CORRESPONDENCE

Comparing Nasopharyngeal and BAL SARS-CoV-2 Assays in Respiratory Failure

To the Editor:

Patients with acute respiratory failure concerning coronavirus disease (COVID-19) require a prompt, accurate diagnosis for appropriate triage and management. PCR assays for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA can be performed on upper or lower respiratory samples. Nasopharyngeal (NP) and BAL have generally good concordance for viral respiratory infections (1). However, reports have described patients diagnosed with SARS-CoV-2 by BAL after initial negative NP testing (2). We studied a series of patients who were critically ill with a clinical concern for COVID-19, who had NP and BAL PCR testing to determine NP and BAL test characteristics and accuracy.

Methods

We retrospectively reviewed adult patients intubated for acute hypoxic respiratory failure with a clinical concern for COVID-19 who were tested with both NP and BAL PCR assays for SARS-CoV-2 RNA. We included patients who had BAL assays performed within 5 days after an NP assay, and BAL was considered the definitive diagnostic assay. Statistical analyses were performed with Microsoft Excel version 15.39 for macOS (Microsoft) and in GraphPad PRISM 8 (version 8.4.3 for macOS). Mann-Whitney tests were used to compare nonparametric groups. The study was approved by our institutional review board (STU00212283).

Results

We reviewed 123 patients intubated for acute hypoxic respiratory failure and tested for SARS-CoV-2 with a BAL test within 5 days after an NP test. The median duration between an NP and a BAL swab was 1 day (interquartile range, 1–2.75 d). The NP tests were run on the following platforms: 52 Abbott ID NOW, 5 Becton-Dickinson, 28 Cepheid, 33 in-house, and 5 not listed. The BAL tests were run on the following platforms: 0 Abbott ID NOW, 10 Becton-Dickinson, 84 Cepheid, and 29 in-house. The median age was 63 (interquartile range, 46–70) years, and 39 (31.7%) were female. Overall, 79/123 (64.2%) patients ended up having COVID-19.

Seventy cases had both NP and BAL tests positive; 39 cases had both NP and BAL tests negative; 5 cases had positive NP and negative BAL; and 9 cases had negative NP and positive BAL (Table 1). In comparison with BAL, sensitivity of an NP assay was 88.6%, specificity was 88.6%, positive predictive value was 93.3%, negative predictive value was 81.3%, and accuracy was 88.6%. Of the 14 discordant NP and BAL cases, the NP tests were performed on 6 Abbott ID NOW, 2 Becton-Dickinson, 4 Cepheid, and 2 in-house–developed PCR platforms, whereas the BAL tests were performed on 2 Becton-Dickinson, 11 Cepheid, and 2 in-house platforms. Of the subset of 57 patients who had

Author disclosures are available with the text of this letter at www.nature.com.

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Table 1. Nasopharyngeal and BAL SARS-CoV-2 Results for Patients Intubated for Respiratory Failure Who Had Tests Done within 5 Days of Each Other

|                | BAL Positive | BAL Negative |
|----------------|-------------|-------------|
| NP positive    | 70          | 5           |
| NP negative    | 9           | 39          |

| Statistic      | Value       | 95% CI       |
|----------------|-------------|--------------|
| Sensitivity    | 88.6%       | 79.5–94.7%   |
| Specificity    | 88.7%       | 75.4–96.2%   |
| Positive predictive value | 93.3% | 85.9–97.0% |
| Negative predictive value | 81.3% | 69.9–89.0% |
| Accuracy       | 88.6%       | 81.4–93.6%   |

Definition of abbreviations: CI = confidence interval; NP = nasopharyngeal; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2. Discordant tests: NP tests included 6 Abbott ID NOW, 2 Becton-Dickinson, 4 Cepheid, and 2 in-house platforms. BAL tests had 2 Becton-Dickinson, 10 Cepheid, and 2 in-house platforms.

NP and BALs run on the same platform, 29 had both NP and BAL tests positive, 22 had both NP and BAL tests negative, 2 had positive NP and negative BAL, and 4 had negative NP and positive BAL results (sensitivity, 87.9%; specificity, 91.7%; positive predicted value, 93.4%; negative predicted value, 84.6%).

BALs identified concurrent bacterial pneumonia in 42 (34%) patients; there were more bacterial coinfections found in the group without COVID-19 (24/44, 54.5%) than in the group with COVID-19 (18/79, 22.8%; P < 0.001) (Table 2). All-cause mortality in the cohort was 20 out of 123 (16.3%); mortality was 11/79 (13.9%) in the group with COVID-19 and 9/44 (20.5%) in the group without COVID-19.

Discussion

In patients who are critically ill and intubated for acute hypoxic respiratory failure, NP assays for SARS-CoV-2 RNA have good test characteristics and accuracy compared with BAL assays. NP specimens are less invasive, easier, and potentially safer to collect than BAL specimens, especially in centers in which bronchoscopy is not routinely performed for patients with suspected COVID-19.

However, patients with negative NP but positive BAL assays are reported (2). Wang and colleagues found SARS-CoV-2 RNA in 14 out of 15 (93%) BAL samples but in only 126 out of 398 (32%) pharyngeal swabs from patients with COVID-19 (3). These generated concerns that an NP assay may be insufficient to exclude COVID-19 and that BAL would be necessary for definitive diagnosis. Our data suggest that NP assays can reasonably diagnose intubated patients with suspected COVID-19. We suspect that patients who are critically ill may have a higher viral load in the nasopharynx, making an NP assay perhaps more sensitive than in patients with a less severe disease. Sampling error may create false-negative results, especially from the nasopharynx. Although we cannot control for this possibility in our cohort, we had institutional quality-control measures in place to optimize sample collection. There may also be biologic differences between upper- and lower-airway SARS-CoV-2 RNA expression, as not all patients with COVID-19 develop lower respiratory symptoms. Nevertheless, in this cohort of patients with acute hypoxia requiring intubation, we suspect that upper- and lower-airway SARS-CoV-2 RNA expression would be similar.

Our pathology department used several different test platforms for SARS-CoV-2 detection, including Abbott ID NOW, Becton-Dickinson, Cepheid, and an in-house testing platform. Most BAL samples were run using Cepheid tests based on early in-house validation of this platform for BAL samples. However, attribution of discordant results to the assay platform is difficult, as BAL returns a deeper respiratory tract sample, and happened later in the clinical course (though here we only included those that occurred within 5 days of the NP swab). Newer methods of SARS-CoV-2 sampling, such as through saliva (4), have recently shown robust test characteristics; it will be interesting to see in future studies how saliva results may compare with BAL samples.

Although the data suggest good overall correlation between NP and BAL assay results, a striking number of discordant results remain. For a patient who is critically ill with suspected COVID-19, a negative NP assay is reassuring but not a definitive exclusion of the disease. These false negatives have important implications for use of personal protective equipment and cohorts. BAL has the added benefit of finding concurrent bacterial infection in patients. A recent study of 79 patients with concern for COVID-19 who had BAL performed detected SARS-CoV-2 RNA in two patients who had multiple negative NP swabs (5). They identified 22 “alternative etiologic agents” in 22 patients. We perform BAL for confirmation if the NP test is negative in a ventilated patient with high clinical suspicion for COVID-19; we furthermore find BAL helpful even in patients with positive NP swabs, as it can identify bacterial superinfection and help target treatment (detailed manuscript in progress) or rule out bacterial superinfection, thereby encouraging deescalation of antibiotic therapy. We implemented an aerosol-minimizing protocol at our institution and have found the procedure to have reassuringly low infectious risk to operators (6).

Overall, we find that NP and BAL SARS-CoV-2 tests have reasonably high concordance in patients with respiratory failure when tested within 5 days of each other but still with some discordance. We also found a high rate of bacterial coinfection in the patients with COVID-19. It may be reasonable to consider performing BAL in patients with suspected COVID-19 infection after negative NP swabs, and even in those with positive NP swabs, to evaluate for presence or absence of bacterial superinfection.

Table 2. Patient Demographics for Cohort

|                | Female | Age [Median (IQR)] | Bacterial Coinfection | Mortality |
|----------------|--------|--------------------|-----------------------|-----------|
| All            | 39/123 (32%) | 63 (46–70)        | 42/123 (34.1%)       | 20/123 (16.2%) |
| COVID-19       | 25/79 (31.5%) | 62 (45–70)        | 18/79 (22.8%)        | 11/79 (13.9%) |
| Non–COVID-19   | 14/44 (31.8%) | 65 (50–70)        | 24/44 (54.5%)        | 9/44 (20.5%)  |
| P value        | NS     | NS                 | P < 0.001            | NS        |

Definition of abbreviations: COVID-19 = coronavirus disease; IQR = interquartile range; NS = nonsignificant.
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Lung DNA Methylation in Chronic Obstructive Pulmonary Disease: Relationship with Smoking Status and Airflow Limitation Severity

To the Editor:

Tobacco smoking is the main environmental risk factor of chronic obstructive pulmonary disease (COPD) (1). Yet, despite that it induces marked transcriptomic and epigenetic changes (2), not all smokers develop the disease (1) because of reasons that are still unclear (3). DNA methylation, which involves the addition of a methyl group to a cytosine

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