Letter to the Editor

Letter to the editor: The effect of hydroxychloroquine on COVID-19

Dear Editor,

We have read the article "Comparing ICU admission rates of mild/moderate COVID-19 patients treated with hydroxychloroquine, favipiravir, and hydroxychloroquine plus favipiravir" with great interest [1]. The study compared ICU admission rates of the hospitalized COVID-19 patients between the treatment groups from a large center in Turkey. The following points require clarification for a better interpretation of the findings:

1 Power calculation was not presented. It would have helped to evaluate the limitations and implications of the study.
2 The inclusion rate was too low and difficult to relate to the exclusion criteria. A flowchart depicting eligible subjects and the reason for excluding them should have been provided.
3 Factors related to poor prognosis were more common in favipiravir treatment groups than hydroxychloroquine only group, including older age, male sex, comorbidities (diabetes mellitus, hypertension, malignancy, etc.), inflammatory markers, radiological signs of more severe pulmonary disease, and higher SOFA scores. Propensity score matching should have been used for the adjustment.
4 In propensity models, standardized differences with a threshold of 10% were chosen to define imbalance. This threshold signified a wide caliper problem, which could cause substantial bias for such imbalanced data. Tighter caliper and closer matches would be preferred to modifying the propensity score, as mentioned above [2].
5 Analysis with trimming could have introduced selection bias.
6 Synthetic Minority Oversampling Technique (SMOTE) is an approach for classification of data in case of an imbalance [3]. However, imbalance between treatment groups in that study had an impact on the outcome, but not on classification.
7 Sub-group analysis is a common variation of sensitivity analysis, which is relevant for this study comparing the treatment outcomes but was not performed in the analysis [4].
8 Data about the duration of hospitalization, treatment decision, and drug-related adverse events were not given. The study used patient data between March 15 and June 1, 2020. During this period Turkish Ministry of Health released four documents on the treatment algorithm and criteria for hospitalization of COVID-19 patients [5]. Favipiravir was mainly reserved for more severe disease, which was evident in the higher frequency of more severe COVID-19 patients receiving favipiravir treatment. Thus, time matching should have been added to adjust for these differences due to changes in the treatment algorithm.

In conclusion, two crucial domains of randomized clinical trials are balancing confounders and concealment of the treatment decision. These aim to minimize the influence of confounders and sources of bias. In observational studies, treatment decisions are primarily based on prognostic factors, which are difficult to control. In this retrospective study comparing the treatment effect of hydroxychloroquine and favipiravir on COVID-19 related ICU admission, the groups had significant differences in the frequency of confounders, and the choice of treatment was related to disease severity. The authors used propensity score modeling as an attempt to adjust the confounders. However, without propensity matching, the authors failed to balance these confounders. We think that this approach threatened the validity of the study findings and conclusions.

References

[1] Guner R, Hasanoglu I, Kayaaslan B, Aypak A, Akinci E, Bodur H, et al. Comparing ICU admission rates of mild/moderate COVID-19 patients treated with hydroxychloroquine, favipiravir, and hydroxychloroquine plus favipiravir. J Infect Public Health 2021;14(March (3)):365–70, http://dx.doi.org/10.1016/j.jiph.2020.12.017.
[2] Lunt M. Selecting an appropriate caliper can be essential for achieving good balance with propensity score matching. Am J Epidemiol 2014;179(January (2)):226–35, http://dx.doi.org/10.1093/aje/kwt212.
[3] Elreedy Dina, Atiya Amir F. A Comprehensive Analysis of Synthetic Minority Oversampling Technique (SMOTE) for handling class imbalance. Inf Sci 2019;505:32–64, http://dx.doi.org/10.1016/j.ins.2019.07.070.
[4] Salciccioli JD, Crutain Y, Komorowski M, Marshall DC. Sensitivity analysis and model validation. 2016 September 10. In: MIT Critical Data, editor. Secondary analysis of electronic health records. Cham (CH): Springer; 2016., http://dx.doi.org/10.1007/978-3-319-43742-2_17. Chapter 17.
[5] https://www.ekmud.org.tr/haber/453-t-c-saglik-bakanligi-covid-19-rehberleri-arsivi. (Last access on June 5, 2021, 0033, Istanbul). The website provided information in Turkish.Accordingly, the Turkish Ministry of Health documents were dated March 23, 2020, April 2, 2020, April 9, 2020, and April 12, 2020. Briefly, regimens including favipiravir were approved for patients not responding to hydroxychloroquine (March 23, 2020), for severe or deteriorating cases of COVID-19 pneumonia (April 2, 2020), for patients with lymphopenia or high inflammatory markers, or extensive bilateral COVID-19 pneumonia (April 9, 2020), and for severe COVID-19 pneumonia or COVID-19 cases not responding to hydroxychloroquine treatment (April 12, 2020). [Translated by the authors].

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