with the Ethical Standards of the Institutional Ethics Committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from all patients prior to their enrollment in this study.

## RESULTS

### Patient characteristics

During the study period, 348 symptomatic ED patients had both a chest CT and RT-PCR test for diagnosing COVID-19. The median age of these patients was 62 years and 61.4% were male [Table 1]. Most patients (74.5%) had one or more comorbidities. Cardiovascular comorbidity was highly prevalent, as was chronic pulmonary disease (27.0%).

### Diagnostic accuracy of chest computed tomography for coronavirus disease 2019 in all patients and subgroups

In total, 287 (82.4%) patients were admitted to the hospital. 96 patients had mild COVID-19 disease, 103 patients had moderate COVID-19 disease, 117 patients had severe COVID-19 disease, and 32 patients had ARDS. Of the chest CT scans, 243 (69.8%) were judged as suspicious for COVID-19. In 217 (62.3%) patients, the PCR was positive for SARS-CoV-2 [Table 2]. In 22 of these patients, a PCR was necessary on a second sample to confirm the suspected diagnosis, because the first PCR was negative or inconclusive. In total, 62.3% of patients had a positive PCR and 69.8% had a positive CT, resulting in a sensitivity of 94.2%, specificity 76.7%, and LR +2.94 and (LR) –0.18. Sensitivity was higher in patients with severe COVID-19 ( $n = 117$ , 98.5%) and with ARDS ( $n = 32$ , 100%) [Tables 2 and 3 and Figures 1–14].

### Diagnostic accuracy of the chest computed tomography in relation to disease severity

Of all patients, 57.1% were classified as mild/moderate COVID-19 disease according to categorization of COVID-19 suspected/confirmed patients into mild, moderate, and severe COVID-19 disease and ARDS as per the WHO guidelines and as per the Government of India guidelines [Table 3]. The sensitivity of the CT tended to be higher in those with ARDS (100.0%,  $P = 0.017$ ) and severe COVID-19 disease (98.5%,  $P = 0.027$ ) than in patients with mild COVID-19 disease (82.5%,  $P = 0.047$ ) and moderate COVID-19 disease (89.3%,  $P = 0.039$ ) [Table 3].

### Analysis of discordant computed tomography and polymerase chain reaction results

In 131 patients with a negative PCR, 94 CT scans were judged as not suspicious for COVID-19. The PPV was 74.4% and NPV 92.1%. In 48 (13.7%) patients, discordant findings between CT and PCR were observed. In most cases, the CT scan was considered suspicious for COVID-19, while the PCR was negative (37/48, 77.0%). In the majority of these, the diagnosis at discharge was pulmonary infection ( $n = 26$ ; 54.1%). Among these patients, 17 had other viral pathogens (influenza A virus:  $n = 4$ ; *Human metapneumovirus*:  $n = 8$ ; Rhinovirus:  $n = 3$ ; and non-COVID corona virus:  $n = 2$ ) isolated and in 9 patients, bacterial pathogens (mycoplasma [ $n = 6$ ] and chlamydia [ $n = 3$ ]) were isolated.

In 11 (3.1%) patients with a suspicious CT scan and a negative PCR, another diagnosis than pulmonary infection was made. Seven patients had another pulmonary diagnosis (bronchiectasis [ $n = 2$ ], asthma [ $n = 4$ ], and pleural effusion due to ascites [ $n = 1$ ]), while in 4 patients, a cardiac diagnosis (heart failure [ $n = 3$ ] and acute coronary syndrome [ $n = 1$ ]) was made.

In 11 (3.1%) patients, CT scans were not suspicious for COVID-19, while the PCR was positive. In 2 of these patients, a second PCR was positive after a first negative test. In these cases, the CT scan was not repeated to check for new abnormalities. In one patient, respiratory symptoms were present for <48 h, in 6 patients, symptoms were present for more than 48 h, and in 2 patients, symptom duration was not clear.

## DISCUSSION

In this cross-sectional study in patients presenting at the ED with a clinical suspicion of COVID-19, the results showed that 62.3% of patients had a positive PCR and 69.8% a positive CT, resulting in a sensitivity of 94.2%, specificity of 76.7%, and LR of + 2.94 and (LR) -0.18. The PPV was 74.4% and NPV 92.1%. In 86.3% of all patients, the results of the chest CT and the PCR test were concordant; however, in 3.1% of patients with a positive PCR, CT scans were not considered suspicious for COVID-19. In addition, in about 28.2% of patients

**Table 1: Demographics and patient characteristics**

<i>n</i> (%), median (IQR)	All patients ( <i>n</i> =348)
Demographics	
Age (years)	62 (44-78)
Male	214 (61.4)
Female	134 (38.5)
Comorbidity	
No comorbidity	72 (20.6)
Hypertension	92 (26.4)
Diabetes mellitus	46 (13.2)
Myocardial infarction	28 (8.0)
Cerebrovascular disease	12 (3.4)
Heart failure	17 (4.8)
Peripheral vascular disease	11 (3.1)
COPD	94 (27.0)
Malignancy	3 (0.8)
Chronic kidney disease	37 (10.6)
Chronic liver disease	18 (5.1)
Chest CT	
CT suspicious for COVID-19	243 (69.8)
RT-PCR	
PCR SARS-CoV2 positive	217 (62.3)
Admission	287 (82.4)

IQR: Interquartile range, COPD: Chronic obstructive pulmonary disease, CT: Computed tomography, COVID-19: Coronavirus disease 2019, RT: Reverse transcriptase, PCR: Polymerase chain reaction, SARS-CoV2: Severe Acute Respiratory Syndrome Coronavirus 2

**Table 2: Overview of chest computed tomography and polymerase chain reaction results**

	PCR SARS-CoV2 positive	PCR SARS-CoV2 negative	Total
CT suspicious for COVID-19	206	37	243
CT not suspicious for COVID-19	11	94	105
Total	217	131	348

CT: Computed tomography, COVID-19: Coronavirus disease 2019, PCR: Polymerase chain reaction, SARS-CoV2: Severe Acute Respiratory Syndrome Coronavirus 2

**Table 3: Diagnostic accuracy of chest computed tomography for diagnosing coronavirus disease-2019 in relation to disease severity**

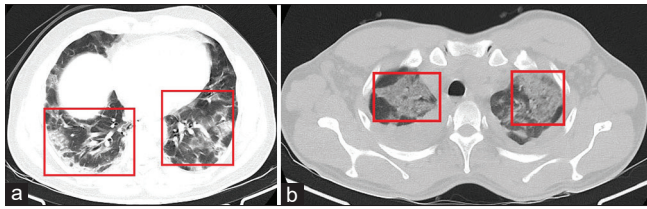
	<i>n</i> (%)	Sensitivity	Specificity	PPV	NPV	LR+	LR-
Total	348 (100)	94.2	76.7	74.4	92.1	2.94	0.18
Disease severity							
Mild	96 (27.5)	82.5	71.7	67.4	84.1	2.13	0.44
Moderate	103 (29.5)	89.3	72.1	70.3	89.7	2.89	0.17
Severe	117 (33.6)	98.5	68.4	75.2	95.3	2.91	0.03
ARDS	32 (9.1)	100.0	56.2	82.1	100.0	2.27	0.14

PPV: Positive predictive value, NPV: Negative predictive value, ARDS: Acute respiratory distress syndrome, LR: Likelihood ratio

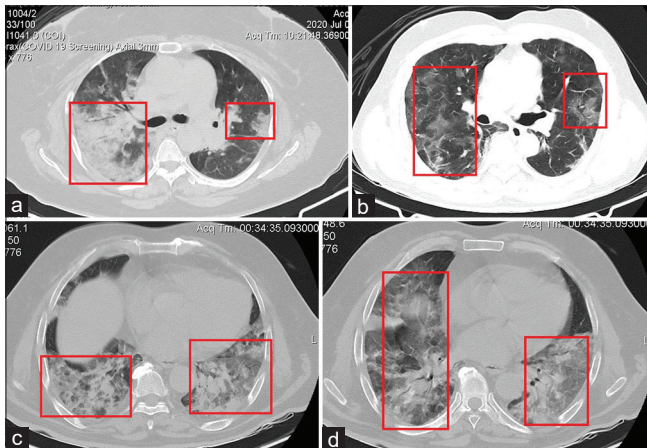
tested negative by PCR, the CT was positive. Most of these patients had a discharge diagnosis of pneumonia (70.2%), which was caused by another viral pathogen in 45.9% of patients.

The diagnostic ability of chest CT was found to be rather high, and in 86.3%, concordant findings of CT and PCR were found. Nevertheless, it should be noted that 4.7% of COVID-19 were missed and 9% were incorrectly assigned a suspected COVID-19. In a situation where isolating each patient separately is not possible, these



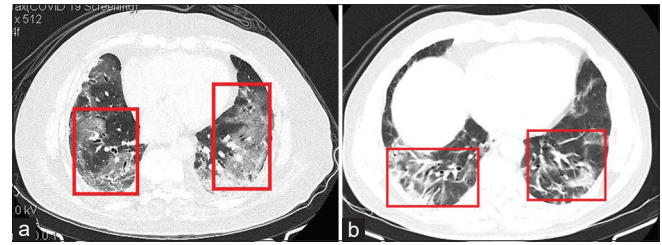


**Figure 1:** Axial computed tomography images in patients with coronavirus disease 2019 pneumonia. 62-year-old male, day 3 after symptom onset showing subpleural areas of mixed ground-glass opacities in basal segments of bilateral lower lobes (a). Follow-up computed tomography image on day 6 showing extensive consolidation in the posterior zone of left upper lobe and basal zone of right lower lobe (b)

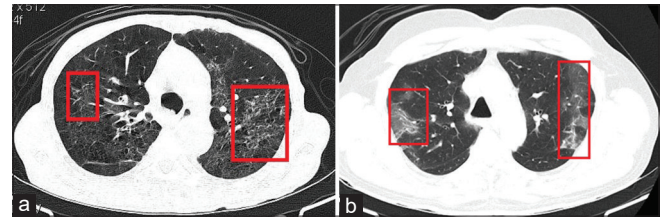


**Figure 3:** Axial computed tomography images in patients with coronavirus disease 2019 pneumonia. 60-year-old male, day 3 after symptom onset: focal ground-glass opacity associated with smooth interlobular and intralobular septal thickening in the right lower lobes (a). 71-year-old female, day 10 after symptom onset: bilateral, peripheral ground-glass opacity associated with smooth interlobular and intralobular septal thickening representing a crazy-paving pattern (b). 63-year-old female, day 20 after symptom onset: bilateral and peripheral predominant consolidation pattern with a round cystic change internally (c). 67-year-old female, day 17 after symptom onset: bilateral, peripheral mixed pattern associated with air bronchograms in both lower and upper lobes, with a small amount of pleural effusion (d)

patients are placed at a COVID-19 cohort, where they can be exposed to COVID-19 positive patients with possible devastating consequences. The results of diagnostic accuracy should be interpreted with care because it is known that both CT and PCR can be false negative in early stages of COVID-19.<sup>[17]</sup> This is why the current study included repeated PCRs and explored discordant test results, which showed that in about 45.9% of patients with false-positive CT scans, other viral pathogens were detected. This study was performed at the end of the respiratory virus season, and the added value of the CT scan might be lower during typical respiratory virus season. It can be argued, in addition, that with increasing incidence of COVID-19, and thus, a higher pre-test probability, the added value of the CT scan will decrease. In other studies, the sensitivity of chest CT for COVID-19 was found to be higher, up to 97% in a study with 1014 Chinese patients, but at the cost of



**Figure 2:** Axial computed tomography images in patients with coronavirus disease 2019 pneumonia. 44-year-old male, day 5 after symptom onset showing mixed ground-glass opacities in posterior segments of right upper lobe and basal segments of bilateral lower lobes (a). Follow-up computed tomography image on day 9 showing extensive consolidation in inferior segments of bilateral upper lobes and lower lobes (b)

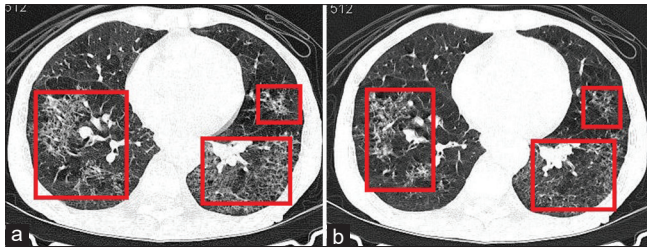


**Figure 4:** Serial axial computed tomography images in a 67-year-old female with coronavirus disease 2019, day 5 after symptom onset showing diffuse bilateral ground-glass opacities with focal consolidations (mixed pattern) and reticulations in the lower lobes (a). Also note the subpleural sparing seen in these lesions (b)

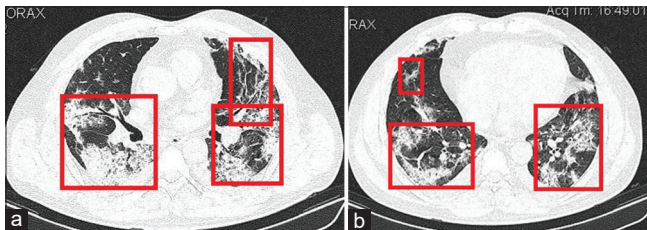
low specificity (25%).<sup>[12]</sup> In another study in 81 Chinese patients with PCR-proven COVID-19, sensitivity was 93%.<sup>[18]</sup> A lower sensitivity of 80% was reported in 30 symptomatic cruise ship passengers.<sup>[13]</sup> In contrast, PCR was found to be negative in 71% of 51 Chinese patients, of whom 98% had CT abnormalities.<sup>[19]</sup> The current study included all chest CTs with abnormalities that could be related to COVID-19 as suspicious, even though the changes were judged to be more likely non-COVID-19-related pneumonia. Considering these cases negative would have improved the specificity, but at the cost of lower sensitivity. In addition, as COVID-19 is a new disease, and the first patient with COVID-19 presented in our hospital on February 15, 2020, and it is possible that with increasing experience the accuracy of the judgment of the chest CT will improve over time. In the current study, main CT features were ground-glass opacity (95%) and basal consolidation (89%) with a subpleural distribution (100%). Other CT features included air bronchogram (57%), vascular enlargement (67%), interlobular septal thickening (62%), and ARDS (9.1%). Lymphadenopathy and pleural effusions were rarely encountered. The CT findings in the current study were consistent with findings of previously published studies.<sup>[5,10,13,18,20-22]</sup>

Evaluation of discharge diagnosis revealed that in 6 (12.5%) of discordant, “false-positive” CT scans, COVID-19 was found likely by the clinicians. Taking these cases into account, the sensitivity of the CT scan increases

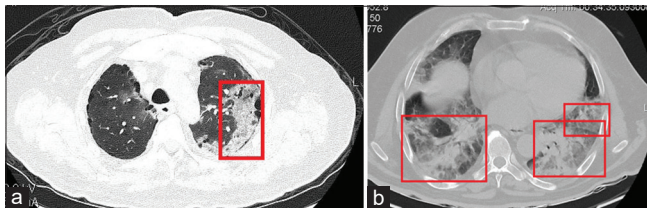




**Figure 5:** Serial axial computed tomography images in a 60-year-old male with coronavirus disease 2019, day 4 after symptom onset showing bilateral peripheral ground-glass opacities with organizing consolidations (mixed pattern) (a). There is also "reversed halo" appearance of central ground glass opacity surrounded by denser consolidation (b)



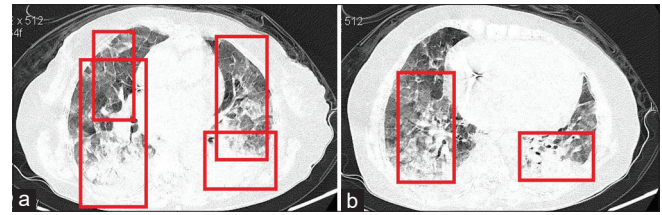
**Figure 7:** Axial computed tomography image in an 81-year-old female with coronavirus disease 2019, day 3 after symptom onset showing ground glass opacification (a). Computed tomography image obtained on day 7 shows ground glass opacification has progressed to airspace consolidation (b)



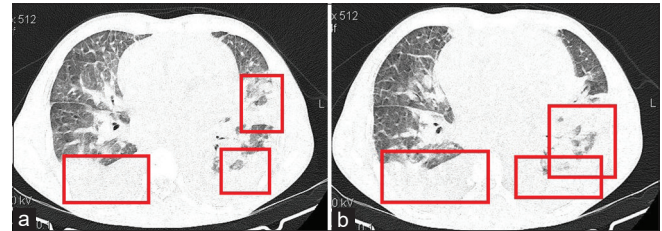
**Figure 9:** Axial computed tomography images in a 63-year-old female with coronavirus disease 2019, day 7 after symptom onset showing patchy consolidation and fibrosis (a) subsequently progressing to organizing pneumonia on day 11 (b)

to 94.2% and specificity to 76.7%. Of the patients with false-negative chest CTs (3.1%), only one patient had a documented short duration of symptoms (<48 h). In total, 22 PCRs were needed to diagnose COVID-19, which underlines the importance of good sampling and repeated testing to definitely exclude COVID-19 in symptomatic patients.

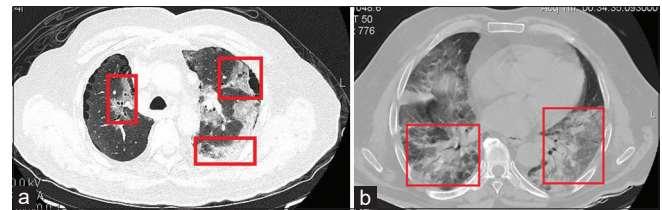
Not surprisingly, the sensitivity of the CT scan was higher in the more severely ill patients. This finding was reported in other studies as well. These findings are not surprising, because in more severe disease, more abnormalities can be expected to be found on the chest CT.<sup>[23]</sup> Interestingly, most patients (63.2%) presented with moderate/severe COVID-19 disease. The main advantage of the CT scan is that the results were available almost immediately after scanning, in contrast to the PCR test, which may take up to 24 h, although this usually takes less time. During this timeframe, highly suspicious patients are kept in



**Figure 6:** Serial axial computed tomography images in a 54-year-old male with coronavirus disease 2019, day 7 after symptom onset showing round areas of mixed ground-glass opacity and consolidation at level of aortic arch (a) and ventricles (b) in right and left lower lobe posterior zones, and upper zones



**Figure 8:** Serial axial computed tomography images in a 31-year-old male with coronavirus disease 2019, day 3 after symptom onset showing multifocal mixed ground-glass opacities with peripheral distribution (a), and air bronchogram can be found in left lower lobe ground-glass opacities (b)

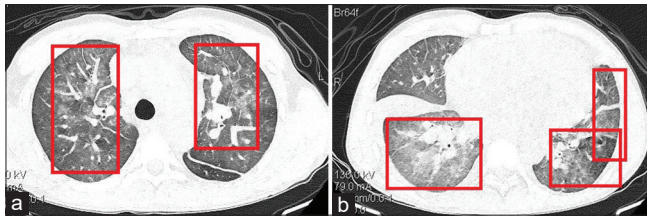


**Figure 10:** Axial computed tomography image in a 40-year-old male with coronavirus disease 2019, day 5 after symptom onset showing peripheral distribution of patchy ground-glass opacities plus reticular pattern (a). Follow-up computed tomography image obtained on day 9 shows peripheral plus central distribution of ground-glass opacities, partial consolidation, and fibrosis streak (b)

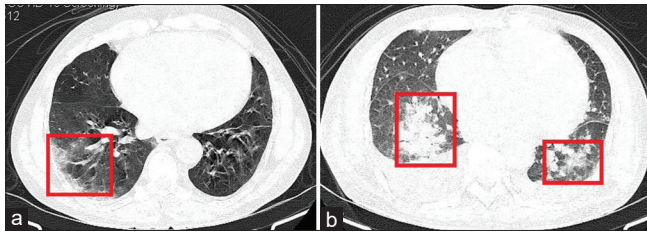
isolation, awaiting the PCR results. A chest CT scan can help differentiate those with high risk (suspicious CT) and those with low risk of COVID-19 (nonsuspicious CT). It would be interesting to investigate whether combining the results of chest CT with clinical characteristics would increase the discriminatory value, which is extremely important especially if patients have to be placed in cohorts.

Primary CT findings of COVID-19 in the 1<sup>st</sup> week of infection are ground-glass and/or consolidative opacities, crazy paving appearance, and bronchovascular thickening with a pattern that is usually bilateral, peripheral, and basal. Pleural effusions and mediastinal lymphadenopathy are rare.<sup>[24]</sup> A reticular pattern associated with interlobular septal thickening was noted to increase progressively from the 2<sup>nd</sup> week, suggesting the development of fibrosis. Mixed pattern of consolidation was observed commonly in the 3<sup>rd</sup> week of symptom onset and ground-glass opacities





**Figure 11:** Serial axial computed tomography images in a 67-year-old female with coronavirus disease 2019, day 3 after symptom onset showing bilateral diffuse ground-glass opacities (a) and reticulation (b)



**Figure 13:** Axial computed tomography image in a 57-year-old male with coronavirus disease 2019, day 1 after symptom onset showing pure ground glass opacity in the right lower lobe (a). Follow-up computed tomography image on day 7 showing consolidation in the bilateral lower lobes (b)

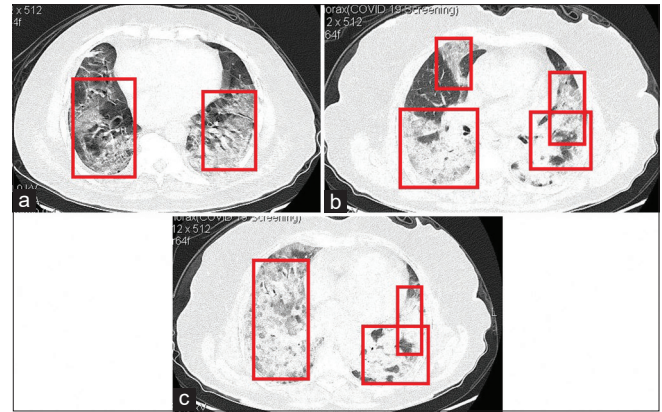
decreased further.<sup>[18]</sup> Chest CT features of COVID-19 are related to the stage of disease, the severity of lung injury, and comorbidities. Characteristic sonological findings include small multifocal and nontranslobar consolidations, irregular and thickened pleural lines, and multifocal and confluent B lines.<sup>[24]</sup> In a study on 138 patients who had been hospitalized, common complications encountered in COVID-19 were ARDS, acute cardiac injury with resultant elevated troponin levels, sepsis, and multiorgan failure.<sup>[25]</sup>

Atypical CT imaging manifestations include the following:

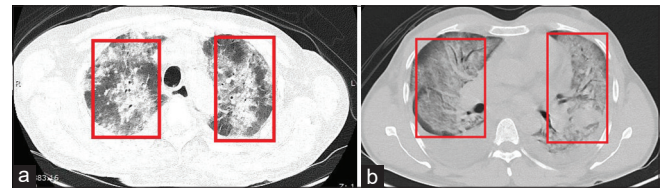
1. Single, or multiple, or extensive subpleural honeycomb-like thickening of interlobular septum, thickening of the bronchial wall, and tortuous and thick strand-like opacities. Several patchy consolidations, occasionally with a small amount of pleural effusion or enlargement of mediastinal lymph nodes
2. Single or multiple solid nodules or consolidated nodules in the center of lobule, surrounded by ground-glass opacities.

### Temporal change in the findings

During the early part of the outbreak, the hospitals in Wuhan, China, were extensively using CT scans for screening patients with symptoms suggestive of novel coronavirus infection. Some studies showed better sensitivity for CT as compared to RT-PCR assay performed within 3 days of onset of symptoms.<sup>[19]</sup> The arguments in favor of such extensive use of CT were that RT-PCR tests of the sputum or nasopharyngeal swabs require several days with a false-negative rate of more than 5% whereas CT imaging can show typical features of COVID-19 helping to rapidly screen and stratify patients.<sup>[20]</sup> Concerns were raised against such sweeping conclusions of the superiority



**Figure 12:** Serial axial computed tomography images in a 55-year-old male with coronavirus disease 2019, day 7 after symptom onset showing multiple ground-glass opacities and septal thickening, the imaging manifestation is the so-called "white lungs" (a-c)



**Figure 14:** Axial computed tomography image in a 77-year-old female with coronavirus disease 2019, day 2 after symptom onset showing slight reticular pattern in the bilateral lower lobes and subpleural areas (a). Axial computed tomography image in a 36-year-old female with coronavirus disease 2019, day 7 after symptom onset showing reticular pattern superimposed on the background of GGO – crazy paving appearance with "white out" lungs in the right middle lobe and bilateral lower lobes (b)

of CT scans for the screening citing several reports that confirmed normal chest CT scan cannot exclude the diagnosis of COVID-19,<sup>[26]</sup> especially for patients with early onset of symptoms. CT scans were normal in 11%–56% of confirmed admitted cases during the early course of the diseases after the onset of symptoms but showed findings in the latter course of the disease.<sup>[21]</sup> However, as the sensitivity of RT-PCR tests improved, the focus of studies shifted from using CT as a diagnostic tool to a prognostication test. A recent study from Italy reported perilesional pulmonary vessel enlargement in areas of lung infiltrates could be an early predictor of lung impairment.<sup>[27]</sup> Even though this finding was reported in several previous studies, no clear relationship to the prognosis of the patients is reported.<sup>[22]</sup>

### Temporal course of the disease

Most of these studies were cross-sectional studies, describing the CT findings at either initial presentation or during advanced symptoms. Among the 49 studies included in this review, there were only 14 studies, which included a total of 762 patients, which have described changes in the CT findings throughout the disease process. Chen *et al.*,<sup>[28]</sup> Wang *et al.*,<sup>[25]</sup> and Pan *et al.*<sup>[29]</sup> reported the temporal changes in a series of 249, 90, and 63 patients,

respectively. All these studies described a similar trend of changes. At the initial presentation, the common changes were patchy ground-glass densities or consolidations in subpleural lower lobe distributions. Re-examination scans done after 3–14 days showed progression and confluence of the GGO and consolidation leading to organizing pneumonia-like appearance in patients with worsening of symptoms. Some patients showed intralobular septal thickening during this phase giving the classical “crazy-paving” appearance. If the initial scans showed nodules, the re-examination showed a reduction in the density of these nodules and merging of these nodules, leading to a ground-glass-like density described as “melting sugar” appearance by Pan *et al.*<sup>[29]</sup> Typically patients with a clinical improvement developed fibrotic stripes on these re-examination CT scans. In patients with further deterioration, needing intensive care unit (ICU) admission, the appearance was like a “white-lung” with diffuse high-density lesions in bilateral lungs.

Stage-based CT imaging manifestations<sup>[30]</sup> include the following:

The CT imaging demonstrates three stages according to the time of onset and the response of body to COVID-19, including:

1. Early stage: This stage refers to the period of 1–3 days after clinical manifestations. CT manifestations include single or multiple scattered patchy or agglomerated ground-glass opacities, separated by honeycomb-like or grid-like thickened of interlobular septa
2. Rapid progression stage: This stage refers to the period about 3–7 days after clinical manifestations started. CT manifestations include a fused and large-scale light consolidation with air bronchogram sign
3. Consolidation stage: This stage refers to the period around 7–14 days after clinical manifestations appeared. CT manifestations include multiple patchy consolidations in slighter density and smaller range than that of the previous stage.

### False-positive computed tomography findings

CT findings of patients with negative results for RT-PCR tests were discussed only in 8 studies and included 530 (13%) patients out of 4145 patients. Considering only studies reporting negative results, the proportion of negative cases to positive cases was 34% (out of 1631 cases). In the large series reported by Ai *et al.*<sup>[12]</sup> of 1014 patients admitted in Wuhan, there were 431 (41%) patients with negative RT-PCR results and 308 of these patients had positive chest CT scans (75%), while 97% (580/601) of the positive cases had positive chest CT scans. All these patients were classified as having typical features of COVID-19 on CT scans. Such a high false positivity rate and low specificity (25%) can be explained by the fact that these cases were from the largest hospital in Wuhan, the central area of the outbreak during that period and many symptomatic patients with findings on chest CT were suspected to have COVID 19 disease to control the epidemic. In another series reported by

Zhu *et al.*,<sup>[31]</sup> out of 116 patients, 84 were negative for the presence of COVID-19 and 32 were positive. Chest CT was performed in all these patients. 94% of the positive cases (30/32) and 67% of the negative cases (56/84) had changes of pneumonia on CT with bilateral involvement seen in 91% (29/32) and 40% (34/84) respectively. The most observed finding of GGO in other series were seen in only 47% of the cases in these series, whereas the more specific findings of a spider web pattern and crazy paving patterns were observed in even fewer patients, 13% (4 patients) and 3% (1 patient) respectively. GGO was observed in 12% of the negative cases also.

In a retrospective study by Cheng *et al.*,<sup>[32]</sup> that included 38 patients with clinical and epidemiological features consistent with COVID 19, 22 patients had negative RT-PCR findings for SARS-CoV-2. 11 patients had positive results. CT showed GGO in 90% (20/22) of the negative patients and all the positive patients whereas mixed GGO was observed in 72.7% (16/22) of the negative patients and 63.6% (7/11) of the positive cases. Consolidation was more frequently observed in negative cases (77.3%) as compared to 54.5% of positive cases. The etiology of the negative cases in the study remains unclear as these patients were rapidly discharged and could not be microbiologically confirmed. These studies demonstrate that the specificity of the most commonly reported CT findings of GGO and consolidation is too low to be able to use them as diagnostic features.

### Role of computed tomography in initial false-negative reverse transcriptase polymerase chain reaction cases

Fang *et al.*,<sup>[19]</sup> have reported better sensitivity of CT as compared to RT-PCR at initial patient presentation. Among the 51 consecutive patients that they studied, only one had a normal CT scan at presentation. Of the 50 patients with abnormal CT scans at presentation, 36 (72%) had typical manifestations and 28%<sup>[14]</sup> had atypical manifestations. The initial RT-PCR test was positive in only 70%<sup>[33]</sup> patients, the second test is done in 1–2 days added 24%<sup>[12]</sup> more positive cases. Two more patients turned positive by the third test (2–5 days) and one patient showed positivity on the fourth test done 7 days after the initial onset of the symptoms. Even though the observations by the authors of better sensitivity at the initial presentation might seem right, the standard recommendation for declaring a patient negative for COVID-19 is the demonstration of negativity for SARS nCoV-2 genes in two consecutive tests done 24 h apart. Following these criteria would have diagnosed 48 (94%) patients in this study within 2 days, even before the CT scan was performed. The average time from initial symptom onset to CT scan was  $3 \pm 3$  days in this study.

Similarly, in a study of 167 patients by Xie *et al.*,<sup>[7]</sup> there were 5 patients (3%) with negative RT-PCR results during initial tests who turned positive on repeat testing. Bilateral multifocal GGO was observed in all these five patients. For a fair comparison, CT was negative in 7 RT-PCR positive patients (4%) at presentation. Despite the conclusions by all these authors that CT is better for screening evaluation



for COVID-19, critical evaluation of their results shows no clear evidence for the same.

### **Pediatric patients have asymptomatic computed tomography changes**

Among the studies in this review, two studies discussed CT features of a total of 23 pediatric patients. Contact history and clinical symptoms of fever and cough were positive for all these patients. 7 patients had no findings on CT scans, 6 patients had unilateral and 10 patients' bilateral lung field changes on CT scans. In the report by Xia *et al.*,<sup>[34]</sup> 60% of the pediatric patients had GGO and 50% had consolidation with positive "halo" sign. 21 out of these 23 patients eventually recovered with two of them under observation until the time of the report. The initial findings and the longitudinal changes throughout the disease were found to be similar to adult patients with the initial patchy GGOs and consolidations progressing to diffuse lesions with septal thickening, air bronchograms in the advanced stages, finally resolving completely or with residual fibrotic strips.

### **Chest computed tomography severity score assessment**

Yang *et al.*<sup>[35]</sup> developed Chest CT Severity Score to rapidly identify patients with severe forms of COVID-19. According to the anatomical structure, the 18 segments of both lungs were divided into 20 regions, in which the posterior apical segment of the left upper lobe was subdivided into apical and posterior segmental regions, while the anteromedial basal segment of the left lower lobe was subdivided into anterior and basal segmental regions. The lung opacities in all of the 20 lung regions were subjectively evaluated on chest CT using a system attributing scores of 0, 1, and 2 if parenchymal opacification involved 0%, <50%, or equal or more than 50% of each region. The CT-SS was defined as the sum of the individual scored in the 20 lung segment regions, which may range from 0 to 40 points.

### **COVID-19 Reporting and Data System**

In March 2020, the "COVID-19 standardised reporting working group" of the Dutch Association for Radiology (NVvR) proposed a CT scoring system for COVID-19.<sup>[33]</sup> They called it CO-RADS (COVID-19 Reporting and Data System) to ensure CT reporting is uniform and replicable. This assigns a score of CO-RADS 1–5, dependent on the CT findings. In some cases, a score of 0 or 6 may need to be assigned as an alternative. If the CT is uninterpretable, it is CO-RADS 0, and if there is a confirmed positive RT-PCR test, it is CO-RADS 6. On 16 March, 2020, an American-Singaporean panel published that CT findings were not part of the diagnostic criteria for COVID-19.<sup>[36]</sup>

### **Recommendations of the WHO on the use of chest imaging in coronavirus disease 2019 (dated June 11, 2020)**

- R1 - For asymptomatic contacts of patients with COVID-19, the WHO suggests not using chest imaging for the diagnosis of COVID-19
- R2.1 - For symptomatic patients with suspected COVID-19, the WHO suggests not using chest imaging

for the diagnostic workup of COVID-19 when RT-PCR testing is available with timely results

- R2.2 - For symptomatic patients with suspected COVID-19, the WHO suggests using chest imaging for the diagnostic workup of COVID-19 when: (1) RT-PCR testing is not available; (2) RT-PCR testing is available, but results are delayed; and (3) initial RT-PCR testing is negative, but with high clinical suspicion of COVID-19
- R3 - For patients with suspected or confirmed COVID-19, not currently hospitalized and with mild symptoms, the WHO suggests using chest imaging in addition to clinical and laboratory assessment to decide on hospital admission versus home discharge
- R4 - For patients with suspected or confirmed COVID-19, not currently hospitalized and with moderate to severe symptoms, the WHO suggests using chest imaging in addition to clinical and laboratory assessment to decide on regular ward admission versus ICU admission
- R5 - For patients with suspected or confirmed COVID-19, currently hospitalized and with moderate to severe symptoms, the WHO suggests using chest imaging in addition to clinical and laboratory assessment to inform therapeutic management
- R6 - For hospitalized patients with COVID-19 whose symptoms are resolved, the WHO suggests not using chest imaging in addition to clinical and/or laboratory assessment to inform the decision regarding discharge.

### **The role of chest imaging in patient management during the coronavirus disease 2019 pandemic - A multinational consensus statement from the Fleischner society**

This consensus statement is based on expert opinion among a panel of 15 thoracic radiologists, 10 pulmonologists and/or intensivists (including one anesthesiologist), and one pathologist, as well as additional experts in emergency medicine, infection control, and laboratory medicine. The panel included individuals from the United States, Italy, China, Germany, France, the United Kingdom, the Netherlands, South Korea, Canada, and Japan, representing nine of the 15 countries with the highest number of confirmed COVID-19 cases reported worldwide as of April 1, 2020. Structured around three scenarios and three key situations, this Fleischner statement provides context for the use of imaging to direct patient management during the COVID-19 pandemic in different practice settings, different phases of epidemic outbreak, and environments of varying critical resource availability.

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

- This statement focuses exclusively on the use of chest radiography and CT of the thorax. Although US has been suggested as a potential triage and diagnostic tool for COVID-19 given the predilection for the disease in subpleural regions, there is limited experience at this time as well as infection control issues
- CT is more sensitive for early parenchymal lung disease, disease progression, and alternative diagnoses including acute heart failure from COVID-19 myocardial injury and when performed with intravenous contrast material, pulmonary thromboembolism
- Avoidance of nonvalue added imaging is particularly important in the COVID-19 patient population to minimize exposure risk of radiology technologists and to conserve PPE
- Patients with functional impairment after recovery from COVID-19 should undergo imaging to differentiate between expected morphologic abnormalities as sequelae of infection, mechanical ventilation, or both versus a different and potentially treatable process
- Although CT findings of COVID-19 infection are nonspecific, their presence in an asymptomatic patient with no or mild respiratory symptoms is concerning in a setting of known community transmission, particularly if there is no better alternative diagnosis.

### Limitations of the study

External validity may be limited in the current study due to its single-center setup. In addition, especially in patients with mild symptoms who were not admitted to the hospital, no second PCR-testing was done after an initial negative result. A third limitation is that many patients who were seriously ill were included in the study.

### CONCLUSION

High diagnostic accuracy of chest CT findings with typical and relatively atypical CT manifestations of COVID-19 leads to a low rate of missed diagnosis. However, chest CT should be reserved for patients with limited to severe respiratory complications unexplained by CXR. Characteristic CT chest findings of COVID-19 include bilateral, basal, pure GGO, mixed GGO, small multifocal, peripheral, translobar, and nontranslobar consolidations. Normal chest CT can be found in RT-PCR positive COVID-19 cases, and typical CT manifestations can be found in RT-PCR negative cases. Therefore, we recommend a combination of both CT and RT-PCR for future follow-up, management and medical surveillance. Radiologists and chest physicians should be familiar with the radiological appearances of COVID-19-related pulmonary syndrome as imaging has a critical role in diagnosing, monitoring disease progression and prognostic follow-up. However, the current guidelines are in the process of constant review as COVID-19 pandemic continues to showcase its effect on the health system of developed and developing countries of the world

alike. For the first time in the era of modern medicine, all of humankind is facing the same threat considering the contagiousness of the coronavirus and the need to reduce nosocomial outbreaks. This also gives us ample opportunity to change our research approach that involves better understanding of disease manifestations and to further explore and promote the applications of chest CT for the safe management of patients and health personnel in the setting of pandemics like the present COVID-19 outbreak and threats we might encounter in the near future. Research findings need to be shared amongst countries to provide best health care to humankind during these uncertain times of a pandemic.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

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