deserve praise for their study, which to date is the highest quality evidence to evaluate the use of ivermectin in patients with this disease.

Propensity score matching, like other adjustment techniques, can only account for between-group differences that are included in the propensity score itself. One possible variable that the authors themselves raise in their discussion, but did not adjust for, is “timing bias” or chronologic bias. The authors state “more of the control group was enrolled in the first weeks of the study.” If care changed in other ways at the same time ivermectin became the norm in the authors’ hospital, then the outcomes could be ascribed falsely to ivermectin. Nationally available data have shown declining in-hospital mortality rates during this time period. Unlike most design flaws, chronicologic bias could be tested for simply by adding date of admission to the propensity score. If this makes matching impossible, then chronicologic bias becomes likely. We hope the authors consider this analysis.

Further, the unusually common administration of ivermectin to admitted patients during this timeframe consecutively, particularly later in the study, suggests that ivermectin was effectively the standard of care at these sites and implies that patients who did not receive it may have differed systematically in other, unmeasured ways. This is a form of confounding by indication, is more statistically intractable, and may have also led to misleading results during the early period of the pandemic with anticoagulation and hydroxychloroquine for hospitalized patients with COVID-19.

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Response
To the Editor:

We appreciate the thoughtful comments of Drs Keller and Sussman. Per their suggestion, we reran the propensity match, adding admission date to the variables for propensity scoring performed in the original article (age, sex, pulmonary condition, hypertension, HIV, severe pulmonary presentation, exposure to corticosteroids, race, WBC count, absolute lymphocyte count, and the need for mechanical ventilation prior to or on the day of study entry). As in the original article, propensity matching was performed with the use of a nearest-neighbor algorithm with 1:1 matching without replacement and a caliper distance of <0.2. With the addition of admission dates, the number of patients in the propensity match decreased to 48 in each group. The difference in mortality rate remained significant in this new date-adjusted propensity-matched cohort, with mortality rate of 22 of 48 patients (45.8%) in the control group and 7 of 48 patients (14.6%) in the ivermectin group (P = .001 by Chi square; OR, 0.20 [95% CI, 0.08-0.54]).

We are in agreement with their second point regarding unmeasured cofounders that are, by definition, not something that can be corrected for without a randomized design. We believe our findings remain very compelling and support the continued need for a well-designed randomized study.

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Spontaneous Pneumothorax (SP) in COVID-19 Is Associated With Worse Outcomes Than SP in Non-COVID-19 Patients, Which Suggests That SP in COVID-19 is A Sign of Disease Severity

Is This Finding a Pure Association or Is There Really a Strong Relationship Between the Two?

To the Editor:

We read with great interest the recent article in CHEST (March 2021) by Miró et al who concluded that spontaneous pneumothorax (SP) is associated with worse outcomes than SP in patients without COVID-19 and in patients with COVID-19 without SP. We would like to comment. When we look carefully to the results, we see that 32.3% of the patients with COVID-19 with SP went to ICU and that patients died significantly more with an OR of 4.07. Compared with the control group that did not have COVID-19 with SP, the ICU admission was only 2.6%, and the mortality rate was 1.6%. Compared now with COVID-19 without SP, ICU admission was only 1.8%, and the mortality rate was 13.8%. Clearly, the two control groups were much less sick when we see the ICU admission compared with COVID-19 with SP. So, there is no certainty that SP is a sign of higher severity on itself because it might be just a pure association and not a strong relationship. Indeed, the difference in severity might be due to other comorbidities not described in the study. The literature is very controversial regarding the mortality rate and this potential relationship. In a study looking at 15 cases of COVID-19, spontaneous pneumomediastinum was associated with a much lower mortality rate of 26%. In another cohort study with 18 patients with SP, the mortality rate was only 27%. In another review, the authors concluded that it should be emphasized that a causal relationship between COVID-19 severity and pneumothorax cannot be concluded. The presence of prior bullous disease, underlying connective tissue disease, hormonal irregularities, environmental exposure, and vigorousness of coughing are unknown considerations. The majority of these precipitating factors were not evaluated in the study of Miro et al. In addition, when comparing COVID-19 with SP with COVID without SP, we found that history of asthma was significantly higher (20% vs 6.8%) as was dyspnea (87.5% vs 54.3%), which are well-known precipitating factors for SP. Regarding the severity of the disease between COVID-19 with SP compared with COVID-19 without SP, classic severity indicators for COVID-19 were not different between the two groups, such as C-reactive protein levels, procalcitonin levels, and aspartate amino transferase levels. In a more recent study, the authors showed the importance early surgical treatment for SP, and we do not know how many of the patients in the study of Miro et al underwent rapid surgery that could save their lives.

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