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

To the Editor:

Despite early and reliable recognition of coronavirus disease 2019 (COVID-19) being 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 (RT)-PCR is routinely used for qualitative and quantitative severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) detection in specimens collected from the upper respiratory tract including nasal or nasopharyngeal swabs, 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 out of 205 patients and in only one case BAL and nasopharyngeal swab were collected simultaneously.

We have retrospectively evaluated the agreement between negative upper respiratory tract and sequential BAL specimens in 79 consecutive inpatients admitted to respiratory units or respiratory high-dependency units of three Italian hub hospitals between 14 March 2020 and 4 May 2020 due to acute hypoxaemic respiratory failure. In the three participating centres, the number of positive PCRs on upper respiratory tract specimens was 7391 out of a total of 35 708 tested.

BAL was performed in the pulmonology units of the University Hospital of Trieste, Trieste, University Hospital of Ancona, Ancona and General Hospital of Pordenone, Pordenone (all Italy) after 24–48 h from at least one negative or indeterminate nasal or nasopharyngeal swab, due to persistence of clinical suspect for COVID-19 as defined by: fever, hypoxaemic respiratory failure, pulmonary infiltrates on chest radiograph or computed tomography (CT) scan, and recent contact with a confirmed case of COVID-19.

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

Among the 79 patients, 59 were males and 20 females (age 65±17 years). 50 patients had two (n=46) or three (n=4) consecutive negative upper respiratory tract specimens; two had the first result reported as indeterminate, that is weak reactivity at the screening test (E and N gene search, according to Centers for Disease Control and Prevention protocol) and a negative confirmation test (RdRp gene search), and one of them repeated the test with a negative result. Only two patients with negative swabs (one with two negative nasopharyngeal swabs and the other with a first indeterminate result) had significantly detectable levels of SARS-CoV-2 RNA in BAL samples, giving a 97.5% overall agreement between upper respiratory tract specimens and BAL analysis (moderate agreement, Cohen's k=0.487). One patient had three negative upper respiratory tract specimens and an indeterminate BAL result, while an alternative aetiologic agent

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Given the strong agreement between negative upper respiratory swabs and BAL, this study suggests that BAL has a limited role in the diagnosis of COVID-19 if thoracic imaging and upper respiratory swabs are concordantly negative https://bit.ly/3gpBC75

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was identified in 22 subjects. 63 patients underwent elective chest CT, which revealed signs compatible with an ongoing viral infection in 38 cases. A normal CT scan was found in 10 cases with negative swabs and none of them had a positive BAL for SARS-CoV-2 (100% agreement).

Given the rapid spread 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 negative upper respiratory tract specimens 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]. 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 two cases with a positive BAL test following negative and/or indeterminate upper respiratory tract specimens, the 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 upper respiratory tract specimens 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 upper respiratory tract specimens 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.

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References

1 Huang C, Wang Y, Li X, *et al.* Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; 395: 497–506.
2 Zhou Z, Guo D, Li C, *et al.* Coronavirus disease 2019: initial chest CT findings. *Eur Radiol* 2020; 30: 4398–4406.
3 Wang W, Xu Y, Gao R, *et al.* Detection of SARS-CoV-2 in different types of clinical specimens. *JAMA* 2020; 323: 1843–1844.
4 Fang Y, Zhang H, Xie J, *et al.* Sensitivity of chest CT for COVID-19: comparison to RT-PCR. *Radiology* 2020; 296: E115–E117.
5 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. *Radiol Cardiothorac Imaging* 2020; 2: e200152.
6 Chung M, Bernheim A, Mei X, *et al.* CT imaging features of 2019 novel coronavirus (2019-NCoV). *Radiology* 2020; 295: 202–207.
7 Wahidi MM, Lamb C, Murgu S, *et al.* 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* 2020; 27: e52–e54.