3. The authors report a tracheostomy rate of 21.2%. This figure far exceeds ARDS tracheostomy rates in a global sample (13%) (9) and in the supine group of the PROSEVA trial (5.2%), study populations that are both characterized by greater ARDS severity than the cohort of Ziehr and colleagues. Tracheostomy has been shown to improve short-term but not long-term survival in patients with ARDS (9).
4. The authors registered an ICU discharge rate of 75.8%, a result that is discordant with other reports (2) and enthusiasm about which warrants caution. A common frontline observation is that patients with COVID-19 are highly susceptible to complicated hospital courses following initial ICU discharge, punctuated by returns to the ICU and a remarkable propensity for sudden death. Data about this aspect of critical illness in COVID-19 are lacking, but the ICU discharge rate reported by Ziehr and colleagues risks conveying a prematurely optimistic message.

The arguments presented herein are a call for care in adopting the results of the study by Ziehr and colleagues as demonstration that SARS-CoV-2 lung disease fully conforms to the ARDS paradigm and as the latest benchmark for ICU outcomes in this condition. Frontline experience suggests that reality lies somewhere between published extremes. ■

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Oleg Epelbaum, M.D., A.T.S.F.*
Westchester Medical Center
Valhalla, New York

ORCID ID: 0000-0002-6920-0540 (O.E.).

*Corresponding author (e-mail: oleg.epelbaum@wmchealth.org).

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Reply to Epelbaum

From the Authors:

We thank Dr. Epelbaum for the opportunity to further discuss our data. Dr. Epelbaum raises several important points for discussion.

Massachusetts General Hospital and Beth Israel Deaconess Medical Center are tertiary care hospitals at the epicenter of the coronavirus disease (COVID-19) response in Boston, Massachusetts. As of May 16, 2020, the hospitals have cared for more than 700 critically ill patients with COVID-19. Our motivation to publish our frontline systematic observations stemmed from concern that anecdotal reports, susceptible to cognitive biases (1), were gaining significant attention and impacting practice patterns for respiratory failure (2).

As of May 16, 2020, our cohort of 66 patients had a median follow-up of 53 days (range, 48–67 d) with 14 total deaths (21.2%) (3). Fifty-one patients (75.8%) had left the ICU, and 46 patients (70.0%) were discharged alive from the hospital. Six patients (9.1%) remained hospitalized. Fifteen of 66 patients (21.2%) received a tracheostomy; 8 patients (53%) were decannulated. We agree that further studies are needed about the timing and use of tracheostomy in COVID-19 respiratory failure. Dr. Epelbaum states that reports from New York and Italy are discordant with the mortality in our cohort; however, the mortality rates are in fact quite similar. The cited article from New York has been formally corrected to reflect a mortality of 24.5% among mechanically ventilated patients. In the cited manuscript from Italy, mortality at the time of censoring was 26% for ICU patients (4). All early reports should be interpreted in the context of limited follow-up and absence of risk adjustment. However, our original report described a follow-up period which, to our knowledge, was longer than any published series outside China. We would also emphasize that the 70% hospital discharge rate in our cohort does not support Dr. Epelbaum's statement of "remarkable propensity for sudden death" following initial ICU discharge.

Dr. Epelbaum reports that the comparison of our cohort to the PROSEVA (Prone Positioning in Severe ARDS) (5) trial reveals "'unARDS-like' clinical behavior." First, we caution against direct comparison of our entire cohort to PROSEVA. PROSEVA enrolled

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patients with severe acute respiratory distress syndrome (ARDS), whereas our cohort included all patients intubated for respiratory failure. If we examine comparable patients from our cohort—those with moderate to severe ARDS who were treated with prone positioning—we see similar physiologic responses. Patients in PROSEVA (Figure S2 from Reference 5) had a mean Pa_{O_2}:FI_{O_2} ratio of approximately 110 when supine, prior to first proning session, with improvement to 190 at the end of the first prone session (difference, +80). Patients in our cohort improved from a median Pa_{O_2}:FI_{O_2} ratio of 150 when supine to 232 during the first prone session (difference, +82).

Finally, we share Dr. Epelbaum's concern about the use of off-label therapies for ARDS, including statins. Preclinical and observational data published prior to COVID-19 suggested a role for statins for the treatment of viral infections, including severe acute respiratory syndrome coronavirus (SARS-CoV), 2009 influenza A (H1N1), and Middle East respiratory syndrome (6, 7). Therefore, at the time of our study, hospital guidelines recommended initiating statins for accepted secondary indications frequently present in patients with COVID-19 and not for ARDS *per se*. We agree that statin therapy has not shown benefit in unselected patients with ARDS and requires further study. We also agree that off-label therapies should ideally be used in the context of clinical trials.

Frontline experience remains critical to inform real-time patient care and shape future research. We urge the continued rigorous study of these observations to accurately inform the management of critically ill patients with COVID-19. ■

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David R. Ziehr, M.D.
Massachusetts General Hospital
Boston, Massachusetts
and
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Jehan Alladina, M.D.*
Massachusetts General Hospital
Boston, Massachusetts

Camille R. Petri, M.D.
Jason H. Maley, M.D.
Massachusetts General Hospital
Boston, Massachusetts
and
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Ari Moskowitz, M.D.
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Benjamin D. Medoff, M.D.
Kathryn A. Hibbert, M.D.
B. Taylor Thompson, M.D.
C. Corey Hardin, M.D., Ph.D.
Massachusetts General Hospital
Boston, Massachusetts

ORCID IDs: 0000-0002-8029-7259 (D.R.Z.); 0000-0003-0136-6859 (J.A.); 0000-0003-4120-3069 (C.R.P.).

*Corresponding author (e-mail: jalladina@mgh.harvard.edu).

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Cigarette Smoking and COVID-19: A Complex Interaction

To the Editor:

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing coronavirus disease (COVID-19), has expanded from Wuhan throughout China and is being exported to a growing number of countries worldwide. Despite the fact that the main complications of COVID-19 affect the lung, the prevalence of current smokers among hospitalized patients with COVID-19 has been reported consistently lower than the prevalence of smokers among the general population for that specific geographical area (1), even if one might have anticipated the opposite. Thus, the epidemiological data seem to question the role of coexisting active smoking as a risk factor for COVID-19 pneumonia.

The data from Cai and colleagues, recently published in the *Journal* (2), report upregulation of pulmonary ACE2 (angiotensin-converting enzyme 2) gene expression in ever-

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