



Early View

Research letter

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Limited role for bronchoalveolar lavage to exclude Covid-19 after negative upper respiratory tract swabs: a multicenter study

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Manuscript

Despite an early and reliable recognition of Covid-19 is essential for disease control both at a community and hospital level, clinical picture and thoracic imaging alone are not sufficiently specific to distinguish it from other respiratory infections [1, 2]. Real-time reverse transcriptase-polymerase chain reaction (rRT-PCR) is routinely used for qualitative and quantitative SARS-CoV-2 detection in specimens collected from the upper respiratory tract (URs) including *nasal (Ns) or nasopharyngeal swabs (NPs)*, but a second-line investigation like bronchoalveolar lavage (BAL) is often required to diagnose or exclude SARS-CoV-2 infection in a clinical context of possible Covid-19. A significantly lower positive rate in nasopharyngeal swabs (32%) compared to BAL samples (93%) was recently reported [3]; however, BAL was collected in only 15 of 205 patients and in only one case BAL and nasopharyngeal swab were collected simultaneously.

We have retrospectively evaluated the agreement between negative URs and sequential BAL specimens in 79 consecutive inpatients admitted to respiratory units or respiratory high-dependency units of three Italian hub hospitals between March 14, 2020 and May 04, 2020 due to acute hypoxemic respiratory failure. In the three participating Centers, the number of positive PCRs on URs have been 7391 out of a total of 35708 URs tested.

BAL was performed in the Pulmonology Units of the University Hospital of Trieste, University Hospital of Ancona and Pordenone General Hospital after 24-48 hours from at least one negative or indeterminate Ns or NPs, due to persistence of clinical suspect for Covid-19 as defined by: fever, hypoxemic respiratory failure, pulmonary infiltrates on chest X-ray or CT-scan and a recent contact with a confirmed case of Covid-19.

BAL was performed under local anesthesia and mild sedation, instilling repeated aliquotes of sterile saline into the most involved parenchymal area according to radiological findings. At least 50cc of lavage fluid were collected from each procedure. No patients experienced complications or worsening of the respiratory status after the procedure. All specimens were analyzed using rRT-PCR in the virology lab of the respective hospital. A cycle threshold value higher than 40 was interpreted as negative. Each patient signed informed consents for both the endoscopic procedure and data collection.

Among the 79 patients, aged 65 ± 17 years, 59 were males and 20 females. 50 patients had 2 (n= 46) or 3 (n= 4) consecutive negative URs; 2 had the first result reported as indeterminate, that is weak reactivity at the screening test (E and N gene search, according to CDC protocol) and a negative confirmation test (RdRp gene search), and 1 of them repeated the test with a negative result. Only 2 patients with negative swabs had significantly detectable levels of SARS-CoV-2 RNA in BAL samples, one with 2 negative NPs and the other with a first indeterminate result, giving a 97.5% overall agreement between URs and BAL analysis (moderate agreement, Cohen's $k=0.487$). An alternative etiologic agent was identified in 22 subjects and one patient had 3 negative URs and 1 indeterminate BAL result. In our population, 63 patients underwent elective chest CT, which revealed signs compatible with an ongoing viral infection in 38 cases. Normal CT scan were found in 10 cases with negative swabs and none of them had a positive BAL for SARS-CoV-2 (100% agreement).

Given the rapid spreading of Covid-19, diagnostic test accuracy has become of paramount importance in order to offer the best care to patients and to protect both community and medical staff. In our population, we have observed a high concordance between URs and BAL, which is currently considered the gold standard to detect pathogens in the presence of pulmonary infiltrates. We speculate that no concomitant pulmonary infections were detected in most cases mainly due to the fact that all patients had already started an empirical antibiotic treatment regimen 2 ± 1 days in advance. False negative swabs have already been described in patients showing baseline thorax CT features compatible with viral pneumonia [4] and a recent consensus statement on chest CT findings related to Covid-19 defined three patterns of appearance: typical, indeterminate and atypical [5]. In our study, in the only 2 cases with a positive BAL test following negative and/or indeterminate URs, CT-scan

showed a typical appearance for Covid-19: crazy paving pattern and peripheral bilateral ground glass opacities [6].

To our knowledge, this is the largest described BAL series in Covid-19. Given the strong agreement between negative URs and BAL and according to the recent American Association for Bronchology and Interventional Pulmonology statement [7], our findings support a limited role for BAL in the diagnosis of Covid-19 if thoracic imaging and URs are concordantly negative.

Although BAL might not add information to the diagnose of COVID-19, we highlight that it might be necessary in patients with a negative nasopharyngeal swab to establish a different diagnosis of either infectious or noninfectious nature.

Take-home message

Given the strong agreement between negative upper respiratory swabs and BAL, we suggest that BAL has a limited role in the diagnosis of Covid-19 if thoracic imaging and upper respiratory swabs are concordantly negative.

Disclosures

The authors have no conflicts of interest to declare.

References

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* Lancet Publishing Group; 2020; 395: 497–506.
2. Zhou Z, Guo D, Li C, Fang Z, Chen L, Yang R, Li X, Zeng W. Coronavirus disease 2019: initial chest CT findings. *Eur. Radiol.* Springer; 2020; .
3. Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, Tan W. Detection of SARS-CoV-2 in Different Types of Clinical Specimens. *JAMA - J. Am. Med. Assoc.* American Medical Association; 2020.
4. Fang Y, Zhang H, Xie J, Lin M, Ying L, Pang P, Ji W. Sensitivity of Chest CT for COVID-19: Comparison to RT-PCR. *Radiology* NLM (Medline); 2020; : 200432.
5. Simpson S, Kay FU, Abbara S, Bhalla S, Chung JH, Chung M, Henry TS, Kanne JP, Kligerman S, Ko JP, Litt H. 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. *Radiol. Cardiothorac. Imaging* [Internet] Radiological Society of North America (RSNA); 2020 [cited 2020 May 11]; 2:

e200152 Available from: <http://pubs.rsna.org/doi/10.1148/ryct.2020200152>.

6. Chung M, Bernheim A, Mei X, Zhang N, Huang M, Zeng X, Cui J, Xu W, Yang Y, Fayad ZA, Jacobi A, Li K, Li S, Shan H. CT imaging features of 2019 novel coronavirus (2019-nCoV). *Radiology* Radiological Society of North America Inc.; 2020; 295: 202–207.
7. Wahidi MM, Lamb C, Murgu S, Musani A, Shojaee S, Sachdeva A, Maldonado F, Mahmood K, Kinsey M, Sethi S, Mahajan A, Majid A, Keyes C, Alraiyes AH, Sung A, Hsia D, Eapen G. American Association for Bronchology and Interventional Pulmonology (AABIP) Statement on the Use of Bronchoscopy and Respiratory Specimen Collection in Patients with Suspected or Confirmed COVID-19 Infection. *J. Bronchology Interv. Pulmonol.* NLM (Medline); 2020; .