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## Letter to the Editor

# Problems with the analysis in “Treatment with Hydroxychloroquine, Azithromycin, and Combination in Patients Hospitalized with COVID-19”



Dear Editor,

I am writing to comment on the article “Treatment with Hydroxychloroquine, Azithromycin, and Combination in Patients Hospitalized with COVID-19” by Samia Arshad et al. (Arshad et al., 2020). In this observational study, the patients were deliberately assigned to the treatment protocols based on their underlying medical conditions. This introduces a bias into the study, and as with all observational studies, there is the hope that the subsequent adjustments, based on a regression model in this instance, will compensate for this bias. This hope is not justified. To understand why it is necessary to examine the results for individual variables in the regression model and judge whether they are plausible. If they are not plausible, then you can conclude that the regression model is almost certainly flawed.

The process of allocating patients to treatment groups results in the “neither drug” group having a disproportionately high share of patients with cardiovascular comorbidity. The Arshad et al. (2020) study finds that the Hazard Ratio for cardiovascular comorbidity is 1.062 (from Table 2 of Arshad et al., 2020) and is not statistically significant. Similarly, it finds that the Hazard Ratios for COPD comorbidity and Hypertension are not statistically significant. Other studies have shown the increased risk of death due to cardiovascular comorbidities to be around 300% (see, for example, Dhakal et al., 2020), not 6%, so the (not statistically significant) 6% is just not plausible. Other implausible results are that having a BMI of 30 or higher reduces that patient's risk of death by 22%, and being white increases it by 74%.

Another major flaw in the study is that it makes a substantial adjustment to the death rate if the patient receives ventilator

support. A hypothetical thought experiment reveals the inappropriateness of such an adjustment. Consider a treatment protocol A which results in all the patients on that protocol requiring ventilator support, and which is being compared with a treatment protocol B in which none of the patients require ventilator support. If the actual death rate for protocol A was twice the actual death rate for protocol B, after making the Hazard Ratio adjustment of 2.159 for ventilator use (from Table 2), protocol A would be judged to have a lower death rate than protocol B. This is clearly not an appropriate result.

As a result of the flaws in the analysis, the conclusions reached in Arshad 2020 are invalid.

## Conflict of interest

No conflict of interest to declare.

## Ethical approval

Approval was not required.

## References

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