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False-Negative Nasopharyngeal Swabs and Positive Bronchoalveolar Lavage: Implications for Chest CT in Diagnosis of COVID-19 Pneumonia

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The precise role of imaging in the diagnosis of coronavirus disease 2019 (COVID-19) is still debated. Early proponents praised chest CT for the initial diagnosis of COVID-19 pneumonia. They pointed to the reported high sensitivity of CT and more rapid results than laboratory testing (1,2). Other studies found a lower sensitivity of CT. Commentators have highlighted frequent false-negative findings at CT early in the course of infection and a low specificity of "typical" findings as seen in other conditions. In this issue of *Radiology*, the study by Patrucco et al (3) provides evidence bolstering the case for CT as a problem-solving tool and gateway to further testing when initial COVID-19 testing is negative.

What is the preferred reference standard for the detection of severe acute respiratory coronavirus 2 (SARS-CoV-2) infection? Real-time polymerase chain reaction (PCR) testing with a single upper respiratory tract sample, usually a nasopharyngeal swab, is common. But false-negative results may occur. Viral shedding in the upper respiratory tract appears to peak just before or just after symptom onset. It declines thereafter and may fluctuate daily (4). Repeat nasopharyngeal PCR testing can serve as an improved reference standard by widening the window of opportunity for detection of viral shedding and minimizing the impact of suboptimal sample collection. In a large clinical study of upper respiratory tract swabs in 2413 patients with initially negative nasopharyngeal PCR results (5), 19% later tested positive for COVID-19 in the setting of a high infection prevalence of 43%. A much-cited early study on the diagnostic performance of CT for COVID-19 (1) included a small number of patients with multiple upper respiratory tract PCR tests. Among 64 patients with initial negative results, 15 (23%) later tested positive, of whom 14 (93%) had CT findings deemed typical for COVID-19 pneumonia prior to or at the time of the positive test. In spite of these results, many imaging studies have not used repeat PCR as a reference standard for assessment of diagnostic accuracy. In studies that do report repeat PCR testing for initially negative results, the proportion of retested patients of the entire study population is often small or unclear (1,2).

Sputum or bronchoalveolar lavage (BAL) samples from the lower respiratory tract may also provide increased diagnostic yield samples for PCR testing. In the first several days after infection, viral replication peaks in the upper respiratory tract. But independent replication in the lower respiratory tract also occurs. Viral load is detectable days to weeks after the onset of symptoms, when the sensitivity of PCR performed on lower respiratory tract samples is declining (6). A landmark early study (4) reported a higher sensitivity of BAL fluid (93%) and sputum samples (72%) than nasal swabs (63%) and pharyngeal swabs (32%). But this was a small study of 205 patients, with only 15 patients who underwent BAL testing.

Patrucco and colleagues (3) present a single-center retrospective study of the diagnostic performance of chest CT in patients suspected of having COVID-19 pneumonia, an imaging analysis of a subset of patients from a recently published study of 131 patients tested by using BAL for SARS-CoV-2 (7). They evaluated 46 patients who underwent a chest CT examination after two consecutive negative nasopharyngeal swab PCRs, using BAL an average of 1–2 days after the upper respiratory tract swabs as the reference standard (3). Eighteen of 46 (39%) of patients tested positive on BAL for SARS-CoV-2. Two radiologists scored CT images according to two validated systems for assessing the likelihood of COVID-19 pneumonia. They found a high proportion of positive PCR tests in patients with scores corresponding to high levels of suspicion. As determined by the Society of Thoracic Radiology/Radiological Society of North America (STR/RSNA) classification (8), a positive BAL PCR result was present in 11 of 15 patients with a CT scored as typical and in 13 of 22 patients with a CO-RADS 4 or 5 score (corresponding to high or very high suspicion). No patients with a positive BAL PCR result had negative findings at CT, and a minority had abnormal CT images with findings deemed uncommon in COVID-19. The study by Patrucco et al is, to my knowledge, the only published study to assess the performance of established COVID-19 CT reporting guidelines in the setting of double-negative nasopharyngeal swab PCR with BAL as a reference standard.

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Conflicts of interest are listed at the end of this article.

See also the article by Patrucco et al in this issue.

A key implication of the study is that even multiple negative nasopharyngeal PCR tests may not be reassuring in the setting of high clinical suspicion for COVID-19, suggesting a major role for CT as a problem-solving modality. A high percentage of SARS-CoV-2–positive BAL PCR tests (73%) were found in patients with CT images classified as typical for COVID-19 by using STR/RSNA guidelines or very high level of suspicion by using CO-RADS score (73%). But atypical appearances were uncommon and no CT images were negative for pneumonia in the SARS-CoV-2–positive group. Thus, CT might play a prudent role in suggesting further testing even when two or more PCRs from nasopharyngeal samples are negative, but suspicion remains. This is already the practice at some institutions and is concordant with some international guidelines.

The study also raises important questions relating to existing practice and research. If a substantial percentage of patients with even two or more negative nasopharyngeal PCRs test positive with BAL, then why is a single nasopharyngeal PCR often used as a clinical reference standard? Is the clinical sensitivity of one PCR even lower than previously thought, and should lower respiratory tract testing be more frequently used? A minority of imaging studies use serial nasopharyngeal PCRs or lower respiratory tract samples. Does this mean existing studies underestimate the diagnostic performance of CT? These concerns are likely overstated. Regarding sensitivity, the performances of upper and lower respiratory tract testing and imaging tests appear to vary with the time elapsed since infection. In the early course of the disease, upper respiratory tract samples have higher sensitivity than do lower respiratory tract samples, but the reverse may be true in the later course of the disease (6). In the study by Patrucco et al, the BAL testing was performed a median of 14 days after symptom onset, when viral load may be higher in the lower respiratory tract than in the upper respiratory tract, and much later than the typical timing of nasopharyngeal swab testing at the onset of symptoms (6). Further, BAL is an invasive aerosolizing procedure requiring highly trained personnel. Also, many patients may not expectorate sputum in quantities sufficient for reliable testing, making widespread use of these tests unreasonable. Finally, BAL is unlikely to be positive in asymptomatic patients with a low pretest probability. One study of BAL samples in 177 outpatients (9) found no patients with a negative SARS-CoV-2 nasopharyngeal PCR and a positive BAL result.

Caution is required in generalizing the 39% positivity rate of BAL in patients with two negative nasopharyngeal PCR tests in the study by Patrucco et al (3). Other clinical studies have found a much lower positive rate for BAL (10). Unfortunately, the sample size of the study is small, and diagnostic yield depends on patient characteristics, disease prevalence, timing and quality of testing, and characteristics of the institutional pathway for repeat or lower respiratory tract testing. Also, patients undergoing lower respiratory tract and serial nasopharyngeal PCR testing are a highly selected group. They are usually symptomatic patients at high risk of disease progression with a moderate to high clinical suspicion of COVID-19. These patients are more likely to be male, older, and have clinical risk factors for severe disease (5). Patrucco and colleagues do not provide a complete reporting of these variables, a common limitation of this and other studies, making generalizability of the yield difficult.

The most important implications of the study are for the potential role of chest CT in COVID-19 diagnosis. First, for patients with persisting clinical suspicion of COVID-19 in spite of two or more negative nasopharyngeal PCR tests, CT might be performed as a "gatekeeper." The yield of lower respiratory tract testing may be high in patients with CT patterns typical for COVID-19 and very low in patients with negative or atypical CT findings. Second, for patients initially presenting with typical CT findings, even two negative nasopharyngeal PCR tests might not be enough to confidently exclude a diagnosis of COVID-19, especially later in the course of the disease. Lower respiratory tract PCR testing might be performed when available and feasible, or a diagnosis of "presumptive positive" assigned based on a combination of clinical suspicion and elimination of alternative diagnoses. Also, additional laboratory and clinical variables can improve specificity. For example, Patrucco and colleagues observed higher BAL specificity in patients with normal or low white blood cell count and typical CT findings. Some critics might question if CT or testing with lower respiratory tract samples is warranted in the setting of a high pretest probability of disease, arguing that these patients should be considered positive for isolation purposes. But this misses the point that accurate diagnosis of COVID-19 is increasingly important for therapeutic purposes, just as a diagnosis of an alternative disease that may mimic COVID-19 may alter therapy.

In conclusion, the study by Patrucco et al supports a role for CT as a problem-solving modality in the setting of clinical suspicion of COVID-19 and initial negative PCR results. Their study provides a cautionary tale against the premature exclusion of COVID-19 when imaging findings are typical and alternative diagnoses are not suggested by the clinical scenario.

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References

1. Ai T, Yang Z, Hou H, et al. Correlation of Chest CT and RT-PCR Testing for Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases. Radiology 2020;296(2):E32–E40.
2. Fang Y, Zhang H, Xie J, et al. Sensitivity of Chest CT for COVID-19: Comparison to RT-PCR. Radiology 2020;296(2):E115–E117https://doi.org/10.1148/radiol.2020200432.
3. Patrucco F, Carriero A, Falaschi Z, et al. COVID-19 diagnosis in case of two negative nasopharyngeal swabs: association between chest CT and bronchoalveolar lavage results. Radiology 2021;298:E152–E155.
4. Wang W, Xu Y, Gao R, et al. Detection of SARS-CoV-2 in Different Types of Clinical Specimens. JAMA 2020;323(18):1843–1844.
5. Green DA, Zucker J, Westblade LF, et al. Clinical Performance of SARS-CoV-2 Molecular Tests. J Clin Microbiol 2020;58(8):e00995-20.
6. Wölfel R, Corman VM, Guggemos W, et al. Virological assessment of hospitalized patients with COVID-2019. Nature 2020;581(7809):465–469 [Published correction appears in Nature 2020 Dec 11. doi: 10.1038/s41586-020-2984-3.].
7. Patrucco F, Albera C, Bellocchia M, et al. SARS-CoV-2 Detection on Bronchoalveolar Lavage: An Italian Multicenter experience. Respiration 2020. 10.1159/000511964. Published online October 19, 2020.
8. 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 - Secondary Publication. J Thorac Imaging 2020;35(4):219–227.
9. Chang J, Swenson KE, Sung A, Bedi H. Coronavirus Disease 2019 Test Correlation Between Nasopharyngeal Swab and BAL in Asymptomatic Patients. Chest 2020. 10.1016/j.chest.2020.11.006. Published online November 17, 2020
10. Geri P, Salton F, Zuccatosta L, et al. Limited role for bronchoalveolar lavage to exclude COVID-19 after negative upper respiratory tract swabs: a multicentre study. Eur Respir J 2020;56(4):2001733.