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The diagnosis of pandemic coronavirus pneumonia: A review of radiology examination and laboratory test

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ABSTRACT

Since the outbreak of novel coronavirus disease 2019 (COVID-19), epidemic prevention strategies have been implemented worldwide. For the sake of controlling the infectious coronavirus pneumonia, early diagnosis and quarantine play an imperative role. Currently, the mainstream diagnostic methods are imaging and laboratory diagnosis, which differ in their efficacy of diagnosis. To compare the detection rate, we reviewed numerous literature on pneumonia caused by coronaviruses (SARS, MERS, and SARS-CoV-2) and analyzed two different ways of diagnosis. The results showed that the detection rate of computed tomography (CT) diagnosis was significantly higher than that of real-time quantitative polymerase chain reaction (qPCR) ($P = 0.00697$). Still, clinicians should combine radiology and laboratory methods to achieve a higher detection rate, so that instant isolation and treatment could be effectively conducted to curb the rampant spread of the epidemic.

1. Introduction

Toward the end of December 2019, a novel coronavirus (SARS-CoV-2) appeared in Wuhan, China, causing the outbreak of coronavirus disease 2019 (COVID-19) [1,2]. Since the hospitalization of the index patient on December 12, 2019, the virus has gradually spread to the globe [3]. As of March 17, 2020, 179,112 cases have been confirmed worldwide, and 7426 patients have died [4]. Molecular analysis indicates that SARS-CoV-2 probably originated from bats after passage in intermediate hosts, which highlights the high zoonotic potential of coronaviruses [5]. Furthermore, SARS-CoV-2 is closely related to two bat-derived severe acute respiratory syndrome (SARS)-like coronaviruses, namely bat-SL-CoVZC45 and bat-SL-CoVZXC21, yet it is more distant from SARS-CoV and MERS-CoV. Furthermore, homology modeling revealed that SARS-CoV-2 might be able to combine with human angiotensin-converting enzyme 2, which is identical to the characteristic of SARS-CoV [6,7].

SARS-CoV-2 has been testified to be transmitted from person to person in community or hospital [8]. The estimated median incubation period is 5.1 days, while, under conservative assumptions, 101 of every 10,000 cases would develop symptoms after 14-day active monitoring or isolation [9]. Common symptoms at the onset of illness included fever, cough, and myalgia or fatigue; less common symptoms were sputum production, headache, hemoptysis, and diarrhea [10]. Likewise, as for Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Disease (MERS), both of which are coronavirus-associated pneumonia, almost all patients suffer from fever at diagnosis [11].

For the sake of curbing the rapidly spreading coronavirus, early detection plays a pivotal role in epidemic control, including laboratory tests, imaging diagnosis, and other similar methods [12]. Nevertheless, the imaging findings of coronaviruses-associated pneumonia might overlap with those caused by other morbific viruses [13]. Coincidentally, the seemingly relatively accurate Polymerase Chain Reaction (PCR) test, a Nucleic Acid Amplification Test (NAAT), actually has a certain degree of false negatives [14,15]. If patients are released based on false-negative results of this test, the consequences could be disastrous.

Therefore, in this review, we focus on early radiology or laboratory examinations and diagnoses of coronavirus pneumonia that would help confirm the infection of SARS-CoV, MERS-CoV, or SARS-CoV-2.

2. Imaging diagnosis

Imaging diagnosis belongs to the auxiliary examination and plays a significant role in the diagnosis and routine treatment of coronavirus diseases [16,17]. For every patient suspected of infection, chest

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Table 1
Chest Radiography of Coronavirus Pneumonia.

Pneumonia	Abnormality (Mean ± SD)	Imaging Manifestation (Mean)	Lesions Location (Mean)	Ref.
SARS	58～90 % (72 ± 12)	GGO: 33 %Consolidation: 78 %	Unifocal: 55 %,Multifocal: 45 %Unilateral: 61 %Bilateral: 39 %Low lung zone: 74 %	[16,19,20,21,22,23,24]
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 %	[25,26,27,28,29,30,31,32,33]
COVID-19	15～100 % (56 ± 40)	GGO: 24 % Pneumothorax:1%	Unifocal: 48 %Multifocal: 52 %Unilateral: 22 %Bilateral: 78 % Interstitial: 7%	[10,34,35,36,37]

radiograph should be performed. In order to further understand the condition of the chest, computed tomography (CT) scan (especially high-resolution CT scan) can provide doctors with more information. Except for contrast-enhanced CT, imaging examination is included in the morphological category, and different pathogens with semblable pathological and immune processes might give similar results [13]; yet, rapid and simple imaging tests are indispensable for concentrated outbreaks of infectious SARS, MERS, and COVID-19. The principal techniques comprise chest radiography and thoracic CT scan. The former possesses density specificity, which could roughly determine lung lesions through the transparency in quick, and the latter has spatial specificity and could accurately parse the transverse section, including surrounding tissues, blood vessels, and lesions, of lungs [18].

2.1. Chest radiography

(Table 1) For patients suspected to have SARS, MERS, or COVID-19 infection, the first test to be performed is a chest radiograph. The average abnormality rate of chest radiography in patients with SARS was 72 %, 33 % of which were GGO and 78 % were consolidation [16,19–24]. For MERS, an average of 86 % of patients exhibited abnormalities in chest radiography, with 65 % GGO, 18 % consolidation, 17 % bronchovascular markings, 11 % air bronchogram, and 4% diffuse reticulonodular pattern [25–33]. COVID-19 showed an average chest radiographic abnormality rate of 56 %, GGO in 24 %, and pneumothorax in 1% of patients [10,34–37]. Analysis of the abnormality rates of the three groups revealed no significant difference among them ($P = 0.1734$).

In addition to the main manifestations, the spatial location of the lesion is also important. For SARS-induced lesions, the average of unilateral involvement was 61 %, bilateral involvement was 39 %, single infiltration was 55 %, and multiple infiltration was 45 %; moreover, the lower lung zone was more susceptible, with an average probability of 74 % [22–24]. For MERS, the average of unilateral involvement was 40 %, bilateral involvement was 60 %, single infiltration was 40 %, multiple infiltration was 60 %, and interstitial infiltration was 67 % [31,32,38]. For COVID-19, unilateral involvement was 22 %, bilateral involvement was 78 %, single infiltration was 48 %, multiple infiltration was 52 %, and interstitial infiltration was 7% [35–37]. In summary, the bilateral involvement was more common in MESR and COVID-19 than in SARS, and single and multiple infiltrations are similar in SARS and MERS.

Based on the data, chest radiography has the capability to diagnose coronavirus pneumonia to some extent, but there is still room for missed diagnosis. Thus, a further CT scan is particularly imperative.

2.2. Computed tomography

(Table 2) CT scan was previously used as a second-line examination of chest lesions. However, with the advent of low-dose CT and high-resolution CT, this auxiliary examination has become prevalent, which can be attribute to the powerful analytical diagnosis capabilities [39]. For patients suffering from SARS, the average abnormality rate was 98 %, with 81 % of it being GGO, 49 % consolidation, 87 % interlobular septal thickening, 74 % crazy paving pattern, and 4% parapneumonic effusion [22,23,40]. For patients with MERS infection, the abnormality rate of CT was 100 %, with 86 % of abnormality for GGO, 65 % for consolidation, 38 % for pleural effusion, and 35 % for interlobular septal thickening [32,41]. The average abnormality rate of COVID-19 is 89 %, with 84 % of that for GGO, 65 % for consolidation, 48 % for interlobular septal thickening, 39 % for air bronchogram, 16 % for crazy paving pattern, and 12 % for pleural effusion; for other lesions, see Table 2 [10,36,37,42–57]. The analysis illustrated that although the abnormality rates of the three groups were not significantly different ($P = 0.1453$), the average rates in SARS and MERS were higher than that in COVID-19, which is most likely because of the current network development informing the outbreak of COVID-19 among people of China. Therefore, the entire population has been informed about the seriousness of the problem through the Internet. Early examinations were adopted, and many patients at early stages of infection manifested only fever or no symptoms, which indicated that lung disease had not yet appeared. Because of the limited number of CT scans in studies related to SARS and MERS, the high detection rate might be under suspicion. Interestingly, several studies reported that lung features of SARS under the high-resolution CT scan were identical to those of bronchiolitis obliterans, the steroid-responsive disease [58,59], which provided imaging basis for corticosteroid treatment of coronavirus pneumonia [60].

Because CT has spatial specificity, it can identify the variability of the lesion to a higher extent than chest radiography. In SARS, 61 % of lesions were unifocal, 39 % were multifocal, 74 % were unilobar, 26 % were multilobar, 48 % were unilateral, 52 % were bilateral, 71 % had lower lobe involvement, and 84 % were peripheral or subpleural [22,23,40]. In MERS, 14 % of lesions were unilateral, 86 % were bilateral, 14 % had lower lobe involvement, 71 % were peripheral or subpleural [32,41]. In COVID-19, 31 % of lesion were unifocal, 69 % were multifocal, 26 % were unilobar, 74 % were multilobar, 20 % were unilateral, 80 % were bilateral, 56 % had lower lobe involvement, 82 % were peripheral or subpleural, and 71 % were central [37,44–50,57]. Coincident with chest radiography, the distribution of MERS and COVID-19 pneumonias was more diffuse and they were more prone to bilateral involvement, probably due to their pathological mechanism.

Overall, the efficacy of the CT scan was significantly higher than that of chest radiography ($P = 0.01747$). Although CT scan is still limited for identifying specific viruses and differentiating between viruses [54], given its robust diagnostic reliability for coronavirus pneumonia, CT scan should be considered as the primary imaging examination.

3. Laboratory diagnosis

(Table 3) Compared with macroscopic morphological examinations,

Table 2
CT Scan of Patients with Coronavirus Pneumonia.

Pneumonia	Abnormality (Mean ± SD)	Imaging Manifestation (Mean)	Lesions Location (Mean)	Ref.
SARS	93～100 % (98 ± 4)	GGO: 81 %Consolidation: 49 % Interlobular septal thickening: 87 % Crazy paving pattern: 74 % Parapneumonic effusion: 4%	Unifocal: 61 %Multifocal: 39 %Unilobar: 74 %Multilobar: 26 %Unilateral: 48 %Bilateral: 52 % Peripheral or subpleural: 84 %Lower lobe: 71 %	[22,23,40]
MERS	100 %[a]	GGO: 86 %Consolidation: 52 % Pleural effusion: 38 % Interlobular thickening: 35 %	Unilateral: 14 %Bilateral: 86 % Peripheral or subpleural: 71 %Lower lobe: 14 %	[32,41]
COVID-19	69～100 % (89 ± 11)	GGO: 84 %Consolidation: 65 % Interlobular septal thickening: 48 % Air bronchogram: 39 % Bronchus distortion: 18 % Pleural effusion: 12 % Pleural thickening: 60 % Pleural retraction sign: 33 % Reticular pattern: 63 %Vacuolar sign: 55 % Microvascular dilation sign: 45 % Fibrotic streaks: 37 % Subpleural line: 34 % Vascular enlargement: 71 % Traction bronchiectasis: 52 % Crazy paving pattern: 16 % Combined linear opacities: 80 %	Unifocal: 31 %Multifocal: 69 %Unilobar: 26 %Multilobar: 74 %Unilateral: 20 %Bilateral: 80 % Peripheral or subpleural: 82 %Central: 71 % Lower lobe: 56 %	[10,36,37,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57]

[a] There were only two articles related to the abnormality rate of MERS, and both articles reported a rate of 100 %.

Table 3
Laboratory Examination of Patients with Coronavirus Pneumonia.

Pneumonia	RT-PCR (mean ± SD)	qPCR (mean ± SD)	Serological test (mean ± SD)	Ref.
SARS	38～88 % (62 ± 35)	50～86 % (75 ± 13)	34～99 %(78 ± 27)	[15,24,66,67,69,70,71,72]
MERS	55～89 % (72 ± 24)	58～90 % (74 ± 23)	100 %[a]	[68,73,74]
COVID-19	/[b]	50～97 % (72 ± 15)	/[b]	[37,56,75,76]

[a] There was only one article related the serological test of MERS.
[b] Lack of data.

Table 4
Comparison between CT Scan and qPCR results of Patients with Coronavirus Pneumonia.

Pneumonia	CT Scan (mean ± SD)	qPCR (mean ± SD)	P value
SARS	93～100 % (98 ± 4)	50～86 % (75 ± 13)	0.0302
MERS	100 %	58～90 % (74 ± 23)	0.3516
COVID-19	69～100 % (89 ± 11)	50～97 % (72 ± 15)	0.00697

microcosmic etiological tests, including nucleic acid detection and serological detection, with high specificity, could serve as benchmarks for the laboratory detection of the virus [61–63]. In the past three decades, significant progress has been made in virus diagnostic testing, ranging from virus culture to rapid antigen detection, and recently to high-sensitivity NAAT, including PCR [64]. Simple and rapid antigen immunoassay has been the primary method for the detection of various viruses, but there are still some limitations to overcome because of its low sensitivity [64].

3.1. Serological test

Serological tests include neutralization test, enzyme-linked immunosorbent assay (ELISA), immunofluorescent assay (IFA), and immunochromatographic test (ICT). Confirmation of coronavirus infection was made by identifying the nucleocapsid (N) protein in the serum by N antigen-capture ELISA and N antigen-capture chemiluminescent immunoassay [65]. For patients with SARS, the average positive rate of serum tests was 78 % [15,66,67], whereas for MERS, it was only 42 % [68]. No serological tests for COVID-19 have been reported.

3.2. PCR

The most commonly used nucleic acid detection is PCR, including conventional reverse transcription PCR (RT-PCR) and real-time quantitative PCR (qPCR). For SARS patients, the average positive rate of conventional RT-PCR was 62 % and that of qPCR was 75 % [15,24,66,67,69–72]. In patients possessing MERS, the average positive rate of RT-PCR was 72 % and that of qPCR was 74 % [68,73,74]. In patients with COVID-19, the traditional method has been discontinued, and it was comprehensively altered by qPCR, with the average positive rate of 72 % [37,56,75,76]. For SARS and MERS, there was no statistical difference between RT-PCR findings (P = 0.4386), and no significant difference in the positive rate of qPCR among the three coronaviruses (P = 0.919).

Interestingly, studies have shown that paired serology was positive in 96.2 % of patients in whom RT-PCR was positive in 64 % of the same patients [77]. Nonetheless, because seroconversion would delay until 2–3 weeks after infection in usual [78], the serologic test was positive in 8.3 % of patients in the first two weeks [77]. Overtly, for the rapid outbreaks of coronavirus-associated pneumonia, especially COVID-19, the serological examination should never be the first choice for laboratory diagnosis.

4. Discussion

According to the current diagnostic criteria, laboratory examination such as a swab test for qPCR has become a standard and formative evaluation for the diagnosis of SARS-CoV-2 infection [79]. However, the laboratory test is time-consuming, and the shortage of supply test kits might not meet the needs of the growing suspected cases worldwide. Also, qPCR testing for SARS-CoV-2 could be falsely negative due to laboratory error or insufficient viral material in the specimen [56].

For a more precise diagnosis, we compared the abnormality rate in CT scan with the positive rate in qPCR. Partly because of the lack of literature on MERS, no significant difference was found (P = 0.3516). However, in SARS and COVID-19, there was a significant difference between CT scan and qPCR findings (P = 0.0302, P = 0.00697) (Table 4). Although the specificity of qPCR could reach 100 % [65,76,77], a sufficient virus titer of the specimen was required. Notably, except for bronchoalveolar lavage fluid (BALF) (100 %), the sputum showed the highest positive rate (74.4 % ~ 88.9 %), followed by nasal swabs (53.6 % ~ 73.3 %) [76]. The reasons could be the timing of specimen collection, specimen transport, testing, etc. Lower respiratory tract specimens should be considered to improve the sensitivity of qPCR, particularly if results of the nasopharyngeal and oropharyngeal tests were negative; however, with high clinical suspicion, follow-up serological testing should also be applied [15]. Most importantly, clinicians should implement appropriate infection control practices for patients with clinically suspected infection [15], specifically with negative initial qPCR results, notably who possessed typical abnormality in CT scan or chest radiography. Additionally, a single swab was relatively insufficient. In a previous study on MERS infection, 89 %of patients had a positive result after one swab, 96.5 % had a positive result after two consecutive swabs, and the positive result reached 97.6 % after three consecutive swabs [73]. Thus, the initial negative result could be unpersuasive unless repeated tests were performed.

Regarding CT scan, the low rate of missed diagnosis of COVID-19 (3.9 %) verified that the radiologic diagnosis might be useful as a standard method for the rapid diagnosis of not only SARS and MERS but also COVID-19 to optimize the management of patients [54]. Under such circumstances, the CT scan might serve as an important tool for the diagnosis of NCP patients. Xie et al. [56] reported five patients with SARS-CoV-2 infection who had initial negative RT-PCR results, but typical CT scan showed findings such as GGO or consolidation. After isolation for presumed COVID-19, all patients were eventually confirmed to have SARS-CoV-2 infection by repeated swab tests [56]. In the study of Ai et al. [75], 75 % of patients with negative qPCR results had positive chest CT findings. Through analysis of serial RT-PCR assays and CT scans, the mean interval time between the initial negative to positive qPCR results was 5.1 ± 1.5 days [75].

CT scan requires patients to withstand higher radiation, and the consequences of this exposure depend on the expertise of radiologists. Under such a severe epidemic outbreak, CT scan might provide a vital supplement for consummating the diagnosis of COVID-19 patients. Because of the imperious demand for batch detection, the combination of repeated laboratory examination and CT scan could be helpful for individuals with high clinical suspicion of coronavirus infection but

negative qPCR screening result. Once confirmed to be positive, even if a false positive result is obtained, the most strict sequestration should be practiced for eliminating severe risk of transmission.

5. Conclusion

In this review, we retrieved studies related to SARS, MERS, and COVID-19. Although the results showed that the detection rate of computed tomography (CT) was significantly higher than real-time quantitative polymerase chain reaction (qPCR), clinicians should combine radiology and laboratory methods to achieve a higher detection rate, so that rapid isolation and treatment could be conducted to effectively curb the rampant spread of COVID-19 pandemic. Although the virus is spreading rapidly, the success eventually belongs to us.

Authors' contributions

Junhua Zheng and Ke Wu participated in study design; Zhong Zheng performed data collection and analysis; Zhixian Yao drafted the manuscript; all author provided critical review of the manuscript and approved the final draft for publication.

Role of the Funder/Sponsor

The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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Declaration of Competing Interest

The authors declare no conflicts of interest.

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