Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

of intubation.[3] Because the indication for tracheal intubation should be carried out uniformly in an institution, it is reasonable to consider the time of intubation as the time when the pathophysiologic condition is similar across patients. In contrast, the time of admission may not represent the same stage of coronavirus disease 2019. In other words, some patients may arrive at the hospital at an early stage, but others may arrive at a late stage.

Another possible solution to the immortal time bias is the use of Cox regression model with time-varying covariates.[4] In this model, the survival outcome is considered as the time-to-event variable. Intubation is a covariate that can happen at any time during hospitalization. This will allow adjustment for other time-varying confounders.

Furthermore, if we want to consider different probabilities of receiving tracheal intubation during the time course of hospitalization, the time-dependent propensity score matching can be used.[5] Because the authors have stated that the intubation is determined by the treating physician without explicit criteria, the propensity of receiving intubation varied across patients during the hospital stay.

Li Hong, MD
Dongyang, Zhejiang, China

AFFILIATIONS: From the Department of Infectious Diseases, Affiliated Dongyang Hospital of Wenzhou Medical University.

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CORRESPONDENCE TO: Li Hong, MD; e-mail: 13505898639@163.com

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Finding an Evidence-Based and Clinically Important Role for BAL in the Setting of Suspected SARS-Cov-2 Infection

To the Editor:

We read with interest the study by Hamed et al[1] in this issue of *CHEST* that compares nasopharyngeal swabs (NPS) and BAL for the detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The authors demonstrate a significant viral gradient from the upper to the lower respiratory tract and a significantly higher sensitivity with the BAL than with the NPS (96% vs 67%). They conclude that a BAL should be obtained in the absence of an existing positive result for SARS-CoV-2.

Given the lack of studies comparing the sensitivity of bronchoscopy and less invasive methods,[2,3] this is certainly a most welcome research. However, the retrospective design, nonconsecutive enrollment, relatively small sample size, and extreme specificity of the study population deserve mention. The study cohort, in particular, is composed exclusively by critically ill patients (86.5% intubated or on extracorporeal membrane oxygenation) with SARS-CoV-2 infection (100% disease prevalence). It is very likely that pretest clinical probability of disease in this population was extremely high. Doubts remain on the reproducibility of the results in a cohort of patients in which SARS-CoV-2 infection was only one of the possible diagnoses. Furthermore, the clinical utility of invasive testing in patients with a very high pretest probability of SARS-CoV-2 infection is lower, because a negative test might not lead to a significant change in the patient's treatment.

In the only other comparative study, a BAL was performed within 48 hours of at least one negative NPS in 79 patients with hypoxemic respiratory failure whose condition did not require intubation.[4] A 97.5% agreement between the two tests was observed, and only two patients with a negative NPS were diagnosed with coronavirus disease 2019 on the BAL. Although the authors do not specify the final diagnosis in patients with negative NPS and BAL for SARS-CoV-2 infection, it is likely that the prevalence of

coronavirus disease 2019 in this population was very low, making it completely different from that enrolled by Hamed et al.[1]

In conclusion, the two aforementioned studies underline the critical importance of the population being examined. It is key that BAL and less invasive methods be compared prospectively in a cohort of consecutive patients with suspected SARS-Cov-2 infection who have been enrolled based on criteria decided beforehand, preferably across a wide spectrum of disease severity. This would allow us to decide reliably when it is clinically useful to perform an invasive procedure that, in this specific setting, implies organizational complexity and risks to the health-care staff.

Rocco Trisolini, MD
Giuseppe Bello, MD
Massimo Antonelli, MD
Rome, Italy

AFFILIATIONS: From the Interventional Pulmonology Unit (R. Trisolini) and the Department of Anaesthesia and Intensive Care (G. Bello and M. Antonelli), Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore.

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CORRESPONDENCE TO: Rocco Trisolini, MD; e-mail: rocco.trisolini@policlinicogemelli.it

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Response

To the Editor:

We note with interest the letter from Trisolini et al in response to our recent report of nasopharyngeal-lung gradient in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) among critically ill patients.[1] They draw attention to the apparently contrasting findings of Geri et al,[2] who found that BAL in patients who are not ventilated with hypoxemic respiratory failure with negative nasopharyngeal polymerase chain reaction (PCR) for SARS-CoV-2 identified only two additional cases of coronavirus disease 2019 (COVID-19). In our report, we noted that 33% of patients with positive deep lung samples (BAL or endotracheal aspirate) had negative nasopharyngeal PCR.[1] Our finding of both false-negative nasopharyngeal swabs and higher viral load in the lungs is consistent with other reports. Wang et al[3] noted a significantly higher positivity rate for BAL (93%) compared with a nasal swab (63%), findings which were replicated in a recent metanalysis of seven diagnostic studies[4] that included those of Wang et al.[3]

We believe the key to understanding these apparently divergent results lies in the differences in the populations that were examined. Our study and those analyzed by Bwire et al[4] included only patients with PCR-confirmed COVID-19 and examined viral detection at different sites, whereas Geri et al[2] investigated patients with undifferentiated respiratory failure. Our study included patients who were admitted at the peak of the first wave of the pandemic in the United Kingdom, and the ICUs that were involved were largely or completely occupied by patients with COVID-19, whereas the prevalence in centers in the study by Geri et al[2] was 21%. Furthermore, all patients had sufficiently severe respiratory failure to merit admission to ICU, and all but one were receiving ventilatory support. Finally, 40% of the patients in the study of Geri et al had no evidence of viral pneumonitis on CT scans. Overall, it appears the divergent results arise from differing pretest probabilities of infection. With a relatively low pretest probability, it is perhaps unsurprising that Geri et al[2] detected only an additional 2.5% cases by bronchoscopy. We do not believe this invalidates the use of deep lung samples to investigate undifferentiated severe respiratory failure, especially as we enter the influenza season in the northern hemisphere. Sampling of the distal lungs can aid the identification of both SARS-CoV-2 and other viral or bacterial pathogens, although the relative roles of