Response to reviewers' comments

Reviewer #1:

The paper is well conceived and i congratulate the authors in reporting their observational study.

We would like to thank the reviewer for his encouraging comment. It is our great honor that the study has captured the reviewer's attention

Reviewer #2:

Briefly, in this study, the authors report that HCV positivity in patients with COVID-19 was overall greatly associated with in-hospital fatality. Their findings could be potentially interesting because COVID-19 has resulted in "slowing or stopping" many hepatitis elimination programs, including hepatitis C viral infection (J Hepatol. 2021 Jan;74(1):31-36. doi: 10.1016/j.jhep.2020.07.042.).

We would like to thank the reviewer for his encouraging comment. It is our great honor that the study has captured the reviewer's attention

My suggestions:

There are several grammar errors in the main text (therefore I suggest firstly English editing), and the authors should use appropriately the acronyms when employed for the first time in the text.

Thank you. We have run the manuscript through English editing and the new version is included. All changes for acronyms suggested by the reviewer were also done.

It needs to be explained the reason for the high prevalence of both HCV and HIV infections found among the study populations (local epidemiology? Higher prevalence of drug injectors in the analyzed cohort?).

We would like to thank the reviewer for raising such an important point. According to the reviewer's comment the following paragraph was added to the discussion page 10, Lines 14-17

"There is a local higher prevalence of injection drug abuse in the community wherefrom the study cohort was included (Bronx, New York), which is reportedly significantly associated with increased incidence and prevalence of HCV and may explain the higher HCV prevalence in our cohort.[6]"

I think that in the multivariate analysis for in-hospital mortality (table 2) the authors should include no more than 10 variables since too many variables can compromise the reliability of the results.

We agree with the reviewer that the number of the analyzed variables is significantly large. The reason why we decided to include all these variables for analysis is that, despite the extensive research done on this aspect, no definite and reliable predictors of mortality have been reached yet. Statistically speaking, a statistical test should be run on all possible predictors for feature selection for determination of which variables should be included in the multivariate model. Moreover, we think that some of the other variables such as D-Dimer and LDH among others are important to be analyzed being reportedly important predictors of outcomes in COVID-19 patients. Looking at the predictive effect of HCV while ignoring strong predictors of mortality in the literature may lead to missing information.

Importantly, from the statistical standpoint, it is not enough to have a variable significantly different in its mean values at baseline between groups to be a predictor of outcomes. Similarly, a non-different variable between groups at baseline does not mean statistically that it won't predict outcomes. A time dependent analysis such as survival curves and cox-regression does not depend on simple one-point analyses such as T-test. An explanation of this issue can be found here:

"https://www.diva-portal.org/smash/get/diva2:1067479/FULLTEXT01.pdf"

We quote from this reference (page 3)

"One could think that survival time is a variable just like any other and that analyzing these times could be done using standard methods for random variables such as logistic regression or t-tests. However, there are several problems with those simple approaches. At the end of a study not all subjects included may have experienced the event of interest. We do not know the time until the event of these subjects but we do know that they have not experienced the event during the time of the study. There will also be subjects that are lost to follow, whose where-abouts are not known at the end of the study. However, they may have been part of the study for a long time before they went missing. And we do know that they did not experience the event during this time. Objects for which we have not observed the event of interest are called censored. And if we fully exclude those so called censored observations from the analysis, we will lose a lot of information. Another drawback with the standard methods is that all events will be equal weighted, it does not matter if the event occurs after two weeks or two years. As we will see survival analysis take both of these problems into account….."

I suggest considering only the following variables: age, gender, hypertension, DM, HIV, COPD, HCV, congestive heart failure, coronary artery disease, and procalcitonin, that were significantly different at baseline in the comparison among HCV and non-HCV groups. So the authors should omit from the multivariate analysis (table 2) the variables of platelets, neutrophilic count, D-dimer, ferritin, lactate dehydrogenase, bilirubin, and albumin, whose baseline values were not significantly different in the HCV and non-HCV groups. They should add among the analyzed variables included in Tables 3 and 4, "conjugated bilirubin" (and maybe also albumin) as another important liver lab test/s also because their levels were significantly different at baseline among HCV and non-HCV groups.

We would like to clarify the following regarding the differences in the analyses done in table 1 and table 2. As can be seen in the tables, the comparisons in table 1 were done in subgroups between patients with HCV and patients without HCV, while Cox-regression analyses in table 2 were done in all patients and one of the variables was HCV itself. While D-dimer, for example, was not different between patients with and without HCV, it was a very powerful predictor of outcomes. This basically may be explained as, if HCV and D-Dimer are both powerful predictors of outcomes, the predictive ability of HCV may be just be an association to D-Dimer effect if it was different between patients with or without HCV. If that difference occurred at baseline then patients should be matched first and the predictive ability of HCV should be rechecked (Similar to what we did for other variables in the propensity score matching, as will be explained below). The fact that patients with and without HCV, however, did not have different D-Dimer levels, suggests that the HCV predictive ability for outcomes is independent of that of D-Dimer, which was further confirmed with the multivariate Cox-regression analysis. This type of effect can be extrapolated to all other variables.

On the other hand, in fact, the differences noticed in table 1 such as age, risk factors and procalcitonin, create an argument that there are baseline differences between the groups and, subsequent Cox-regression analysis results may just be confounded by these differences. In other words, HCV predictive ability may be just a result of these differences rather than an effect the is directly related to HCV itself. As such, these differences should be omitted before drawing any conclusions, which was the reason we did a propensity score matching to match for these variables and rechecking the effects and see if the predictive ability of HCV remained or was lost after matching for such big differences.

From all the above, from the statistical standpoint, including only parameters that were different in the subgroup analyses in table 1 would, not only be statistically inappropriate, but also will yield significant errors and confusion in the results.

As such, we think that the statistical validity of our methods hold and is important for the discussion and conclusions driven from our hypothesis, and we would like to ask the permission of the reviewer and the editors to keep them as is.

The authors should also explain if among the 50 HCV patients some of them experienced (or not) a previous antiviral regimen with/without DAA, if yes they should provide the info if the patients achieved an SVR.

We would like to thank the reviewer for raising our attention to such an important point. We have added the following page 8 lines 19-21

"It is to be noted that, all HCV patients in our study received anti-viral treatment. 26 of these patients had sustained viral response (SVR). Viral load was still detectable in the remaining 24 patients (chronic HCV, viral loads: 1688184±1439771, median: ,1380000, SE: 434107, minimum: 269, maximum: 3610259 IU/ml)."

The title of table 5 is "Comparison between patients with chronic HCV and propensity score-matched patients without HCV" but the authors did not explain herein that they also performed a Cox regression analysis with in-hospital mortality as the outcome.

Thank you for the comment. The title was changed accordingly to

"Subgroup comparisons and cox-regression predictors of outcomes for a subset composed of patients with chronic HCV and propensity score matched patients without HCV"

The authors should shorten the discussion section focusing neatly on their findings and the comparison with other comparable studies, rather than centering on the well-known pathogenesis mechanism of SARS-COV-2 infection.

Thank you for the comment. The discussion section was revised and shortened according to the reviewer's comment.

Also, they report in the discussion section that "in a cohort of COVID-19 patients in a single-center, the frequency of history of chronic hepatitis C infection is 4.1%…" but in the abstract, they report a different percentage "…50 (5%)". They should therefore adjust the percentage and substitute it with the right one "4.1%".

We would like to thank the reviewer for raising out attention to this error. Accordingly, the correct percentage (4.1%) was used throughout the manuscript