Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

CHEST

Chest CT Imaging Signature of Coronavirus Disease 2019 Infection

In Pursuit of the Scientific Evidence

Hugo J. A. Adams, MD, PhD; Thomas C. Kwee, MD, PhD; Derya Yakar, MD, PhD; Michael D. Hope, MD; and Robert M. Kwee, MD, PhD

BACKGROUND: Chest CT may be used for the diagnosis of coronavirus disease 2019 (COVID-19), but clear scientific evidence is lacking. Therefore, we systematically reviewed and meta-analyzed the chest CT imaging signature of COVID-19.

RESEARCH QUESTION: What is the chest CT imaging signature of COVID-19 infection?

STUDY DESIGN AND METHODS: A systematic literature search was performed for original studies on chest CT imaging findings in patients with COVID-19. Methodologic quality of studies was evaluated. Pooled prevalence of chest CT imaging findings were calculated with the use of a random effects model in case of between-study heterogeneity (predefined as $I^2 \geq 50$); otherwise, a fixed effects model was used.

RESULTS: Twenty-eight studies were included. The median number of patients with COVID-19 per study was 124 (range, 50-476), comprising a total of 3,466 patients. Median prevalence of symptomatic patients was 99% (range, >76.3%-100%). Twenty-seven of the studies (96%) had a retrospective design. Methodologic quality concerns were present with either risk of or actual referral bias (13 studies), patient spectrum bias (eight studies), disease progression bias (26 studies), observer variability bias (27 studies), and test review bias (14 studies). Pooled prevalence was 10.6% for normal chest CT imaging findings. Pooled prevalences were 90.0% for posterior predilection, 81.0% for ground-glass opacity, 75.8% for bilateral abnormalities, 73.1% for left lower lobe involvement, 72.9% for vascular thickening, and 72.2% for right lower lobe involvement. Pooled prevalences were 5.2% for pleural effusion, 5.1% for lymphadenopathy, 4.1% for airway secretions/tree-in-bud sign, 3.6% for central lesion distribution, 2.7% for pericardial effusion, and 0.7% for cavitation/cystic changes. Pooled prevalences of other CT imaging findings ranged between 10.5% and 63.2%.

ABBREVIATIONS: COVID-19 = coronavirus disease 2019; RT-PCR = real-time reverse transcriptase polymerase chain reaction

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INTERPRETATION: Studies on chest CT imaging findings in COVID-19 suffer from methodologic quality concerns. More high-quality research is necessary to establish diagnostic CT criteria for COVID-19. Based on the available evidence that requires cautious interpretation, several chest CT imaging findings appear to be suggestive of COVID-19, but normal chest CT imaging findings do not exclude COVID-19, not even in symptomatic patients.

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KEY WORDS: chest; COVID-19; CT; meta-analysis; systematic review

Coronavirus disease 2019 (COVID-19) has been designated a pandemic by the World Health Organization, continues to disseminate rapidly around the globe, and poses a major public health problem.[1] Many countries are using a combination of containment and mitigation activities to battle the spread of COVID-19 infection, with the primary aim to delay major surges of patients and to level the demand for hospital beds, while protecting the most vulnerable from infection.[1] Screening of patients with suspected COVID-19 infection is crucial for hospitals to keep those who actually are infected strictly isolated from other patients and health care workers without COVID-19 infection.

Real-time reverse transcriptase polymerase chain reaction (RT-PCR) assay of nasal and pharyngeal swab specimens is currently the gold standard for the diagnosis of COVID-19.[2] However, it generally takes several hours before the results of RT-PCR testing become available, and its sensitivity is insufficient to reliably exclude COVID-19 due to factors like sampling or laboratory errors.[3-6] RT-PCR testing therefore should be repeated in those individuals with a persistent clinical suspicion of COVID-19 infection.[3-6] Altogether, RT-PCR testing is rather time-consuming and suboptimal for the rapid triaging of patients.

Meanwhile, several reports have indicated a possible role for chest CT scans in the diagnosis of this disease.[3,7-9] Chest CT scanning may be used for the diagnosis of COVID-19 infection in several settings. First, health care institutions that adopt a strategy of containment may decide to use chest CT scanning for the evaluation of patients in whom COVID-19 needs to be excluded, in addition to RT-PCR. Second, chest CT scanning may have a potential role as a problem-solving diagnostic tool in patients in whom RT-PCR testing remains negative, despite persistent clinical suspicion. Third, CT scans that are performed as part of standard clinical care, for reasons other than COVID-19 evaluation (eg, oncologic follow-up CT scans), may reveal lung abnormalities that can suggest the diagnosis of COVID-19, even in asymptomatic individuals.[3,7-9] Given the diagnostic potential of chest CT scanning, it is imperative for radiologists to have knowledge of the typical imaging characteristics of COVID-19 infection. Although several previous studies have described chest CT characteristics of COVID-19 infection, these individual studies may suffer from low sample sizes and differences in study design and methods. Of interest, the Fleischner Society recently published an expert opinion statement on the use of chest imaging (including radiography and CT scanning) in patient treatment during the COVID-19 pandemic, with the intent to offer guidance to physicians on the use of thoracic imaging across a breadth of health care environments.[10] However, the Fleischner Society also acknowledged that the evidence base that supported the use of imaging across the scenarios presented was scant and that their advice may undergo refinement through rigorous scientific investigation.[10] A systematic review and meta-analysis is required to overcome the limitations of individual studies and to provide an up-to-date overview that can be used to optimize the diagnostic interpretation of chest CT scanning for COVID-19 infection.

The purpose of this study was to review systematically and meta-analyze the chest CT imaging signature of COVID-19 infection.

Materials and Methods

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline.[11]

Systematic Literature Search

A search in Medline and Embase was performed for studies that reported the prevalence of chest CT imaging findings in patients with COVID-19 infection (Corona OR Coronavirus OR Covid-19

OR SARS-Cov-2 OR 2019nCoV OR Wuhan-virus) AND (Computed tomography OR Computerized tomography OR Computed tomographic OR CT OR CAT OR HRCT). In addition, the journal *Radiology: Cardiothoracic Imaging* (articles published by this journal are not listed in Medline/Embase yet) was searched manually for potentially relevant articles. The search was updated until May 17, 2020.

Study Selection

Original studies that reported the prevalence of chest CT imaging findings in patients with RT-PCR or gene sequencing confirmed COVID-19 were eligible for inclusion. Only studies that provided a detailed description of chest CT imaging findings according to the glossary of terms for thoracic imaging of the Fleischner Society[12] were included. Reviews, conference abstracts, editorials, case reports/series, and studies that involved <50 patients were excluded. Studies that enrolled patients from the same hospital in the same inclusion period as another larger study were excluded.

With the use of the aforementioned selection criteria, titles and abstracts of studies were reviewed. Full-text versions of potentially eligible articles were retrieved. Full-text articles were then scrutinized to determine definitively whether the study was eligible for inclusion. Study selection was performed independently by two reviewers (H. J. A. A. and R. M. K). Any discrepancies were solved by consensus with a third reviewer (T. C. K).

Study Quality Assessment

Quality of included studies was assessed. Study quality aspects were adopted from the Quality Assessment of Diagnostic Accuracy Studies tool[13] and edited according to our study research question (Table 1).

Study Data Extraction

For each included study, publication date, country of origin, study design (retrospective or prospective), number, sex, and age of included patients, inclusion criteria, number of symptomatic patients, duration of symptoms before chest CT scanning, disease severity (based on reported descriptive data), chest CT interpreters, and time interval between chest CT scanning and RT-PCR/gene sequencing were extracted. For each included study, the frequency of chest CT imaging findings (ie, normal findings and all individually reported lung abnormalities according to the glossary of terms for thoracic imaging of the Fleischner Society[12] on a patient level) were extracted.

Statistical Analysis

Prevalences of chest CT imaging findings were pooled if supported by data from at least two studies. Between-study heterogeneity was assessed with the I^2 statistic. Pooled prevalences were calculated with the use of a random effects model in case of heterogeneity (predefined as $I^2 \geq 50$); otherwise, a fixed effects model was used. Statistical analyses were performed with the Open Meta Analyst software package.

Results

Literature Search

The study selection is given in Figure 1; 165 studies were potentially eligible for inclusion. After we reviewed the full text, 137 studies were excluded (e-Appendix 1). Finally, 28 studies that were published between February 20 and May 15, 2020, were included. [14-41] Principal study characteristics are displayed in e-Table 1. The median number of patients with COVID-19 per study was 124 (range, 50-476); a total of 3,466 patients were included in this systematic review. Median prevalence of symptomatic patients was 99% (range, >76.3-100%). Reported duration of symptoms before chest CT scanning varied from 0 to 39 days, whereas reported disease severity varied from mild to critical. The frequencies of chest CT imaging findings that were reported by individual studies are shown in e-Table 2.

Methodologic Quality Assessment

The methodological quality assessment is displayed in Table 2. Risk of bias with respect to method of patient selection was rated "unclear" in 13 studies,[14,20-23,27,28,32-34,36,38,41] because these studies did not report whether patients were randomly or consecutively included. Risk of bias with respect to patient spectrum was rated "high" in eight

TABLE 1] Criteria Used to Assess the Methodologic Quality of Included Studies

Quality Items[a]	Signaling Questions[a]
Method of patient selection	Were patients randomly or consecutively included?
Patient spectrum	Was a sample of patients with coronavirus disease 2019 included?
Flow and timing	Was the interval between chest CT scan and real-time polymerase chain reaction or gene sequencing adequately short (ie, ≤72 h)?
Interobserver variation	Was the degree of observer variation in chest CT image interpretation reported?
Blinding to reference standard	Were the interpreters of chest CT image blinded to real-time polymerase chain reaction or gene sequencing results?

Adapted from Whiting P et al[13] and edited according to our study research question.
[a]Each quality item was rated as at "low risk," "high risk," or "unclear" risk of bias. If the signaling question that belonged to a quality item was answered with "yes," then the quality item was considered at low risk of bias. If the signaling question that belonged to a quality item was answered with "no," then the quality item was considered at high risk of bias. If the signaling question that belonged to a quality item could not be answered with "yes" or "no," then the quality item was considered at unclear risk of bias.

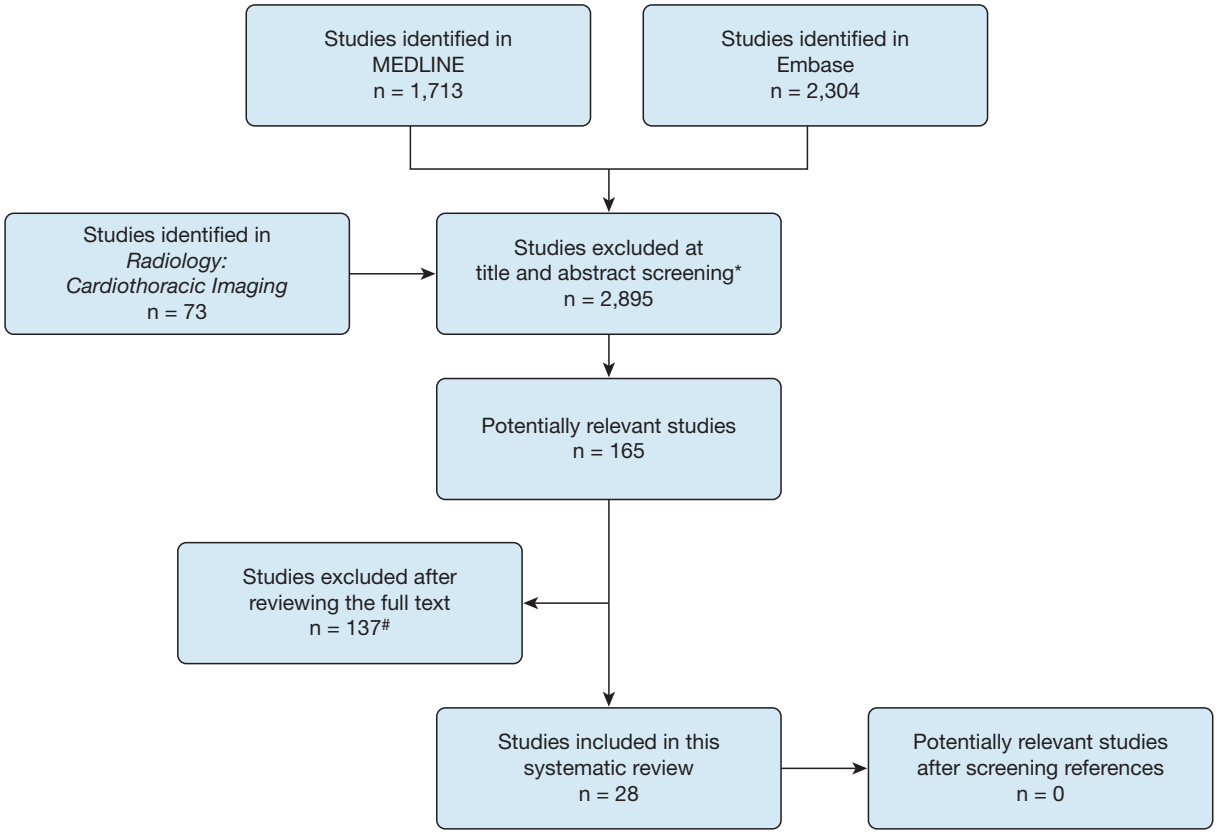

Figure 1 – *Flowchart of the study selection process. The asterisk indicates that, after duplicates were discarded, 3,060 articles remained. The number sign indicates that 72 studies were excluded because they included <50 patients, that 46 studies were excluded because they did not provide a detailed description of chest CT imaging findings, that 13 studies were excluded because of (potential) duplicate reporting of patient data, that four studies were excluded because of reporting the sum of findings of multiple chest CT scans performed in the same patients at different times, that one study was excluded because it evaluated the value of CT scans of other regions of the body than the chest, and that one study was excluded because it included patients without real time polymerase chain reaction-confirmed coronavirus disease 2019 infection (e-Appendix 1).*

studies,[14,19,20,23,25,29,31,38] because these studies excluded patients with normal chest CT imaging findings. Risk of bias with respect to patient spectrum was rated "unclear" in two studies,[34,39] because the number of patients with normal chest CT imaging findings was not reported. Risk of bias with respect to flow and timing was rated "unclear" in 24 studies,[15,16,18-24,26-32,34-41] because these studies did not report the time interval between CT scanning and RT-PCR/gene sequencing. Risk of bias with respect to flow and timing was rated "high" in two studies,[14,25] because the time interval between CT and RT-PCR procedures exceeded 72 hours (maximum of 7 and 14 days, respectively). Risk of bias with respect to observer variation was rated "high" in 27 studies,[14-38,40,41] because these studies did not report data on observer agreement. Finally, risk of bias in the domain blinding to the reference standard was rated "unclear" in 14 studies,[15,16,20,22,23,27,30-32,34-37,41] because these studies did not report whether the interpreters of chest CT scans were blinded to the RT-PCR results.

Pooled Prevalences of Chest CT Imaging Findings

Pooled prevalences of chest CT imaging findings in patients with COVID-19 are shown in Table 3. Pooled prevalence of normal chest CT imaging findings was 10.6% (95% CI, 7.6%-13.7%). Pooled prevalences of multifocal (Figs 2, 3, 4, 5), diffuse (Fig 6), and single/focal involvement of the lungs were 63.2% (95% CI, 38.8%-87.6%), 26.4% (95% CI, 9.3%-43.5%), and 10.5% (95% CI, 4.3%-16.7%), respectively.

Location of Lung Abnormalities: Pooled prevalence of bilateral involvement was 75.8% (95% CI, 70.5%-81.1%), whereas pooled prevalence of unilateral involvement was 15.0% (95% CI, 11.7%-18.4%). Pooled prevalences of involvement of the left lower lobe, right lower lobe, left upper lobe, right upper lobe, and middle lobe were 73.1% (95% CI, 63.9%-82.4%), 72.2% (95% CI, 62.8%-81.5%), 55.4% (95% CI, 41.2%-69.7%), 51.9% (95% CI, 34.2%-69.5%), and 49.3% (95% CI, 38.3%-60.3%), respectively. Pooled prevalences of peripheral (Fig 2), central

TABLE 2] Risk of Bias for Each Quality Item for Each of the 28 Included Studies

Study	Method of Patient Selection	Patient Spectrum	Flow and Timing	Interobserver Variation	Blinding to Reference Standard
Bai et al[14]	Unclear	High risk	High risk	High risk	Low risk
Bernheim et al[15]	Low risk	Low risk	Unclear	High risk	Unclear
Caruso et al[16]	Low risk	Low risk	Unclear	High risk	Unclear
Chen et al[17]	Low risk	Low risk	Low risk	High risk	Low risk
Chen et al[18]	Low risk	Low risk	Unclear	High risk	Low risk
Colombi et al[19]	Low risk	High risk	Unclear	High risk	Low risk
Fan et al[20]	Unclear	High risk	Unclear	High risk	Unclear
Feng et al[21]	Unclear	Low risk	Unclear	High risk	Low risk
Guan et al[22]	Unclear	Low risk	Unclear	High risk	Unclear
Han et al[23]	Unclear	High risk	Unclear	High risk	Unclear
Inui et al[24]	Low risk	Low risk	Unclear	High risk	Low risk
Li et al[25]	Low risk	High risk	Low risk	High risk	Low risk
Liu et al[26]	Low risk	Low risk	Unclear	High risk	Low risk
Liu et al[27]	Unclear	Low risk	Unclear	High risk	Unclear
Luo et al[28]	Unclear	Low risk	Unclear	High risk	Low risk
Lyu et al[29]	Low risk	High risk	Unclear	High risk	Low risk
Tabatabaei et al[30]	Low risk	Low risk	Unclear	High risk	Unclear
Wang et al[31]	Low risk	High risk	Unclear	High risk	Unclear
Wang et al[32]	Unclear	Low risk	Unclear	High risk	Unclear
Wen et al[33]	Unclear	Low risk	Low risk	High risk	Low risk
Wu et al[34]	Unclear	Unclear	Unclear	High risk	Unclear
Xu et al[35]	Low risk	Low risk	Unclear	High risk	Unclear
Xu et al[36]	Unclear	Low risk	Unclear	High risk	Unclear
Yang et al[37]	Low risk	Low risk	Unclear	High risk	Unclear
Yu et al[38]	Unclear	High risk	Unclear	High risk	Low risk
Zhang et al[39]	Low risk	Unclear	Unclear	Low risk	Low risk
Zhao et al[40]	Low risk	Low risk	Unclear	High risk	Low risk
Zhu et al[41]	Unclear	Low risk	Unclear	High risk	Unclear

and peripheral, and central lesion distribution were 59.0% (95% CI, 48.1%-70.0%), 36.2% (95% CI, 24.4%-48.1%), and 3.6% (95% CI, 2.1%-5.1%), respectively. Prevalence of posterior predilection (Figs 3, 5) was 90%.

Alveolar Abnormalities: Pooled prevalences of ground-glass opacity (Fig 2, 4, 5, 6), consolidation, combination of both ground-glass and consolidation (Fig 3), and linear opacities (Fig 4) were 81.0% (95% CI, 76.6%-85.4%), 51.5% (95% CI, 43.1%-59.9%), 48.7% (95% CI, 41.7%-55.7%), and 40.7% (95% CI, 28.1%-53.3%), respectively. Pooled prevalences of nodules and cavitation/cystic changes were 19.8% (95% CI, 11.8%-27.8%) and 0.7% (95% CI, 0.1%-1.3%) , respectively.

Interstitial, Bronchovascular, and Pleural Abnormalities: Pooled prevalences of septal thickening/reticular pattern and crazy paving were 49.6% (95% CI, 39.3%-59.9%) and 34.9% (95% CI, 23.4%-46.5%), respectively. Pooled prevalences of air bronchogram (Figs 3, 6), bronchiectasis, bronchial wall thickening, and airway secretions/tree-in-bud sign were 40.2% (95% CI, 30.0%-50.4%), 24.2% (95% CI, 12.2%-36.1%), 14.3% (95% CI, 5.5%-23.2%), and 4.1% (95% CI, 1.5%-6.7%), respectively. Pooled prevalence of vascular thickening (Fig 5) was 72.9% (95% CI, 64.4%-81.4%). Pooled prevalences of pleural thickening and pleural effusion were 34.7% (95% CI, 14.4%-55.0%) and 5.2% (95% CI, 3.8%-6.7%), respectively.

TABLE 3] Pooled Prevalences of Chest CT Findings in Patients With COVID-19 Infection

Variable	Chest CT Finding	Studies (Patients), No.	Pooled Prevalence, %	95% CI	I^2 Statistic, %	Random/Fixed Effects Model
Normal findings	Normal findings	18 (2,135)	10.6	7.6-13.7	85.9	Random
Extent of lung lesions	Multifocal	7 (965)	63.2	38.8-87.6	99.3	Random
	Diffuse	4 (617)	26.4	9.3-43.5	96.7	Random
	Single/focal	7 (965)	10.5	4.3-16.7	94.7	Random
Location						
Lung laterality	Bilateral	21 (2,863)	75.8	70.5-81.1	93.1	Random
	Unilateral	20 (2,743)	15.0	11.7-18.4	85.8	Random
Lung lobe						
	Left lower lobe	10 (928)	73.1	63.9-82.4	92.0	Random
	Right lower lobe	10 (928)	72.2	62.8-81.5	92.2	Random
	Left upper lobe	10 (928)	55.4	41.2-69.7	95.9	Random
	Right upper lobe	10 (928)	51.9	34.2-69.5	97.8	Random
	Middle lobe	10 (928)	49.3	38.3-60.3	92.2	Random
Peripheral/ central	Peripheral	20 (2,296)	59.0	48.1-70.0	97.4	Random
	Central and peripheral	17 (1,891)	36.2	24.4-48.1	97.6	Random
	Central	19 (2,206)	3.6	2.1-5.1	85.0	Random
Posterior	Posterior predilection	1 (60)	90.0	NA	NA	NA
Abnormalities						
Alveolar	Ground-glass opacity	26 (3,247)	81.0	76.6-85.4	95.7	Random
	Consolidation	26 (3,247)	51.5	43.1-59.9	96.4	Random
	Mixed ground-glass and consolidation	16 (1,917)	48.7	41.7-55.7	90.4	Random
	Linear opacity	15 (2,118)	40.7	28.1-53.3	98.2	Random
	Nodule	11 (1,311)	19.8	11.8-27.8	97.7	Random
	Cavitation/cystic change	8 (829)	0.7	0.1-1.3	42.6	Fixed
		0 (0)				
Interstitial	Septal thickening/ reticulation	12 (1,164)	49.6	39.3-59.9	92.9	Random
	Crazy paving	15 (1,712)	34.9	23.4-46.5	98.1	Random
Bronchovascular	Vascular thickening	9 (1,065)	72.9	64.4-81.4	91.0	Random
	Air bronchogram	17 (1,913)	40.2	30.0-50.4	96.5	Random
	Bronchiectasis	8 (861)	24.2	12.2-36.1	97.3	Random
	Bronchial wall thickening	6 (701)	14.3	5.5-23.2	94.6	Random
	Airway secretions/tree-in-bud sign	6 (675)	4.1	1.5-6.7	79.7	Random
Pleural	Pleural thickening	7 (1,128)	34.7	14.4-55.0	99.1	Random
	Pleural effusion	27 (3,396)	5.2	3.8-6.7	85.4	Random
Signs	Halo sign	7 (972)	34.5	13.8-55.3	98.9	Random
	Reversed halo sign	6 (878)	11.1	4.5-17.7	94.1	Random
Other abnormalities	Lymphadenopathy	21 (2,415)	5.1	3.2-6.9	93.0	Random
	Pericardial effusion	3 (272)	1.6	0.1-3.1	0	Fixed

NA = not applicable.

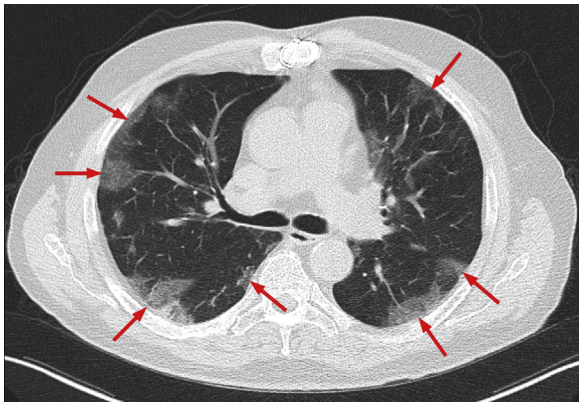

Figure 2 – *A 76-year-old man with real-time polymerase chain reaction-confirmed coronavirus disease 2019 had had a cough and fever for 2.5 weeks. Axial chest CT image shows bilateral, multifocal ground-glass opacities that were predominantly located peripherally (arrows).*

Signs and Other Abnormalities: Pooled prevalences of the "halo sign" and the "reversed halo sign" were 34.5% (95% CI, 13.8%-55.3%) and 11.1% (95% CI, 4.5%-17.7%), respectively. Pooled prevalences of lymphadenopathy and pericardial effusion were 5.1% (95% CI, 3.2%-6.9%) and 1.6% (95% CI, 0.1%-3.1%), respectively.

Discussion

The number of studies on chest CT imaging in COVID-19 has increased rapidly since the pandemic outbreak of this disease. However, both individual studies, non-systematic reviews, and expert opinion articles may contain claims that are not substantiated by evidence. This is potentially dangerous because health care providers need to be provided with unbiased, reliable data to make the right clinical decisions. For other diseases that are already known and that do not pose an imminent threat to humanity, scientific evidence can be accumulated and reflected on at a relatively slower pace. However, COVID-19 does not provide this relative luxury, hence the potentially higher risk for health care providers to make clinical decisions based on missing, incomplete, or incorrect information. Because of the potential of chest CT scanning in adjunct to clinical examination and RT-PCR for the diagnosis of COVID-19 and the rapid proliferation of studies on this topic, a systematic review and a meta-analysis were performed to assess the methodologic quality of these studies and to determine the frequency of different chest CT imaging findings that are found in this disease.

Twenty-seven of 28 studies (96%) that were included had a retrospective design. Methodologic quality concerns were present in all 28 included studies. Methodologic concerns were a failure to report whether patient recruitment was consecutive or random (13/28 [46%] of studies), the exclusion of patients without any abnormalities on CT imaging (8/28 [29%] of studies), a failure to report the time interval between CT and RT-PCR/gene sequencing (24/28 [86%] of studies) or a time interval of up to 7 or 14 days (2/28 [7%] of studies), a lack of information on observer agreement variability in the interpretation of chest CT (27/28 [96%] of studies), and a failure to report whether the chest CT image was interpreted without knowledge of CT and RT-PCR/gene sequencing results (14/28 [50%] of studies). Importantly, some journals provide so-called "ultra-rapid" peer review services (within 24 hours) for COVID-19-related research.[42] It has been reported that such a service may result in a series of high-quality research publications with downloads that are 6 to 30 times greater than the average articles that are published in the same journal and that several of these COVID-19 publications have been in the top two or three trending articles on PubMed.[42] However, the results of the present study challenge the claim that only high-quality research is published with such a policy. In fact, the results indicate the lack of a solid scientific foundation for chest CT scanning in COVID-19 and the need for more high-quality studies. Our findings resonate with a previous review that concluded that the published literature reporting on chest CT features in COVID-19 consisted of limited retrospective studies with methodologic quality issues.[43]

Within the boundaries of the available evidence, a critical finding of this systematic review and meta-

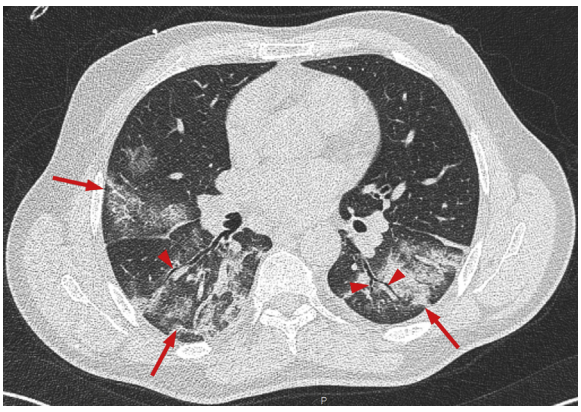

Figure 3 – *A 57-year-old man with real-time polymerase chain reaction-confirmed coronavirus disease 2019 had had a cough, dyspnea, and fever for eight days. Axial chest CT image shows bilateral, multifocal ground-glass opacities/consolidations (arrows) with a posterior part/lower lobe predilection. Air bronchograms are also present (arrowheads).*

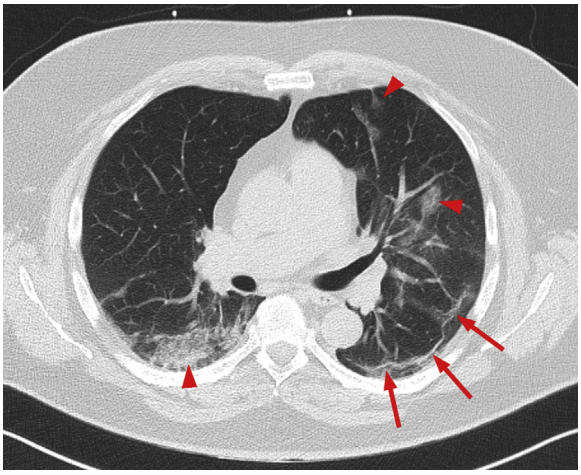

Figure 4 – *A 62-year-old man with real-time polymerase chain reaction-confirmed coronavirus disease 2019 had experienced fatigue and fever for one week. For two days, a cough and dyspnea were also present. Axial chest CT image shows subpleural curvilinear opacity in the left lower lobe (arrows). In addition, there are multifocal areas of consolidation and ground-glass opacity in both lungs (arrowheads).*

analysis was that 10.6% of patients with proven COVID-19 (almost all of these patients were symptomatic) had normal chest CT imaging findings. The substantial prevalence of normal chest CT imaging findings is clinically relevant because it implies that a negative chest CT scan cannot exclude COVID-19 with sufficient certainty, not even in symptomatic patients. Although it has been reported that normal findings at chest CT scanning may occur more frequently in the first days after symptom onset,[44] a nonnegligible number of symptomatic patients with normal chest CT imaging findings are

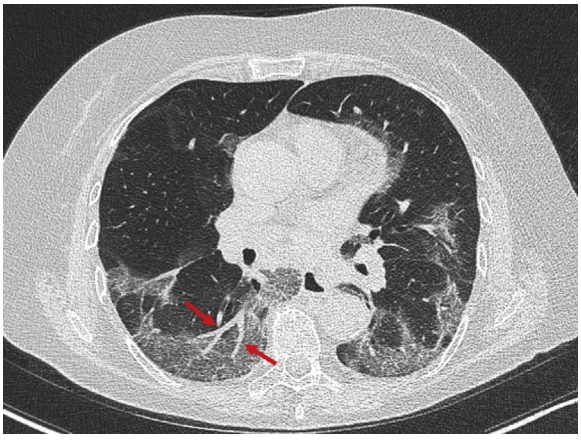

Figure 5 – *A 71-year-old woman with real-time polymerase chain reaction-confirmed coronavirus disease 2019 had had symptoms of progressive dyspnea, nausea, and diarrhea for one week. Axial chest CT image shows bilateral, multifocal ground-glass opacities that are distributed in a posterior part/lower lobe predilection. Vascular thickening is present in the right lower lobe (arrows).*

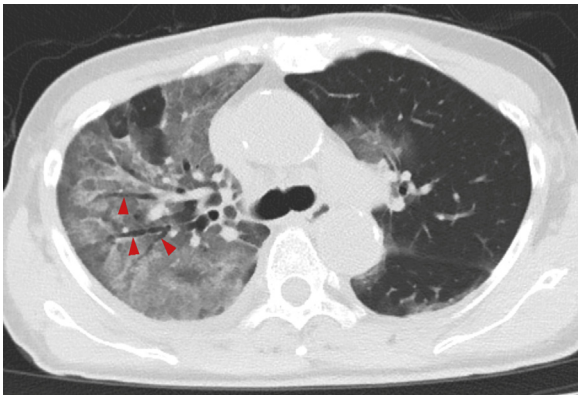

Figure 6 – *A 69-year-old woman with real-time polymerase chain reaction-confirmed coronavirus disease 2019 had been sick for ten days with a cough, dyspnea, and fever that fluctuated. There had been no improvement after antibiotic therapy. Axial chest CT image shows extensive area of ground-glass opacity with predominant diffuse right lung involvement and the presence of air bronchograms (arrowheads).*

observed during the later stage of the infection.[44-46] Therefore, it is questionable whether chest CT images can be used for accurate stratification of patients in a screening setting that aims strictly to isolate individuals with COVID-19 from those without. Importantly, six imaging findings were observed in >70% of COVID-19-confirmed cases; these included posterior predilection, ground-glass opacity, bilateral abnormalities, left lower lobe involvement, vascular thickening, and right lower lobe involvement, in order of decreasing frequency. In geographic regions in which COVID-19 is endemic, the observation of these chest CT imaging findings should raise the suspicion of possible COVID-19 infection. On the other hand, several imaging findings were observed in ≤5% of COVID-19-positive cases; these included pleural effusion, lymphadenopathy, airway secretions/tree-in-bud sign, central lesion distribution, pericardial effusion, and cavitation/cystic changes, in order of decreasing frequency. The isolated observation of one or more of these chest CT imaging findings therefore may be suggestive of another diagnosis, although it should be noted that COVID-19 cannot be eliminated completely from the differential diagnosis. Altogether, the aforementioned chest CT imaging findings on both sides of the spectrum regarding observed frequencies in COVID-19 may be helpful to imaging physicians to determine the likelihood of COVID-19. However, some caution is warranted, because these chest CT imaging findings were extracted from studies that generally provided no to little information on the presence and types of pulmonary comorbidities (which may cause CT scanning abnormalities that are not

related to COVID-19) in the patients who were included. Finally, other chest CT imaging findings were found to be of relatively lower value in terms of true-positive or false-negative rates.

This systematic review and meta-analysis had some limitations. First, only RT-PCR-confirmed COVID-19 cases were included. Chest CT features of COVID-19 may overlap with those of other entities, which include, but are not limited to, other viral and (atypical) bacterial pneumonias, interstitial lung diseases, drug-induced lung disease, alveolar hemorrhage, and pulmonary edema due to a wide range of cardiogenic or other noncardiogenic causes.[47] The individual chest CT scan abnormalities that were retrieved by our analysis are nonspecific; if a mixed group of infections were studied (as would be typical in most settings, except in the epicenter of a COVID-19 outbreak), it can be expected that specificity will be further compromised. Future studies are required to test which chest CT criteria achieve optimal sensitivity and specificity in differentiating COVID-19 from other entities in different clinical settings and with different disease prevalence rates. Second, the various chest CT imaging findings based on the Fleischner Society's glossary terms were assessed individually and pooled regarding frequency of appearance in COVID-19. However, a combination of chest CT imaging findings will likely be necessary to establish an appropriate confidence scale for the diagnosis of COVID-19. Of interest, a Radiological Society of North America Expert consensus statement on reporting chest CT imaging findings related to COVID-19 was published recently.[48] Four categories for reporting CT imaging findings potentially attributable to COVID-19 were proposed, and three of these categories used a combination of chest CT imaging findings.[48] Furthermore, there are no published studies yet that have evaluated this chest CT classification scale, to our knowledge. However, this categorization and the corresponding CT criteria were based on a limited number of studies that were selected by an expert committee.[48] The findings of the present systematic review and meta-analysis may be helpful to further develop existing confidence scales for COVID-19, such as the one that was issued recently under auspices of the Radiological Society of North America.[48] The presented data may also serve as an input for machine learning-based diagnostics. Third, the majority of studies that were included originated from China. Nevertheless, there is no a priori assumption as to whether chest CT imaging findings in COVID-19 would be different in non-Chinese populations. Fourth, temporal changes on chest CT imaging during the course of disease could not be assessed. Although several of the studies that were included also reported some information on temporal changes on chest CT images during the course of disease,[15,22,27,28,32,34-38,40] they had from a considerable amount of flaws and limitations in the analysis of temporal changes on chest CT images. None of these studies described sufficient details of the patients who underwent chest CT imaging at different time points to understand potentially confounding factors on the temporal course of chest CT imaging findings (such as pulmonary comorbidities and therapies that were administered). Time points of chest CT imaging during the course of disease were dissimilar among all studies, and all studies provided mere descriptive data without performing comprehensive statistical analyses to assess for differences in chest CT imaging findings between different time points.[15,22,27,28,32,34-38,40] Furthermore, one study compared different patients who underwent chest CT imaging at different time points rather than evaluating the time course of chest CT imaging findings in the same patients.[15] In the other studies that did perform an intrapatient evaluation during the course of disease, either only a subset of patients underwent follow-up chest CT imaging, which caused selection bias,[22,27,28,32,34-38] or chest CT imaging findings were insufficiently reported.[40] Consequently, the available data on temporal changes on chest CT images are unreliable, lack clinical applicability, and cannot be summarized systematically. The same concerns apply to the studies that were excluded from this systematic review and meta-analysis. A prospective well-designed study is still required to determine the natural evolution of chest CT imaging findings in COVID-19.

In conclusion, studies on chest CT imaging findings in COVID-19 suffer from methodologic quality concerns. More high-quality research is necessary to establish diagnostic CT imaging criteria for COVID-19. Based on the available evidence that should be interpreted with caution, several chest CT imaging findings appear to be suggestive of COVID-19, but normal chest CT imaging findings do not exclude COVID-19, not even in symptomatic patients.

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