Chest CT Imaging Signature of COVID-19 Infection
In Pursuit of the Scientific Evidence

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: ●●●●.

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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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. 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. 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. 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. RT-PCR testing therefore should be repeated in those individuals with a persistent clinical suspicion of COVID-19 infection. 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. 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. 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. 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.

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

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 Item(s) | Signaling Question(s) |
|-----------------|-----------------------|
| **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 al13 and edited according to our study research question.

"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.

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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 three studies were excluded because of (potential) duplicate reporting of patient data, that four studies were excluded because of not reporting the sum of findings of multiple chest CT scans performed in the same patients at different times, that one study was excluded because the time interval between CT and RT-PCR procedures exceeded 72 hours (maximum of 7 days), 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, 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, 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, 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, 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, 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, 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, and 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. Q8

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
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 and 5) was 90%.

Alveolar abnormalities: Pooled prevalences of ground-glass opacity (Fig 2, 4, 5, and 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 and 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 2

| Study                  | Method of Patient Selection | Patient Spectrum | Flow and Timing | Interobserver Variation | Blinding to Reference Standard |
|------------------------|-----------------------------|------------------|-----------------|-------------------------|-------------------------------|
| Bai et al14             | Unclear                     | High risk        | High risk       | High risk               | Low risk                      |
| Bernheim et al15        | Low risk                    | Low risk         | Low risk        | High risk               | Low risk                      |
| Caruso et al16          | Low risk                    | Low risk         | Low risk        | High risk               | Low risk                      |
| Chen et al17            | Low risk                    | Low risk         | Low risk        | High risk               | Low risk                      |
| Chen et al18            | Low risk                    | Low risk         | Low risk        | High risk               | Low risk                      |
| Colombi et al19         | Low risk                    | High risk        | Unclear         | High risk               | Low risk                      |
| Fan et al20             | Unclear                     | High risk        | Unclear         | High risk               | Unclear                      |
| Feng et al21            | Unclear                     | Low risk         | Unclear         | High risk               | Low risk                      |
| Guan et al22            | Unclear                     | Low risk         | Unclear         | High risk               | Low risk                      |
| Han et al23             | Unclear                     | High risk        | Unclear         | High risk               | Unclear                      |
| Inui et al24            | Low risk                    | Low risk         | Low risk        | High risk               | Low risk                      |
| Li et al25              | Low risk                    | High risk        | Unclear         | High risk               | Low risk                      |
| Liu et al26             | Low risk                    | Low risk         | Low risk        | Unclear                 | High risk                     |
| Liu et al27             | Unclear                     | Low risk         | Unclear         | High risk               | Unclear                      |
| Luo et al28             | Unclear                     | Low risk         | Unclear         | High risk               | Low risk                      |
| Lyu et al29             | Low risk                    | High risk        | Unclear         | Low risk               | Low risk                      |
| Tabatabaei et al30      | Low risk                    | Low risk         | Unclear         | High risk               | Low risk                      |
| Wang et al31            | Low risk                    | High risk        | Low risk        | High risk               | Unclear                      |
| Wang et al32            | Low risk                    | Low risk         | Low risk        | High risk               | Unclear                      |
| Wen et al33             | Unclear                     | Low risk         | Low risk        | High risk               | Low risk                      |
| Wu et al34              | Unclear                     | High risk        | Unclear         | Low risk               | Unclear                      |
| Xu et al35              | Low risk                    | Low risk         | Unclear         | High risk               | Unclear                      |
| Xu et al36              | Unclear                     | Low risk         | Unclear         | High risk               | Unclear                      |
| Yang et al37            | Low risk                    | Low risk         | Unclear         | High risk               | Unclear                      |
| Yu et al38              | Unclear                     | Low risk         | Low risk        | High risk               | Low risk                      |
| Zhang et al39           | Low risk                    | Unclear         | Unleard         | High risk               | Unlear                      |
| Zhao et al40            | Low risk                    | Low risk         | Unclear         | High risk               | Low risk                      |
| Zhu et al41             | Unclear                     | High risk        | Low risk        | Low risk               | Unclear                      |
| Variable | Chest CT Finding | Studies (Patients), No. | Pooled Prevalence, % | 95% CI | I² | 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** | Bilateral | 21 (2,863) | 75.8 | 70.5-81.1 | 93.1 | Random |
| **Lung laterality** | 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** | 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 | 97.7 | 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 | Random |
| **Interstitial** | Septal thickening/reticulation | 12 (1,164) | 49.6 | 39.3-59.9 | 92.9 | 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 available.
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. 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. 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.

Within the boundaries of the available evidence, a critical finding of this systematic review and meta-
Onset, a nonnegligible number of symptomatic patients with 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, a nonnegligible number of symptomatic patients with normal chest CT imaging findings are observed during the later stage of the infection. 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. 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. 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. 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. 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. 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, 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. 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. 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, or chest CT imaging findings were insufficiently reported. 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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Additional Information: The e-Appendix and e-Tables can be found in the Supplemental Materials section of the online article.

References

1. Bedford J, Enria D, Giesecke J, et al. COVID-19: towards controlling of a pandemic. Lancet. 2020;395(10229):1015-1018.

2. Binnicker MJ. Emergence of a novel coronavirus disease (COVID-19) and the importance of diagnostic testing: why partnership between clinical laboratories, public health agencies, and industry is essential to control the outbreak. Clin Chem. In press.

3. Han Y, Yang H. The transmission and diagnosis of 2019 novel coronavirus infection disease (COVID-19): a Chinese perspective. J Med Virol. In press.

4. Sharifstein JM, Becker SJ, Mello MM. Diagnostic Testing for the Novel Coronavirus. JAMA. In press.

5. World Health Organization. https://apps.who.int/iris/bitstream/handle/10665/331329/WHO-COVID-19-laboratory-2020.4-eng.pdf?sequence=1 &isAllowed=y. Accessed 2021.

6. Zhang W, Du RH, Li B, et al. Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes. Emerg Microbes Infect. 2020;9(1):386-389.

7. Ai T, Yang Z, Hou H, et al. Correlation of CT findings with clinical type of patients with COVID-19 in Wuhan, China: a report of 1014 cases. Radiology. 2020;200643.

8. Kim H. Outbreak of novel coronavirus (COVID-19): what is the role of radiologists? Eur Radiol. 2020;30(6):3266-3267.

9. Salehi S, Abedi A, Balakrishnan S, Gholamrezaehad A. Coronavirus disease 2019 (COVID-19): a systematic review of imaging findings in 919 patients. AJR Am J Roentgenol. 2020;1-6.

10. Rubin GD, Ryerson CJ, Haramati LB, et al. The role of chest imaging in patient management during the COVID-19 pandemic: a multinational consensus statement from the Fleischner Society. Chest. In press.

11. PRISMA. Transparent reporting of systematic reviews and meta-analyses. 2015. http://www.prisma-statement.org/. Accessed 2021.

12. Hansell DM, Bankier AA, MacMahon H, McLeod TC, Muller NL, Remy J. Fleischner Society: glossary of terms for thoracic imaging. Radiology. 2008;246(3):697-722.

13. Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Med Res Methodol. 2003;3:23.

14. BaiHX, Hsieh B, Xiong Z, et al. Performance of radiologists in differentiating COVID-19 from viral pneumonia on chest CT. Radiology. 2020:200823.

15. Bernheim-A, Mei X, Huang M, et al. Chest CT findings in coronavirus disease-19 (COVID-19): relationship to duration of infection. Radiology. 2020;295(3):204603.

16. Caruso D, Zerunian M, Polici M, et al. Chest CT and COVID-19 in Rome, Italy. Radiol. 2020;2021237.

17. Chen A, Huang I, Liao Y, et al. Differences in clinical and imaging presentation of pediatric patients with COVID-19 in comparison with adults. Radiology: Cardiothoracic Imaging. In press.

18. Chen X, Tang Y, Mo Y, et al. A diagnostic model for coronavirus disease 2019 (COVID-19) based on radiological semantic and clinical findings: a multi-center study. Eur Radiol. In press.

19. Colombi D, Bodini FC, Petrini M, et al. Well- aerated lung on admitting chest CT to predict adverse outcome in COVID-19 pneumonia. Radiology. 2020;2021433.

20. Fan N, Fan W, Li Z, Shi M, Liang Y. Imaging characteristics of initial chest computed tomography and clinical manifestations of patients with COVID-19 pneumonia. Ips J Radiol. 2020;38(6):533-538.

21. Feng Y, Ling Y, Bai T, et al. COVID-19 with different severity: a multi-center study of clinical features. Am J Respir Crit Care Med. In press.

22. Guan CS, Lv ZB, Yan S, et al. Imaging Features of Coronavirus disease 2019 (COVID-19): Evaluation on Thin-Section CT. Acad Radiol. 2020;27(5):609-613.

23. Han R, Huang L, Jiang H, Dong J, Peng H, Zhang D. Early clinical and CT manifestations of coronavirus disease 2019 (COVID-19) pneumonia. AFR Am J Roentgenol. 2020;1-6.

24. Ikeda S, Fujikawa A, Jitsu M, et al. Chest CT findings in cases from the cruise ship “Diamond Princess” with coronavirus disease 2019 (COVID-19). Radiology: Cardiothoracic Imaging. In press.

25. Li X, Fang X, Bian Y, Lu J. Comparison of chest CT findings between COVID-19 pneumonia and other types of viral pneumonia: a two-center retrospective study. Eur Radiol. In press.

26. Liu M, Zeng W, Wen Y, Zheng Y, Lv F, Xiao K. COVID-19 pneumonia: CT findings of 122 patients and differentiation from influenza pneumonia. Eur Radiol. In press.

27. Liu Z, Jin C, Wu CC, et al. Association between initial chest CT or clinical features and clinical course in patients with coronavirus disease 2019 pneumonia. Korean J Radiol. 2020;21(6):736-745.

28. Luo Z, Wang N, Liu P, et al. Association between chest CT features and clinical course of coronavirus disease 2019. Respir Med. 2020;168:105989.

29. Lyu P, Liu X, Zhang R, Shi L, Gao J. The performance of chest CT in evaluating the clinical severity of COVID-19 pneumonia: identifying critical cases based on CT characteristics. Invest Radiol. In press.

30. Tabatabaee S, Talari H, Moghaddas F, Rajebi H. Computed tomographic features and short-term prognosis of coronavirus disease 2019 (COVID-19) pneumonia: a single-center study from Kashan, Iran. Radiology: Cardiothoracic Imaging. In press.

31. Wang J, Xu Z, Wang J, et al. CT characteristics of patients infected with 2019 novel coronavirus: association with clinical type. Clin Radiol. 2020;75(6):808-814.

32. Wang K, Kang S, Tian R, Zhang X, Zhang X. Wang Y. Imaging manifestations and diagnostic value of chest CT of coronavirus disease 2019 (COVID-19) in the Xiaogan area. Clin Radiol. 2020;75(3):341-347.

33. Wen Z, Chi Y, Zhang L, et al. Coronavirus disease 2019: initial detection on chest CT in a retrospective multicenter study of 103 Chinese subjects Radiology: Cardiothoracic Imaging. In press.

34. Wu J, Pan J, Teng D, Xu Y, Feng J, Chen YC. Interpretation of CT signs of 2019 novel coronavirus (COVID-19) pneumonia. Eur Radiol. In press.

35. Xu X, Yu C, Qu J, et al. Imaging and clinical features of patients with 2019 novel coronavirus SARS-CoV-2. Eur J Nucl Med Mol Imaging. 2020;47(5):1275-1280.

36. Xu YH, Dong JH, An WM, et al. Clinical and computed tomographic imaging features of novel coronavirus disease caused by SARS-CoV-2. J Infect. 2020;80(4):394-400.

37. Yang W, Cao Q, Qin L, et al. Clinical characteristics and imaging manifestations of the 2019 novel coronavirus disease (COVID-19): A multi-center study in Wenzhou city, Zhejiang, China. J Infect. 2020;80(4):388-393.

38. Yu M, Xu D, Lan L, et al. Thin-section CT imaging of COVID-19 pneumonia: comparison between patients with mild and severe disease. Radiology: Cardiothoracic Imaging. In press.

39. Zhang R, Ouyang H, Fu L, et al. CT features of SARS-CoV-2 pneumonia according to clinical presentation: a retrospective analysis of 120 consecutive
patients from Wuhan city. Eur Radiol. In press.

40. Zhao W, Zhong Z, Xie X, Yu Q, Liu J. CT scans of patients with 2019 novel coronavirus (COVID-19) pneumonia. Theranostics. 2020;10(10):4606-4613.

41. Zhu T, Wang Y, Zhou S, Zhang N, Xia L. A comparative study of chest computed tomography features in young and older adults with corona virus disease (COVID-19). J Thorac Imaging. In press.

42. Moy L, Bluemke D. The Radiology Scientific Expert Panel. Radiology. 2020: 204005.

43. Raptis CA, Hammer MM, Short RG, et al. Chest CT and coronavirus disease (COVID-19): a critical review of the literature to date. AJR Am J Roentgenol. 2020:1-4.

44. Ding X, Xu J, Zhou J, Long Q. Chest CT findings of COVID-19 pneumonia by duration of symptoms. Eur J Radiol. 2020;127:109009.

45. Liang T, Liu Z, Wu CC, et al. Evolution of CT findings in patients with mild COVID-19 pneumonia. Eur Radiol. In press.

46. Wang Y, Dong C, Hu Y, et al. Temporal changes of CT findings in 90 patients with COVID-19 pneumonia: a longitudinal study. Radiology. 2020:200843.

47. Nishino M, Itoh H, Hatabu H. A practical approach to high-resolution CT of diffuse lung disease. Eur J Radiol. 2014;83(1):6-19.

48. Simpson S, Kay FU, Abbara S, et al. Radiological Society of North America Expert Consensus Statement on Reporting Chest CT Findings Related to COVID-19: endorsed by the Society of Thoracic Radiology, the American College of Radiology, and RSNA. J Thorac Imaging. In press.