Diagnostic Tools for Coronavirus Disease (COVID-19): Comparing CT and RT-PCR Viral Nucleic Acid Testing

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OBJECTIVE. Multiple studies suggest CT should be a primary diagnostic tool for coronavirus disease (COVID-19) because they reported sensitivities with CT far superior to that of reverse transcriptase polymerase chain reaction (RT-PCR) testing. This review aimed to assess these reports and found chest CT to have a clinical utility that is limited, particularly for patients who show no symptoms and patients who are screened early in disease progression.

CONCLUSION. CT has limited sensitivity for COVID-19 and a lower specificity than RT-PCR testing, and it carries a risk of exposing providers to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Chest CT should be considered a supplemental diagnostic tool, particularly for patients who show symptoms.

Keywords: chest CT, coronavirus disease, COVID-19, RT-PCR, SARS-CoV-2, sensitivity, severe acute respiratory syndrome coronavirus 2, specificity

doi.org/10.2214/AJR.20.23418

Received April 18, 2020; accepted without revision April 21, 2020.

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AJR 2020; 215:1–5

ISSN-L 0361–803X/20/2154–1

Initially detected in Wuhan, China, coronavirus disease (COVID-19) is caused by a single-stranded RNA virus belonging to the family Coronaviridae [1, 2]. It is thought that COVID-19 originated from bats and infected an intermediate mammalian host before human transmission, showing the zoonotic potential evidenced in similar coronavirus outbreaks such as the severe acute respiratory syndrome coronavirus (SARS-CoV) [3, 4]. As a result of genomic similarities between COVID-19 and SARS-CoV, the virus responsible for COVID-19 has been officially named "severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)" [1, 5]. Although patients with COVID-19 may present with gastrointestinal or upper respiratory symptoms, the most common symptoms are fever, dry cough, and dyspnea [6–8].

Early estimates approximate the mean basic reproduction number for SARS-CoV-2 as 3.28, implicating a rapid spread of the disease and underscoring the need for efficient and accurate screening [9]. Despite heightened public awareness and strong interventional responses, COVID-19 had been diagnosed in more than 2 million individuals worldwide by April 15, 2020. Diagnosis has typically involved testing with reverse transcriptase polymerase chain reaction (RT-PCR) assay, chest CT, or both [10–12]. The number of RT-PCR testing kits is limited; in contrast, CT is often readily available on a case-by-case basis for COVID-19 screening [13–15].

Thin-section chest CT is commonly used for detection and imaging of interstitial lung diseases like COVID-19 [16]. Chest CT as a diagnostic tool has been implemented with protocols of 1- to 5-mm slice thickness, and symptom presentation correlates with the presence of lung abnormalities [16–19]. The symptom presentation has also been found to vary with age and prevalence of preexisting comorbidities [20, 21]. Most individuals infected with SARS-CoV-2, however, show no symptoms [22–24]. The potential for patients without symptoms to spread COVID-19 confirms the importance of early detection and subsequent patient care support and isolation. Some studies also suggest value in follow-up imaging for monitoring and managing COVID-19. Chung et al. [25] performed follow-up chest CT (at 1–4 days and a mean interval of 2.5 days after symptom onset) for eight patients and reported that 63% had mild disease progression, 25% had moderate disease, and only 13% had no worsening of COVID-19 symptoms. These findings highlight the information follow-up CT can provide on disease progression.

RT-PCR testing is a commonly used and highly specific messenger RNA detection and quantification technique that can detect the presence of SARS-CoV-2 in a biologic specimen [26–28]. Real-time RT-PCR test-

ing uses fluorescent dyes to allow scientists to see the results almost immediately. In the United States, the Centers for Disease Control and Prevention have developed the most commonly used assay for COVID-19, which involves a primer for regions of the viral nucleocapsid gene (N1 and N2) and differs from the World Health Organization's assays that target the virus's RNA-dependent RNA polymerase and its envelope genes [26]. This review compares the clinical utility of COVID-19 CT radiologic profiles with that of RT-PCR viral nucleic acid testing. The aim is to show how biased data has affected the literature and to shed light on more reliable calculations of sensitivity according to high-quality methods.

Materials and Methods

Our search strategy included scanning articles in the PubMed database published between January 1, 2020, and April 15, 2020, containing the following keywords in the title or abstract: "CT," "RT-PCR," "sensitivity," and "COVID-19." In addition, we used the medical subject headings search terms "reverse transcriptase polymerase chain reaction," "polymerase chain reaction," "coronavirus," "severe acute respiratory syndrome," "SARS virus," and "sensitivity and specificity." This review focuses on sensitivity because that is the perceived benefit of CT. Guidelines from organizations were included when deemed appropriate, whereas articles that did not involve human subjects or that were not available in English were excluded. Of the search results, articles that were considered to provide relevant data on the clinical utility of CT or RT-PCR testing in diagnosing COVID-19 were selected for review. Additional articles from our search results were included when necessary to allow introductory remarks.

Clinical Utility of CT

A study by Fang et al. [13] evaluated chest CT results from 51 patients on admission. The mean time ± SD from initial disease onset to CT was 3 ± 3 days. Chest CT scans revealed that 98% (50/51) of patients had abnormalities that were consistent with viral pneumonia. Furthermore, 72% of the patients showed typical CT findings, whereas 28% had atypical CT manifestations. Notably, all patients in this study had symptoms including fever or acute respiratory symptoms. Because no patient who did not have symptoms was included, this study may have exaggerated the sensitivity of CT. Similarly, Long et al.'s [27] calculated CT sensitivity of 97% in their study of 36 patients may have been overestimated because of the inclusion of only patients with fevers higher than 38°C or with suspected COVID-19 pneumonia. This overestimation is possible; a study that included patients who had no symptoms found that the sensitivity of CT for COVID-19 was greater in patients who had symptoms (79% of 28 patients) than in patients who had no symptoms (54% of 76 patients) ($p = 0.023$) [29]. Because many individuals infected with SARS-CoV-2 have no symptoms, using cohorts of patients who had symptoms in these studies limits the generalizability of the sensitivities they provide to the broader population infected with SARS-CoV-2.

Although Ai et al. [30] reported a high sensitivity of 97% (601 total patients; 95% CI, 95–98%) for detecting COVID-19 via CT in adults when RT-PCR is used as a reference, the true sensitivity may be lower because of the biased patient cohort consisting of patients with pneumonia. This study also showed how the timeline of negative-to-positive (and positive-to-negative) chest CT scans compares with the respective RT-PCR test timelines. Guan et al. [31] only used patients with confirmed COVID-19 in their patient cohort. This study found chest CT had a sensitivity of 82% (720/877). However, the Guan et al. study is not generalizable to a wider population of individuals infected with SARS-CoV-2 either because their patient cohort, although confirmed to have COVID-19, was also required to have been admitted to an ICU, used a mechanical ventilator, or died. The poor outcome of these patients suggests the exclusion of patients with milder symptoms who are less likely to display abnormal findings in CT images. Thus, in both studies, the reported CT sensitivity may be an exaggeration.

Compared with the information available on sensitivity, very little information is available on the specificity of chest CT for COVID-19, although available reports show it to be especially limited. The Ai et al. [30] article, although biased, reported a specificity of 25% (413 total patients; 95% CI, 22–30%). Given the nonspecific findings on CT in patients with COVID-19, any abnormal chest CT finding was considered a positive result by these studies. One study, however, determined some degree of specificity in CT being able to distinguish COVID-19 pneumonia from other causes of pneumonia [32]. Although their evidence suggests that CT may allow radiologists to distinguish finite stages of COVID-19 pneumonia and differentiate them from non–COVID-19 pneumonia, significant differences were identified in disease severity, age, and prevalence of cardiovascular disease between the study's patient cohorts with and without COVID-19. These three confounding variables weaken the validity of their results.

Compared with studies with biased patient cohorts, studies with fewer methodologic limitations showed lower sensitivities for chest CT in patients with confirmed COVID-19 (Table 1). One retrospective study [33] involving 121 symptomatic COVID-19 cases found that 56% (95% CI, 47–65%) of CT scans taken within 2 days of symptom onset were normal. By contrast, only one patient of those who underwent CT within 2 days of symptom onset had a negative result from an initial RT-PCR test. An expert panel interpreted these results as indicating that up to 50% of CT scans obtained within the first 2 days from symptom onset may be normal [34]. This points to the limited sensitivity of CT shortly after symptom onset, especially compared with RT-PCR testing, and suggests that CT would not be a reliable standalone COVID-19 diagnostic test. In agreement with this result, a study of 104 cases from the Diamond Princess cruise ship found that CT scans were normal in 46% of the 76 patients who had no symptoms and in 21% of the 28 patients who had symptoms ($p = 0.023$) [29]. These lower values for the sensitivity of CT affirm our suspicion that the biases in the previously described studies resulted in their overestimation.

Clinical Utility of RT-PCR

RT-PCR testing can be used as an independent diagnostic tool given its high specificity for COVID-19; however, some reports suggest it has a limited sensitivity. A study by Li and colleagues [35] evaluated the clinical utility of RT-PCR testing in diagnosing COVID-19 among a cohort of 610 patients assumed to have COVID-19 because of positive CT findings of viral pneumonia. They found a positive initial RT-PCR test in 168 patients (implying a sensitivity of 28%). However, this study involved a biased patient cohort and an invalid assumption because not every patient with viral pneumonia has COVID-19. An absence of a reference standard or patients with confirmed COVID-19 may have resulted in the inclusion of patients

TABLE 1: Sensitivity of Initial Chest CT and RT-PCR Testing for Diagnosing Coronavirus Disease (COVID-19)

First Author [Reference]	Total No. of Patients	No. (%) of Patients Confirmed to Have COVID-19		Methodologic Limitations
		On CT	On RT-PCR	
Liu [36]	4880		1854 (38)	Patients determined to have COVID-19 based on typical symptoms or contact with infected people
Fang [13]	51	50 (98)	36 (71)	All patients had fever or acute respiratory symptoms
Long [27]	36	35 (97)	30 (83)	Only included patients with fever > 38°C and suspected COVID-19 pneumonia
Ai [30]	601	583 (97)		Used a biased cohort of patients with pneumonia
Guan [31]	877	720 (82)		Only included patients who had been admitted to ICU, used a ventilator, or died
Xiao [37]	70		55 (79)	RT-PCR sensitivity is for two consecutive tests
Wang [38]	127		91 (72)	
Li [35]	241[a]		168 (70)	
Bernheim [33]	CT: 36; RT-PCR: 102	16 (44)	90 (88)	
Inui [29]	104	63 (61)		

Note—RT-PCR = reverse transcriptase polymerase chain reaction.
[a]Original 610 patients were assumed to have COVID-19 because of CT findings of pneumonia; this limitation was resolved here by only using the 241 patients who eventually had positive RT-PCR tests as the total number of patients.

not infected with SARS-CoV-2, explaining the low sensitivity of RT-PCR testing. This study also noted that 241 patients eventually had a positive RT-PCR test results for COVID-19. Although the study did not provide the calculation, we can retrospectively calculate the sensitivity of RT-PCR testing (168 patients who initially screened positive with RT-PCR assay out of 241 patients who would eventually screen positive for RT-PCR) as more accurate at 70% (assuming there were no false-positives).

In another recent study, Liu et al. [36] analyzed viral nucleic acid test results of 4880 cases suspected of having a respiratory infection in one hospital in Wuhan. This study found a sensitivity of 38% for RT-PCR for the 4818 patients who had nasal and pharyngeal swabs. RT-PCR sensitivity in this study was significantly higher in older patients compared with younger patients and in male patients compared with female patients. However, this study decided that the 4880 patients had COVID-19 according to only typical symptoms or contact with patients with COVID-19 an assumption that weakens the data and casts doubt on the reported sensitivity. Because patients not infected with SARS-CoV-2 may have been included in the study, the sensitivity report may have been an underestimate. Other data from fever clinics reported in this study showed a higher sensitivity of 57% (n = 1707) for RT-PCR results [36].

The Fang et al. [13] study previously described also involved a mean time from initial disease onset to RT-PCR testing of 3 ± 3 days. The RT-PCR findings revealed that 71% (36/51, $p < 0.001$) of patients had initial positive results**.** The authors of this study suggested that the low sensitivity of RT-PCR testing may be attributed to variation in detection rate as a result of improper sampling and immature development of technology. In this cohort, 29% had initial negative RT-PCR results but positive CT results. This group eventually had positive RT-PCR results in follow-up testing (range, 1–7 days), suggesting the limited effectiveness of RT-PCR assay testing for early-stage COVID-19 detection. However, as noted, the cohort for this study involved only patients with fevers or acute respiratory symptoms. It is therefore expected that RT-PCR screening tests would yield positive results for a relatively limited proportion of the patients because a reference standard of patients with confirmed COVID-19 was not used. In contrast, chest CT would have positive results a relatively greater proportion because all the patients had symptoms.

The Bernheim et al. [33] study previously described found a high sensitivity of 88% (90/102) for RT-PCR testing. Because RT-PCR testing is used to confirm diagnosis, the primary reliable method to test sensitivity would be to retrospectively evaluate the RT-PCR results of patients who were eventually confirmed to have COVID-19, which is how Bernheim et al. approached their study. A study by Xiao et al. [37] found 21% of patients with confirmed COVID-19 initially had two consecutive negative RT-PCR results, which current guidelines mandate as one of the requirements for discharge. This means that, for two consecutive RT-PCR results, a sensitivity of 79% (55/70) was observed. Unfortunately, Xiao et al. did not provide data on the sensitivity after the initial RT-PCR test. Another study published in *JAMA* found that RT-PCR testing had a sensitivity of 72% for COVID-19 through sampling from bronchoalveolar lavage fluid, sputum, or nasal swabs. Interestingly, the greatest sensitivity (93%) was observed for bronchoalveolar lavage fluid samples, although the sample size was small at 15 patients [38].

Although the sensitivity of RT-PCR testing for SARS-CoV-2 has been shown by these studies to be fairly high when sampled from bronchoalveolar lavage fluid, sputum, or nasal swabs, it was low when specimens were taken from other areas such as fecal matter or pharyngeal samples. Hao and Li [39] described a case of an unwell adult returning from Wuhan, China, whose initial CT scan showed bilateral ground glass opacification (GGO) subpleural distribution. However, three separate RT-PCR assays of oropharyngeal swab samples were negative for SARS-CoV-2 nucleic acid. A final fourth RT-PCR test was positive for SARS-CoV-2, but this was after significant disease progression was seen on follow-up CT. Al-

though just one case, those results are in agreement with the Wang study [38], which found the RT-PCR test COVID-19 sensitivity in pharyngeal swab samples to be 32% (taken 1–3 days after admission; 95% CI, 31–33%). This may help explain the low sensitivity reported by the biased Liu et al. [36] study, because their methods included pharyngeal swab samples. Although RT-PCR testing reports low sensitivity for SARS-CoV-2 when a pharyngeal sample is used, the greater values for RT-PCR sensitivity given appropriate sampling (i.e., sputum or nasal), compared with the biased studies, affirm our suspicion that those biases resulted in an underestimation of the sensitivity of RT-PCR testing.

Discussion

Because of the novelty and variable symptom presentation of COVID-19, this disease is susceptible to both underdiagnosis and misdiagnosis [40, 41]. Although observed chest CT sensitivities for COVID-19 differ from study to study, many of these reported sensitivities are higher than those reported for RT-PCR testing. However, many studies have overstated the sensitivity of CT and have involved methods riddled with confounding variables and biased patient cohorts [30, 32]. These errors have been reinforced by newer studies that refer to their results as though they were accurate [42–47]. Although we applaud efforts to rapidly share and publish data on COVID-19 for further research, we urge caution against rushing studies that may include the questionable methodologies described in this review. The actual sensitivity of CT for COVID-19 may in fact be less than that of RT-PCR testing (although quality reports are too scarce to ensure that conclusion). In addition, performing CT presents radiology providers with a risk of contracting COVID-19 and becoming vectors to transmit the disease to others [48, 49].

Although RT-PCR testing fills a crucial role in accurately detecting SARS-CoV-2 on a case-by-case basis, it also has inherent problems that limit its utility. Current obstacles to the widespread use of RT-PCR testing include a shortage of testing kits and an extended processing period of several hours before results are obtained [50]. However, given the high specificity and sensitivity of RT-PCR testing, we conclude that only it (and not chest CT) should be used as a primary diagnostic tool. This analysis is in conjunction with the recommendations set forth by the American College of Radiology amid the COVID-19 pandemic. We take these recommendations further by suggesting chest CT may be used as a supplemental tool primarily for patients who have experienced symptoms for more than 2 days or who have symptoms but had negative RT-PCR test results. In addition, although RT-PCR testing can simply be used to detect SARS-CoV-2, chest CT can characterize the disease through detecting pulmonary abnormalities such as GGO [51].

Limitations

Current use of CT may be limited to severe cases of COVID-19 in which symptoms are present before viral testing, given the variable symptom presentation of the disease and the high degree of underdiagnosis. Additionally, many of the studies examined and analyzed in this review are limited to preliminary research on COVID-19 from China. Furthermore, many of the comparative analyses between CT and RT-PCR results were performed on adults and elderly individuals with only a limited number of pediatric cases. These findings, therefore, may not be representative of a larger, more diverse demographic.

The main limitation in gathering accurate sensitivity reports was the prevalence of poor-quality studies and unjustified conclusions [30, 32, 36]. These studies were discussed to show the importance of quality methods and how biases can affect data. Studying patients with pneumonia under the assumption that they have COVID-19 and claiming positive results if any findings of pneumonia are observed may have resulted in overestimations of chest CT sensitivity [30]. In addition, assuming patients have COVID-19 if they have typical symptoms or had been in contact with an individual who was confirmed to have COVID-19 likely resulted in underestimations of the sensitivity of RT-PCR testing [36]. Furthermore, the sensitivity of RT-PCR testing is improved when a proper sample is collected (nasopharyngeal swabs and sputum if possible, as opposed to pharyngeal swabs).

Finally, given the lack of available information on SARS-CoV-2 at the time some of these early studies were conducted, we acknowledge the bias that may be perceived in our critique, given our access to improved protocols and new information (such as that COVID-19 is best confirmed through RT-PCR testing as opposed to CT findings of viral pneumonia). Therefore, our recognition of the limitations of their methods is not meant to imply that the researchers should have known of better approaches at the time.

Conclusion

Although multiple studies suggest RT-PCR testing has a limited sensitivity and chest CT has a superb sensitivity for COVID-19, these reports used limited methods [13, 27, 30, 36]. The methodologic errors of these studies must be pointed out and learned from, because many new studies refer to their results and take them for granted [42–47]. As a result, clinical information available on the sensitivity of COVID-19 diagnostics has been steered toward inaccuracy. Researchers and providers should not only be aware of the prevalence of questionable methodologies in the current literature but also that studies with adequate methods suggest the sensitivity of RT-PCR testing may be comparable with, or even higher than, that of chest CT for COVID-19.

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