The diagnosis of SARS-CoV2 pneumonia: A review of laboratory and radiological testing results

Zhong Zheng1,2 | Zhixian Yao MD1,2 | Ke Wu MD1,2 | Junhua Zheng MD1,2

1Department of Evidence-based Medicine, Shanghai General Hospital, Shanghai Jiao Tong University, School of Medicine, Shanghai, China
2Shanghai Medical Aid Team in Wuhan, Shanghai General Hospital, Shanghai Jiao Tong University, School of Medicine, Shanghai, China

Correspondence
Ke Wu, MD, and Junhua Zheng, MD, Department of Evidence-based Medicine, Shanghai General Hospital, Shanghai Jiao Tong University, School of Medicine, Haining Road 100, 200080 Shanghai, China. Email: doctorwuke@sjtu.edu.cn (KW) and zhengjh0471@sina.com (JZ)

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1 INTRODUCTION

Beginning in December 2019, a novel coronavirus (severe acute respiratory syndrome coronavirus-2 [SARS-CoV-2]) that was found to cause a form of infectious pneumonia (coronavirus disease 2019 [COVID-19]) emerged in Wuhan, China.1-3 The first confirmed case of a patient hospitalized with COVID-19 occurred on 12 December 2019, and since that time the virus has rapidly spread throughout the world.1 As of 17 March 2020, there were over 4,731,458 cases and 316,169 deaths confirmed to be associated with COVID-19.5 Genetic analyses indicate that SARS-CoV-2 most likely arose from bats following passage through unknown intermediate hosts, underscoring the potential zoonotic danger of these coronaviruses.6 While somewhat distantly related to other coronaviruses known to cause infectious pneumonia such as Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV), SARS-CoV-2 is closely related to two SARS-like coronaviruses identified in bats (bat-SL-CoVZC45 and bat-SL-CoVZXC21), and homology modeling suggests that this virus binds to human angiotensin-converting enzyme 2 (ACE2), much as does SARS-CoV.7-9

Abstract

The rapid emergence of coronavirus disease 2019 (COVID-19) has necessitated the implementation of diverse pandemic control strategies throughout the world. To effectively control the spread of this disease, it is essential that it be diagnosed at an early stage so that patients can be reliably quarantined such that disease spread will be slowed. At present, the diagnosis of this infectious form of coronavirus pneumonia is largely dependent upon a combination of laboratory testing and imaging analyses of variable diagnostic efficacy. In the present report, we reviewed prior literature pertaining to the diagnosis of different forms of pneumonia caused by coronaviruses (severe acute respiratory syndrome [SARS], Middle East respiratory syndrome, and SARS-CoV-2) and assessed two different potential diagnostic approaches. We ultimately found that computed tomography was associated with a higher rate of diagnostic accuracy than was a real-time quantitative polymerase chain reaction-based approach ($P = .0041$), and chest radiography ($P = .0100$). Even so, it is important that clinicians utilize a combination of laboratory and radiological testing where possible to ensure that this virus is reliably and quickly detected such that it may be treated and patients may be isolated in a timely fashion, thereby effectively curbing the further progression of this pandemic.

KEYWORDS

chest radiography, computed tomography, coronavirus disease 2019, coronavirus pneumonia, diagnosis, polymerase chain reaction
There is clear evidence of person-to-person SARS-CoV-2 transmission in both hospital and community environments. Following exposure, the median incubation period for this virus is 5.1 days, with ~99% of infected patients developing symptoms within a 14-day monitoring or isolation period. Presenting symptoms most often include cough, fatigue, fever, myalgia, and dyspnea, with many other less common symptoms including alloynia, headache, diarrhea, hemoptysis, and sputum production. This is consistent with the symptoms of SARS and MERS pneumonia, both of which are associated with fever in almost all infected patients upon diagnosis.

Early detection is essential to slow the spread of this pandemic disease, with laboratory testing and imaging being vital to such diagnostic efforts. However, the symptoms of COVID-19 can overlap with those of other serious viral illnesses. Further complicating this diagnostic process is the fact that the polymerase chain reaction (PCR) tests used for COVID-19 diagnosis have a relatively significant false-negative rate. This is a major concern, as the erroneous release of patients with false-negative test results has the potential to facilitate the rapid spread of the virus via community transmission.

In light of these facts, the present review has been designed to evaluate the diagnostic utility of early radiological and laboratory test findings in patients with coronavirus pneumonia to establish the optimal strategies for confirming infection with SARS-CoV, MERS-CoV, or SARS-CoV-2. We searched the literature in Pubmed, Web of Science, and the Cochrane Library, and summarize the findings concerning the diagnostic strategies of SARS, MERS, and COVID-19 for the consideration of clinicians in this report.

2 | STATISTICAL ANALYSIS

The Kruskal-Wallis test was used to compare continuous variables when abnormal distribution was verified by Shapiro-Wilk test, while Barlett’s test was used when normal distribution was verified. The one-way analysis of variance was used to compare the difference between groups after using Levene’s test for homogeneity of variance. The statistics were prepared using Excel (Microsoft Corp., Redmond, WA), and analyzed using R studio (R Foundation for Statistical Computing, Vienna, Austria). A P value of less than .05 was considered to be statistically significant.

### TABLE 1 Laboratory examinations of coronavirus pneumonia

|                  | Range (mean ± SD) | Serological test | References   |
|------------------|-------------------|------------------|--------------|
|                  | RT-PCR            | qPCR             |              |
| SARS             | 38%-88% (62 ± 35) | 50%-86% (75 ± 13)| 34%-99% (78 ± 27)| 17,24,25,34,38     |
|                  | qPCR              | qPCR             |              |
| MERS             | 55%-89% (72 ± 24) | 58%-90% (74 ± 23)| 100%         | 26,39,40          |
| COVID-19         | 50%-97% (74 ± 14) | 62%-100% (88 ± 14)|            | 28,33,41-46       |

Abbreviations: COVID-19, coronavirus disease 2019; MERS, Middle East respiratory syndrome; qPCR, real-time quantitative polymerase chain reaction; RT-PCR, reverse-transcription polymerase chain reaction; SARS, severe acute respiratory syndrome.

*aThere was only one study related to the serological test of MERS.

bLack of data.
patients, RT-PCR and qPCR were associated with 72% and 74% average positive detection rates, respectively.\textsuperscript{26,39,40} In COVID-19 patients, only qPCR is generally used, with the open reading frame 1ab (ORF1ab) and nucleocapsid protein (N) gene regions of SARS-CoV-2 simultaneously tested. Primers for ORF1ab were as follows: forward primer CCTGTTGTTTACACTTAA, reverse primer ACGATTTGTCATCAGCTGA, and the probe 5′-VIC-GCGTCTGCGGTATGTGAAAGGTTATGG-BHQ1-3′. Primers for N were as follows: forward primer GGGGAACTTCTCCTGCTAGAAT, reverse primer CAGACATTTTGCTCTCAAGCTG, and the probe 5′-FAM-TTGCTGCTTGGACAGATT-TAMRA-3′.\textsuperscript{41} And it has a reported 74% average positive detection rate.\textsuperscript{41–46}

No significant differences were observed between SARS and MERS with respect to the diagnostic utility of RT-PCR ($P = .4386$), nor were there any significant differences with respect to average qPCR positive detection rates for SARS, MERS, and COVID-19 ($P = .989$).

Interestingly, paired serological findings were found to be positive in 96.2% of patients among whom RT-PCR was positive in just 64% of people.\textsuperscript{47} As seroconversion requires 2 to 3 weeks following infection in most cases,\textsuperscript{48} such serological testing is only positive in 8.3% of patients within the first 2 weeks.\textsuperscript{47} Based on these limitations, serological testing is unlikely to offer value as a first-line diagnostic tool in the context of rapidly evolving pandemic diseases such as COVID-19.

### 2.2 Imaging diagnosis

Imaging analyses are typically considered to be auxiliary examinations, yet they are integral to the diagnosis of coronavirus pneumonia in many patients.\textsuperscript{49,50} As such, chest radiography is recommended for all patients suspected to be infected with SARS, MERS, or COVID-19, with high-resolution computed tomography (CT) scans is considered to be the most informative. While multiple pathogens may present with similar CT findings in infected patients,\textsuperscript{15} these rapid and straightforward imaging tests are nonetheless essential for the detection of patients suffering from coronavirus pneumonia in hotspot areas of significant known viral transmission. Patient diagnosis is typically dependent upon chest radiography and thoracic CT scans, with the former offering density specificity that enables a rapid assessment of lung lesions and the latter offering better spatial specificity as it allows clinicians to directly evaluate transverse lung sections, as well as surrounding tissues and vasculature.\textsuperscript{51}

#### 2.2.1 Chest radiography

Chest radiography is generally the first test to be ordered in patients suspected to be suffering from SARS, MERS, or COVID-19 (Table 2). With the advancing technology, artificial intelligence (AI) system could serve as a reliable support.\textsuperscript{71} In such radiographs, 72% of SARS patients were found to exhibit abnormalities (78% consolidation, 33% ground-glass opacity [GGO]).\textsuperscript{35,49,52–56} Similarly, 86% of MERS patients exhibit radiographic abnormalities (65% GGO, 18% consolidation, 17% bronchovascular markings, 11% air bronchogram, 4% diffuse reticulonodular patterning).\textsuperscript{57–65} In COVID-19 patients, chest radiographic abnormalities have been observed in 62% of patients (27% GGO, 47% consolidation, and 1% pneumothorax).\textsuperscript{12,45,46,66–70} There were no significant differences

| TABLE 2 | Chest radiography of coronavirus pneumonia |

| Pneumonia | Abnormality | Imaging manifestation | Lesions location | References |
|-----------|-------------|-----------------------|-----------------|-----------|
| SARS      | 58%‐90% (72 ± 12) | GGO: 33% Consolidation: 78% | Unifocal: 55%, Multifocal: 45% Unilateral: 61%, Bilateral: 39% Low lung zone: 74% | 35,49,52–56 |
| MERS      | 60%‐100% (86 ± 14) | GGO: 65% Consolidation: 18% Bronchovascular markings:17% Diffuse reticulonodular pattern:4% Air bronchogram: 11% | Unifocal: 40%, Multifocal: 60% Unilateral: 23% Bilateral: 77% Interstitial: 67% | 57–65 |
| COVID-19  | 15%‐100% (62 ± 35) | GGO: 27% Consolidation:47% Pneumothorax:1% | Unifocal: 48%, Multifocal: 52% Unilateral: 29%, Bilateral: 71% Interstitial: 7% Low lung zone: 50% | 12,45,46,66–70 |

Abbreviations: COVID-19, coronavirus disease 2019; GGO, ground-glass opacity; MERS, Middle East respiratory syndrome; SARS, severe acute respiratory syndrome.
in rates of radiographic abnormalities among these three coronavirus infections ($P = .1827$).

The spatial location of lesions in coronavirus pneumonia patients is also an important diagnostic and prognostic consideration. SARS patients exhibited unilateral and bilateral involvement in 61% and 39% of cases, respectively, with 55% and 45% of patients exhibiting single and multiple infiltration, respectively, and with the lower lung being more susceptible to infection (74% of patients).\textsuperscript{35,55,56} Unilateral and bilateral involvement was observed in 40% and 60% of MERS patients, respectively, with 40% and 60% of patients similarly exhibiting single and multiple infiltration, respectively, and with interstitial infiltration having been detected in 67% of patients.\textsuperscript{53,64,72} Unilateral and bilateral involvement has been detected in 29% and 71% of COVID-19 patients, respectively, with these patients exhibiting single, multiple, and interstitial infiltration in 48%, 52%, and 7% of cases, respectively, and with the lower lung being susceptible to infection (50% of patients).\textsuperscript{45,67,68} These results suggest that COVID-19 and MERS are more commonly associated with bilateral lung involvement relative to SARS, whereas SARS and MERS are associated with similar infiltration rates.

Overall, extant radiographic data suggest that chest radiography can aid in the diagnosis of coronavirus pneumonia, although there is still potential for misdiagnosis. As such, further CT scans are important in affected patients.

### 2.2.2 Computed tomography

CT scans are increasingly common diagnostic tools owing to recent advances in low-dose and high-resolution imaging techniques, similar to chest radiography, AI system involving (Table 3).\textsuperscript{46,92} In CT scans, 98% of SARS patients were found to exhibit abnormalities, with 81% exhibiting GGO, 49% exhibiting consolidation, 87% exhibiting interlobular septal thickening, 74% exhibiting crazy paving pattern, and 4% exhibiting parapneumonic effusion.\textsuperscript{55,56,73} In contrast, 100% of MERS patients were found to exhibit CT abnormalities (86% GGO, 65% consolidation, 38% pleural effusion, 35% interlobular septal thickening).\textsuperscript{6,47} as were 89% of patients with COVID-19 (82% GGO, 45% consolidation, 48% interlobular septal thickening, 35% air bronchogram, 23% crazy paving pattern, 6% pleural effusion) (Table 3).\textsuperscript{12,41,42,45,68,75-91} There were no significant differences in CT abnormality rates among these three groups ($P = .1481$), although rates among SARS and MERS patients were, on average, higher than among COVID-19 patients, potentially as a consequence of disease monitoring practices in China and high disease awareness such that patients are often diagnosed before the manifestation of lung disease. In addition, relatively few studies of CT findings in SARS and MERS patients have been conducted, limiting confidence in these results. Some studies found that high-resolution CT findings in SARS patients were similar to those with steroid-responsive bronchiolitis obliterans,\textsuperscript{33,94} providing a rational basis for treating coronavirus pneumonia with such steroids.\textsuperscript{95}

As CT scans offer excellent spatial specificity, they can be more effectively used to assess lesion variability than can radiographic scans. CT scans of SARS patients identified 61% and 39% of lesions as being unifocal and multifocal, respectively, with 74% and 26% being unilobar and multilobar, respectively, 48% being unilateral, 52% being bilateral, 71% exhibiting lower lobe involvement, and 84% exhibiting peripheral or subpleural involvement.\textsuperscript{55,56,73} In contrast, just 14% of MERS lesions were found to be unilateral, with the remaining 86% being bilateral, and with 14% exhibiting lower lobe involvement and 71% being peripheral or subpleural.\textsuperscript{44,74} Unifocal and multifocal lung lesions were observed in 31% and 69% of COVID-19 patients, respectively, with unilobar and multilobar lesions being detected in 25% and 75% of patients, respectively, and with 21% and 79% exhibiting unilateral and bilateral involvement, respectively, in addition to 56% exhibiting lower lobe involvement, 79% exhibiting peripheral or subpleural involvement, and 71% exhibiting central involvement.\textsuperscript{45,77-83,89} In line with chest radiographic findings, these results suggest that MERS and COVID-19 are associated with more diffuse disease than is SARS, potentially due to underlying differences in the pathological mechanisms of these diseases. And a multicenter cohort illustrates more consolidation in upper lungs on initial CT increases the risk of adverse clinical outcome in COVID-19 patients (right: OR, 1.13; 95% CI, 1.03-1.25; $P = .01$; left: OR,1.15; 95% CI, 1.01-1.32; $P = .04$).\textsuperscript{96}

Overall, data suggest that CT scans offer markedly higher diagnostic efficacy relative to chest radiography ($P = .0100$). However, CT scans cannot reliably identify infections associated with a specific virus, nor can they reliably differentiate between viruses.\textsuperscript{57} Even so, owing to their excellent diagnostic utility, CT scans should be the primary mode of imaging examination in patients with suspected coronavirus pneumonia.

### 3 Discussion

Present guidelines indicate that formal SARS-CoV-2 diagnosis is dependent upon the results of laboratory examinations such as swab test qPCR analyses.\textsuperscript{97} However, such laboratory testing is both time- and resource-intensive, with test kits and swabs not being available in sufficient quantities in some areas of rapid viral spread. These diagnostic approaches are also hampered by the potential for false-negative results due to laboratory errors or a lack of a sufficiently high-quality sample for analysis.\textsuperscript{42,98}

To aid in the more precise diagnostic evaluation of patients with coronavirus pneumonia, we herein compared extant data pertaining to abnormal CT findings and qPCR results in this disease context. While no significant differences between CT and qPCR findings were observed for MERS patients owing to the relatively limited literature surrounding this emerging virus ($P = .3516$), significant differences between CT and qPCR results were observed for both SARS and COVID-19 cases ($P = .0302$, $P = .0041$) (Table 4). While qPCR analyses can achieve 100% specificity,\textsuperscript{22,44,47} to do so they require access to a sufficient viral
specimen. While bronchoalveolar lavage fluid (BALF) samples were associated with a 100% viral positivity rate in one study, sputum samples were associated with a lower positivity rate (74.4%–88.9%), while nasal swab detection rates were lower still (53.6%–73.3%). This may be a consequence of a number of different factors pertaining to sample collection methodology, timing, sample transport, and sample testing parameters. Lower respiratory samples have the potential to offer greater diagnostic sensitivity even when nasopharyngeal and oropharyngeal qPCR tests yield negative results, and serological testing should also be used as a follow-up approach in those with clinically suspected disease. It is also vital that clinicians implement appropriate infection control strategies for all patients with suspected disease, including patients that exhibit negative qPCR findings but that exhibit imaging signs consistent with coronavirus pneumonia. A single swab-based test is also not sufficient to reliably rule out the possibility of infection. In a study of MERS patients, while only 89% of patients were found to be positive after a single swab test, 96.5% were found to be positive following two consecutive swabs, and 97.6% were positive following three consecutive swab tests. Initial negative test results have a high risk of being false-negative findings, and repeated testing is necessary to ensure adequate diagnosis.

### TABLE 3 CT scan of coronavirus pneumonia

| Pneumonia | Abnormality | Imaging manifestation | Lesions location | References |
|-----------|-------------|-----------------------|-----------------|------------|
| SARS      | 93%-100% (98 ± 4) | GGO: 81% | Unifocal: 61% | 55,56,73 |
|           |             | Consolidation: 49%   | Multifocal: 39% |            |
|           |             | Interlobular septal thickening: 87% | Unilobar: 74% |            |
|           |             | Crazy paving pattern: 74% | Multilobar: 26% |            |
|           |             | Parapneumonic effusion: 4% | Unilateral: 48% |            |
|           |             | Interlobular thickening: 35% | Bilateral: 52% |            |
|           |             |                       | Peripheral or subpleural: 84% |            |
|           |             |                       | Lower lobe: 71% |            |
| MERS      | 100%ë | GGO: 86% | Unilateral: 14% | 64,74 |
|           |             | Consolidation: 52%   | Bilateral: 86% |            |
|           |             | Pleural effusion: 38% | Peripheral or subpleural: 71% |            |
|           |             | Interlobular thickening: 35% | Lower lobe: 14% |            |
| COVID-19  | 69%-100% (89 ± 11) | GGO: 82% | Unifocal: 31% | 12,41,42,45,68,75-91 |
|           |             | Consolidation: 45%   | Multifocal: 69% |            |
|           |             | Interlobular septal thickening: 48% | Unilobar: 25% |            |
|           |             | Air bronchogram: 35% | Multilobar: 75% |            |
|           |             | Bronchus distortion: 18% | Unilateral: 21% |            |
|           |             | Pleural effusion: 6% | Bilateral: 79% |            |
|           |             | Pleural thickening: 47% | Peripheral or subpleural: 79% |            |
|           |             | Pleural retraction sign: 33% | Central: 71% |            |
|           |             | Reticular pattern: 63% | Lower lobe: 56% |            |
|           |             | Vascular sign: 55% |                       |            |
|           |             | Microvascular dilation sign: 45% |                       |            |
|           |             | Fibrotic streaks: 37% |                       |            |
|           |             | Subpleural line: 34% |                       |            |
|           |             | Vascular enlargement: 71% |                       |            |
|           |             | Traction bronchiectasis: 52% |                       |            |
|           |             | Crazy paving pattern: 23% |                       |            |
|           |             | Combined linear opacities: 80% |                       |            |

### TABLE 4 Comparison between CT scan and qPCR of coronavirus pneumonia

| Pneumonia | CT Scan, range (mean ± SD) | qPCR, range (mean ± SD) | P value |
|-----------|-----------------------------|-------------------------|---------|
| SARS      | 93%-100% (98 ± 4) | 50%-86% (75 ± 13) | .0302 |
| MERS      | 100% | 58%-90% (74 ± 23) | .3516 |
| COVID-19  | 69%-100% (89 ± 11) | 50%-97% (74 ± 14) | .0041 |

Abbreviations: COVID-19, coronavirus disease 2019; CT, computed tomography; MERS, Middle East respiratory syndrome; SARS, severe acute respiratory syndrome.

There were only two articles related to the abnormality rate of MERS, all of which were 100%.

Abbreviations: COVID-19, coronavirus disease 2019; CT, computed tomography; MERS, Middle East respiratory syndrome; SARS, severe acute respiratory syndrome.

Abbreviations: COVID-19, coronavirus disease 2019; CT, computed tomography; MERS, Middle East respiratory syndrome; qPCR, real-time quantitative polymerase chain reaction; SARS, severe acute respiratory syndrome.

Abbreviations: COVID-19, coronavirus disease 2019; CT, computed tomography; MERS, Middle East respiratory syndrome; qPCR, real-time quantitative polymerase chain reaction; SARS, severe acute respiratory syndrome.
therefore essential to ensure appropriate patient quarantine and management. With respect to CT scans, the relatively low rates of COVID-19 misdiagnosis (3.9%) suggest that radiologic diagnoses may be a reliable means of quickly detecting cases of coronavirus pneumonia so as to facilitate rapid and effective patient quarantine and management. An AI study related to CT scan achieved a test accuracy of 96% (95% CI, 90%-98%), sensitivity 95% (95% CI, 83%-100%) and specificity of 96% (95% CI, 88%-99%) with receiver operating characteristic (ROC) AUC of 0.95 and Precision-Recall (PR) AUC of 0.90, which concluded that AI assistance improved radiologists’ performance in distinguishing COVID-19 from non-COVID-19 pneumonia on chest CT. These scans may also be of value in patients that initially exhibit negative PCR findings. For example, Xie et al reported on five patients that were negative for SARS-CoV-2 in initial qPCR tests, but that exhibited typical COVID-19 CT findings including GGO and consolidation. These patients were isolated, and subsequent repeated qPCR testing eventually confirmed all five of these patients to be infected with SARS-CoV-2. Similarly, research conducted by Ai et al revealed that positive chest CT findings were detected in 75% of symptomatic patients with negative qPCR findings. Serial RT-PCR and CT scans in these patients suggested a mean interval of 5.1 ± 1.5 days between initial negative qPCR and positive qPCR findings. The comprehensive strategy reached a higher sensitivity of 94% in a retrospective study (Table 4).

While CT scans expose patients to higher radiation doses, the relative risks, and benefits of such exposure must be determined by radiologists and clinicians. In the context of severe pandemic disease, CT scans are a valuable tool and may be essential to accurately and quickly identify and isolate COVID-19 patients. However, a combination of both laboratory testing and imaging is essential to accurately identify COVID-19 patients with confidence, and CT scans should be ordered in patients with negative qPCR results that are nonetheless suspected to be suffering from coronavirus pneumonia. When patients test positive for SARS-CoV-2 infection, while there is a small risk of false-positive diagnosis, it is essential that they be strictly isolated from other individuals to limit the ability of this virus to spread through vulnerable communities.

4 CONCLUSION

In summary, in the present review, we surveyed the results of prior studies of SARS, MERS, and COVID-19 patients in an effort to establish which diagnostic approaches are most efficacious in those with coronavirus pneumonia. While we found that CT scans are associated with higher detection rates than are qPCR tests, it is nonetheless important that clinicians utilize a combination of imaging and laboratory findings to inform their diagnostic process such that patients can be rapidly identified and quarantined, thus stemming the spread of these deadly pandemic viruses.

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CONFLICT OF INTERESTS
The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS
JZ and KW participated in the study design; ZZ performed data collection and analysis; ZY drafted the manuscript; all authors provided a critical review of the manuscript and approved the final draft for publication.

ORCID
Zhong Zheng http://orcid.org/0000-0002-3500-9510

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