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Peer Review File

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Responses to Reviewer A

Comment 1: This is an important study addressing an ongoing health threat globally. It can be further improved as follows: a) Please report the prevalence of chronic HBV and HCV infections; b) May compared with some similar studies (e.g. PMID: 32641471); c) Discuss how chronic HBV and COVID-19 interacts (e.g. PMID: 33961298)

Reply 1:

a) The frequency of HBV and HCV infections was not assessed in all of our patients. Differently from Asia, prevalence of HBV and HCV infections in Brazil is very low, around 0.3 to 0.5% (PMID: and PMID:). Most of the studies evaluating the frequency of liver enzymes abnormalities in the West have not evaluated systematically viral infections in those patients with COVID-19 without previous underlying liver disease (please see PMD: 32473607; PMD: 34487314, PMD: 33945064, PMD: 33514597 and PMD: 33534084). Even some studies conducted in the East have not ruled out HBV and HCV infections in their patients with abnormal liver enzymes (see PMD: 32305291). In our study, serology for HBV and HCV was carried out at physician's discretion and those few results (all negative) were not included in the study.

b) PMD: 32641471 assessed HBV and HCV infections in a group of Chinese patients with COVID-19 and found a prevalence of HBV and HCV in these subjects, respectively, of only 4.1% and 0.3%, highlighting that liver enzymes derangements in those patients are rarely asociated with underlying liver disease.

c) Due to those reasons discussed above, it would be out of the scope of the manuscript this discussion

We added in the Patient and Methods section information describing that no investigation of underlying liver disease or HBV and HCV serology were carried out in this study.

Comment 2: Please add some practical recommendations on how to manage COVID-19 patients with liver injury (e.g. PMID: 32585136)

We added in the Discussion section recommendations on how to manage COVID-19 patients with liver injury.

Response to Reviewer B

Comment 1: During the evolution of this pandemic, there have been hundreds of case reports, case series reports and retrospective studies similar to your study that have reported the effect of SARS-CoV-2 on the liver leading to deranged LFTs. Based on the already published literature, it is now an established fact all across the clinical world that SARS-CoV-2 is more likely associated with deranged liver function tests than not. In fact, AASLD has published Clinical Best Practice Advice by expert panel on this topic that mentions the effect of deranged LFTs on overall prognosis. Also its not uncommon to have leucocytosis /leucopenia in patient's with active COVID-19 infection. The article doesn't add anything new to what is already well established and has been heavily published.

Reply 1: As outlined in the discussion section, our study has included more than 1.500 subjects and clearly demonstrated that liver enzymes abnormalities early in the course of COVID-19, detected in the emergency department, are associated with adverse outcomes. This is on of the largest cohorts published thus far from a single center outside Asia and our results confirm previous findings and highlight the association of elevated AST and/or ALT with worse outcomes as well as with inflammatory markers linked to COVID-19 assciated cytokine storm.

Response to Reviewer C

Comment 1: Line 130 Eighty-one (4%) of the 2068 patients initially discharged returned need to change to 2,068.

Reply 1: Corrections were performed in the main text.

Comment 2: Line 133. “Briefly, most were middle-aged women (n=799; 57+18 years).” How about male? What is age distribution?

Reply 2: The age distribution of the entire cohort was 57±18 years. This was not the age distribution of female patients. Changes were made in the text to make this more clear.

Comment 3: Line 139: “Abnormal AST and/or ALT were observed in 762 (50%) of patients. High AST appeared almost twice as frequently as ALT (47% versus 25%). Most patients had AST abnormalities (77%) and ALT (75%) up to double the ULN.” Any statistic significant difference between ALT and AST ?

Reply 3: Before reviewer 3 comments, these differences were not analyzed. This analysis was carried out and introduced in the main text.

Comment 4: Table 1: Age (years) need to be changes to (year-old), need Male data too.

Reply 4: All data refers to the whole cohort not only males. Age was expressed in

years and not years-ole by Journal's convention according to instruction to authors.

Comment 5.Table 2 and table 3: p values 0.0001 not "0,0001". And percentage. For example: 78,5%, need to be 78.5%. Change "," to "."

Reply 4: Changes were made in the Tables