

Response to reviewers

Reviewer # 1

Comment 1- " I have reviewed the manuscript entitled 'The use of hydroxychloroquine and azithromycin combination to treat the COVID-19 infection'. The manuscript is well-written and instructive however I have several comments to be added to the article. These drugs were tried to prescribed in the beginning of the pandemic. We knew very less about Covid-19 at that time. The Covid infection appears to be highly procoagulant disease and the role of these therapies may be limited due to the nature of covid-19 disease in terms of high risk for thrombus and emboli formation. D-dimer and fibrinogen follow-ups are very important for the disease severity and anticoagulation therapy has a great value in highly risk patients."

Our response- We thank the reviewer for their kind comments. As per the suggestion, we have added a separate section in the revised

manuscript entitled –**“Role of hydroxychloroquine and azithromycin combination in high-risk patients”**. In this section we have highlighted the role of thrombotic potential of covid-19 as well as role of D-dimer / Fibrinogen for predicting high risk.

Comment 2- “The authors should discuss the potential roles of these treatment (hydroxychloroquine and azithromycin combination) in highly risk patients which was defined with the help of d-dimer levels. Please consider 'Fibrinogen and D-dimer variances and anticoagulation recommendations in Covid-19: current literature review' and 'Mean serum D-dimer level to predict in-hospital mortality in COVID-19”.

Our response- We thank the reviewer for their kind comments. As per the suggestion, we have added a separate section in the revised manuscript entitled –**“Role of hydroxychloroquine and azithromycin combination in high-risk patients”**. We have discussed both the articles as suggested and added both as new references too. (References no. 31& 32) We also have added a study by Lambach *et al*/(ref.no 34) where

the combination therapy failed to show benefits in high risk patients stratified by D-dimer levels.

Reviewer # 2

Comment 1- “: There are many open access articles with the same subject on the internet. Based on this argument, it is recommended to see the data resulted after a systematic review instead of a narrative one.”

Our response- We thank the reviewer for their kind comments. As per the suggestion, we have a separate Method section in the revised manuscript and described out systematic search criteria utilized for accumulating data for this review, narrative one though.

“Methods - We systematically searched the PubMed and Clinical trials.org databases up to December 25, 2021 using several specific keywords (i.e., “COVID 19”, “HCQS and azithromycin”, or “SARS COV 2”) and retrieved all articles published in the English language that reported efficacy, safety, clinical outcome, and pharmacology for the hydroxychloroquine and azithromycin combination in patients with

COVID-19. We compiled all the data and narrated the past, present, and future of HCQS and azithromycin combination in the context of COVID-19."