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.

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Response

To the Editor:

In the battle against COVID-19, scientists all over the world are doing their best to fight. From January 24, 2020, when the SARS-CoV-2 cases were first reported,[1] to today (February 16, 2021), more than 100,000 related articles have been published. These scientific discoveries have enabled us to better understand our enemies.

In the research article published in *CHEST*,[2] we enrolled the first 192 patients with severe COVID-19 from the Lotus study (Lopinavir Trial for Suppression of SARS-Cov-2, Chinese Clinical Trial Register number, ChiCTR2000029308), which was conducted from January 18, 2020, through February 3, 2020. Longitudinal samples including plasma, oropharyngeal swabs, and anal swabs were collected, and viral RNA was detected with reverse transcription polymerase chain reaction (PCR). Risk factors of patients complicated with viral RNAaemia were analyzed, and its association with clinical prognosis was assessed. With the spread of the epidemic, new cases have emerged worldwide, and increased amounts of evidence suggested that viral RNAaemia was associated with worse outcomes of patients with COVID-19,[3] but the risk factors for RNAaemia are not clear.

Viral RNAaemia, which might result from live virus particles in the blood and debris of virus-infected cells, does not equal viremia. Although it has been proved that viral RNA of SARS-CoV-2 could be detected in the blood of patients with COVID-19, no success at isolating live virus particles has been reported. In vitro study showed that SARS-CoV-2 could infect capillary organoids and produce progeny virus,[4] but whether it was the case in vivo remained uncertain. Isolation of live virions from blood was influenced by a series of factors, such as the presence of neutralizing antibodies and viral load.[5] Furthermore, viral RNA, as a potent trigger of immune response, might also be involved in the pathogenesis of COVID-19. Therefore, no live virion successful isolation does not mean no harm.[3]

Future basic research work is needed to understand the causes of viral RNAaemia and its role in disease pathogenesis. We agree that droplet digital PCR has higher sensitivity than quantitative PCR, and it could detect samples with low levels of nucleic acids. However, it still could not distinguish viral RNAaemia from viremia.

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Chronologic Bias, Confounding by Indication, and COVID-19 Care

To the Editor:

The authors of "Use of Ivermectin Is Associated With Lower Mortality in Hospitalized Patients With Coronavirus Disease 2019"[1] in *CHEST* (January 2021)

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.[2] 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.[3] Unlike most design flaws, chronologic bias could be tested for simply by adding date of admission to the propensity score. If this makes matching impossible, then chronologic 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[4] and hydroxychloroquine[5] 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).[1] 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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