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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Reply to the letter to the editor "Azithromycin, treatment in COVID-19"

Editor: J.-M. Rolain

Dear Editor

We thank the authors of the letter to the editor, "Azithromycin, treatment in COVID-19" for their careful reading of our paper "Safety and effectiveness of azithromycin in patients with COVID-19: An open-label randomised trial" [1] and their precise and helpful comments. We would like to discuss the issues raised by the authors of the letter and to provide further information and an update on our paper.

Regarding the questions on the severity of COVID-19 at admission, all patients in the study were hospitalized based on the available national criteria and approved guidelines at that time. During the pandemic, guidelines have changed in response to rapidly evolving evidence either crediting or discrediting certain options for COVID-19 management. In accordance with our study protocols, patients were included based on clinical criteria suggestive of COVID-19, including oxygen saturation <93%, respiratory distress (rate >30), and positive computed tomography (CT) scan findings indicative of COVID-19. As COVID-19 cannot be differentiated from other infective diseases by clinical manifestation only, any patients with clinical characteristics of COVID-19 were tested for this disease and treated accordingly. The patients included in the study showed clinical signs of COVID-19 from 7 to 10 days before admission (details of clinical signs suggestive of COVID-19 can be found in our paper). The quality and rate of hemoptysis and cough were not assessed as these were not defined as separate variables in our study.

All patients included in our study fulfilled the admission criteria and had severe disease; hence we could not withhold treatment. As mentioned in the letter to the editor, care was taken that all included patients were in the active phase of disease. In our paper, we refrained from elaborating on certain points including which findings are suggestive of COVID-19 on CT scan because these points have been explained in detail elsewhere [7]. All scans in our study were reviewed by trained radiologists who were experienced in COVID-19 because of the high patient load in our hospital. We also understood that the increased severity of pulmonary involvement does not necessarily imply more severe clinical condition, or vice versa. As stated in our paper, the primary set point of our study was based on clinical condition, and not on severity of findings on imaging.

The authors of the letter criticized the randomization in our study. We respectfully disagree with their criticisms for the following reasons. Despite the random allocation used in our study, there were very small differences between the two groups, as expected. The mean difference between oxygen saturation of patients was 0.1 (P=0.920), which was statistically insignificant and clinically unimportant. Also, regarding the 5-year difference between the mean of ages in the two groups, we refer to the World Health Organization (WHO) guideline for COVID-19 complications, in which age 60 years is a threshold for increasing complications [2]. In the Iranian national guidelines, this threshold is set at 65 years of age [3]. Therefore, both guidelines relate to patients aged over 60 years. Assessing the impact of treatment in patients below that age was outside the scope of our study.

The authors of the letter mentioned that some of the patients were discharged with the lower oxygen saturation goal (92%) of the study. This observation is correct, with the reason being these patients were unwilling to continue treatment in the hospital. However, all these patients continued treatment at home with remote monitoring and under close follow-up. Regarding the differences between the two groups in baseline characteristics, such as history of chronic diseases, we emphasize that random allocation and elimination of confounders was the correct approach; there were no statistically significant differences between the groups in our study.

Patient safety was of paramount importance in our study; hence care was taken to ensure all patients received the required medications. All patients enrolled in the study had severe disease; therefore, according to the current national guidelines, initiation of hydroxychloroquine and ritonavir/lopinavir treatment was required. Notably, at the time of our study, ritonavir/lopinavir had been associated with potential benefits in patients with COVID-19 in several studies [4,5]. Although later studies discredited the efficacy of ritonavir/lopinavir for COVID-19 [6], use of this treatment was included in our national guidelines at that time.

As stated in our paper, the most likely serious treatment complication was anticipated to be heart arrhythmias, particularly due to QT-prolongation by hydroxychloroquine and azithromycin; therefore, patients at high risk of cardiac complications were excluded from the study. All study patients were monitored daily using electrocardiography (ECG) to assess cardiac health and enable any signs of arrhythmia or cardiac dysfunction as a side effect of treatment to be identified immediately. No adverse events were observed that required further discussion.

The authors of the letter critiqued the use of some the papers to which we referred in our discussion. In response, we emphasize that no false claim was made in our discussion. The paper demonstrating effectiveness of azithromycin against Zika and Ebola viruses has been cited to be based on an in vitro study [1,8]. Although we agree that effectiveness in human models based on in vitro studies cannot be assumed, in vitro studies are a crucial step before progression to in vivo studies and clinical trials. We took care to include only credible and authentic references in our paper. We emphasize that even if the validity of certain references

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was doubted, we made no definite conclusions or treatment plans based on those papers.

We thank the authors of this letter for pointing out that the correct proportion of patients with myalgia was 40%. However, importantly, despite this error, the statistical calculations for the study were completed correctly. A requested statistic was the number of patients receiving methylprednisolone: there were two patients in the case group and seven patients in the control group. Lastly, we note that no study is perfect; however, we believe our study provided useful information. All treatment modalities for COVID-19 need to be further tested and assessed in multiple large clinical trials at other sites. Again, we appreciate the careful reading of our paper and keen insights provided by the authors of this letter.

Declarations

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