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.

References

1. Patel M, Dominguez E, Sacher D, et al; the Temple University COVID-19 Research Group. Etoposide as salvage therapy for cytokine storm due to coronavirus disease 2019. *Chest*. 2021;159(1):e7-e11.
2. Montero-Baladía M, Buzón L, Astigarraga I, et al. Etoposide treatment adjunctive to immunosuppressants for critically ill COVID-19 patients. *J Infect*. 2020;81(3):452-482.
3. National Institutes of Health Clinical Center. Etoposide in patients with COVID-19 infection. NCT04356690. ClinicalTrials.gov. National Institutes of Health; 2020. Updated January 5, 2021. https://clinicaltrials.gov/ct2/show/NCT04356690.

Response

To the Editor:

We would like to thank Delgado-Lopez et al for their response to our original manuscript.[1] We agree with the sentiment echoed by the writers that, after failure of various antiinflammatory-like corticosteroids and biologic therapies (anti IL-6, anti-IL-1), etoposide has a role in selective patients who still have laboratory and clinical data suggestive of hyperinflammatory syndromes.[1,2] Although the authors have reported on eleven patients with coronavirus disease 2019 who were treated with etoposide as salvage therapy in June 2020, our initial submission was in April 2020 at which time none of the publications had reported any such cases. We are, however, very happy to see the results from the authors' case series reporting similar outcomes as ours. We, like the authors, await the result of the ongoing clinical trial NCT04356690,[3] which will shed more light on the safety and efficacy of etoposide in coronavirus disease 2019.

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FINANCIAL/NONFINANCIAL DISCLOSURES: See earlier cited article for author conflicts of interest.

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DOI: https://doi.org/10.1016/j.chest.2020.11.035

References

1. Patel M, Dominguez E, Sacher D, et al; the Temple University COVID-19 Research Group. Etoposide as salvage therapy for cytokine storm due to coronavirus disease 2019. *Chest*. 2021;159(1):e7-e11.
2. Montero-Baladía M, Buzón L, Astigarraga I, et al. Etoposide treatment adjunctive to immunosuppressants for critically ill COVID-19 patients. *J Infect*. 2020;81(3):452-482.
3. National Institutes of Health Clinical Center. A phase II single-center, randomized, open-label, safety and efficacy study of etoposide in patients with COVID-19 infection. NCT04356690. ClinicalTrials.gov. National Institutes of Health; 2020. Updated September 4, 2020. http://clinicaltrials.gov/ct2/show/ NCT04356690. NCT04356690.

Immortal Time Bias in Comparing Late vs Early Intubation in Patients With Coronavirus Disease 2019

To the Editor:

I read with great interests on the study by Pandya et al[1] in *CHEST* (February 2021), in which they compared the difference between late vs early intubation of patients with coronavirus disease 2019. They found that late intubation was associated with longer length of stay in ICU and duration of mechanical ventilation than the early intubation group. Although it is plausible that the late intubation group may experience prolonged periods of hypoxia that result in pathophysiologic derangements such as hypoxemia and multiorgan dysfunction, the finding may also be attributable to the immortal time bias.[2] Immortal time bias refers to a distortion that modifies an association between an exposure and an outcome, caused when a cohort study is designed so that follow up includes a period of time in which participants in the exposed group cannot experience the outcome and are essentially "immortal."

In the present study, the time from admission to intubation is the immortal time, in which the outcome of mortality cannot occur. When the length of stay in ICU was calculated from admission, this immortal time is attributed inappropriately to the effect of intubation. As a result, the length of stay is prolonged in the late intubation group. A potential solution to the immortal time bias is to reset the time zero of follow up to the time

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.

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FINANCIAL/NONFINANCIAL DISCLOSURES: None declared.

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DOI: https://doi.org/10.1016/j.chest.2020.09.284

References

1. Pandya A, Kaur NA, Sacher D, et al. Ventilatory mechanics in early vs late intubation in a cohort of COVID-19 patients with acute respiratory distress syndrome: a single center's experience. *Chest*. 2021;159(2):653-656.
2. Dall'Olio FG, Di Nunno V, Massari F. Immortal time bias question in the association between toxicity and outcome of immune checkpoint inhibitors. *J Clin Oncol*. 2020;38(1):105-106.
3. Lévesque LE, Hanley JA, Kezouh A, Suissa S. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. *BMJ*. 2010;340:b5087.
4. Zhang Z, Reinikainen J, Adeleke KA, Pieterse ME, Groothuis-Oudshoorn CGM. Time-varying covariates and coefficients in Cox regression models. *Ann Transl Med*. 2018;6(7). 121-121.
5. Zhang Z, Li X, Wu X, Qiu H, Shi H. on behalf of AME Big-Data Clinical Trial Collaborative Group. Propensity score analysis for time-dependent exposure. *Ann Transl Med*. 2020;8(5). 246-246.

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