PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Clinical course and outcome of COVID-19 patients in Mumbai city: An observational study
AUTHORS	de Souza, Rosemarie; Mhatre, Sharayu; Qayyumi, Burhanuddin; Chitkara, Garvit; Madke, Tushar; Joshi, Mohan; Bharmal, Ramesh; Asgaonkar, D; Lakhani, Prem; Gupta, Sudeep; Chaturvedi, Pankaj; Dikshit, Rajesh; Badwe, Rajendra

VERSION 1 – REVIEW

REVIEWER	Arentz, Matthew University of Washington
REVIEW RETURNED	01-Sep-2020

GENERAL COMMENTS	Overview In this descriptive study, the authors characterize factors and outcomes for patients with COVID-19 admitted to a single institution in Mumbai city. This is one of the first studies to describe the epidemiology of hospitalized patients with COVID-19 in India. It adds to the limited medical literature around COVID-19 short term outcomes in LMICs. Although the authors do address factors associated with death and perform a limited multivariate analysis, my opinion is that this analysis does not add significantly to the current body of literature. However, the lack of data on health outcomes in LMICs (and in India, in particular) is an important gap in our understanding of the epidemiology of the disease, and I feel a focus on the descriptive statistics and outcomes is more valuable than identifying statistical associations. General comments: Please review and correct the grammatical errors noted in many parts of the manuscript. Introduction: - the description of COVID-19 care structure is valuable. Is there any insight into how the demographics of patients admitted with COVID-19 to Nair hospital might differ from other DCHs? For instances, is there a different in public/private payer mix? Is there a difference in socioeconomic strata or ethnicity? Methods: - We all patients confirmed at having Sars- CoV2 infection by PCR? If so please clarify this was an inclusion criteria. - It is reasonable that informed consent was waived due to the retrospective observational nature of the study. However, a

	requirement for informed consent should not be waved because of an ongoing health emergency and this line should be removed. - Please better describe your multivariate model. Is it true that you only adjusted for age and gender? Comorbidities are already a known contributor to mortality in many other COVID-19 observational studies lack of adjustment for this will confound any analysis of outcomes of treatment. In addition, patients who died had a very short length of stay, which may have precluded their ability to receive the treatments evaluated in the multivariate analysis. I would consider dropping this analysis altogether (and focusing on Table 1, and perhaps only a univariate analysis of the variables: age, comorbidities, gender, and need for oxygen). - Why did you choose an age of 50 as your dichotomous cutoff? - How did you define severe acute respiratory infection? Results: As noted above, I don't feel that much of the discussion around therapeutics and outcomes adds value. Instead, it would more valuable to expand on other issues such as ethnicity, socioeconomic status, occupation (health care worker vs other), severity of kidney disease and heart disease, severity of cancer, and, ideally a composite index (such as the Charlson comorbidity index) to describe the differences between survivors and non survivors. Discussion I would focus this on how the data differ from those in other areas (as you do in paragraph 5) but with more details. I would de-emphasize the impact of therapies discussed in paragraphs 6 and 7 of the discussion). tables and graphs If only 19 of your patients were in the ICU, what care was provided for other patients who died or worsened on the floor. (I may be understanding table 1 incorrectly, if so, please clarify) I don't feel figure 1 is needed.

REVIEWER	Deuel , Jeremy University of Cambridge
REVIEW RETURNED	02-Oct-2020

GENERAL COMMENTS	The authors studied in-hospital mortality of 689 patients diagnosed with COVID-19 in a single centre in Mumbai. The authors describe a hospitalised population that is in general younger than the average patient hospitalised with COVID-19 in the US or in the EU. Yet the overall in-hospital mortality is higher than in other reported studies. The authors report a higher risk for death for every reported medication. Overall the paper is not well written and major findings, such as the two stated before, are not discussed. MAJOR 1. In the second section of the discussion the authors compare mortality rate of the overal population between countries. This is problematic since this rate is highly dependent upon the testing regime and the test rate within the population. The authors state multiple times that the mortality rate is lower in India than in other

	parts of the world; yet they report an in-hospital mortality of 22.6% (156/689 cases) whereas in the cited study from New York mortality only was 14.2% (373/2634; Richardson et al, JAMA 2020) despite the older population! The authors need to discuss this discrepancy. 2. The authors have a mortality of 8% (2/26) of 10-19 year olds which is much higher than expected. Why is the mortality so high? 3. The authors state a higher risk for death for all medications analysed, yet they must provide a justification for this: Were only the more severely diseased treated? Or are these medications causing the death (which is - given the already available evidence from RCT for most of these medications - highly unlikely)? Are there other explanations? 4. Other from mortality, the clinical course is very poorly described. What was the length of stay? Which complications occurred? How long was ventilation on the ICU? MINOR - The way data is presented in the table has to be optimised for clarity. I am missing a total number per category and the fraction for dead should be given row-wise and not as done column-wise. - The language, choice of wording and punctuation in the article has to be improved - The ethical statement is unclear. The authors must state clearly in the methods section if their study protocol was reviewed by an ethical committee, if and how data were anonymised, who had access to the primary data and what data were extracted from "Medical record case file". The justification why an informed consent was not necessary is not clear to me.

VERSION 1 – AUTHOR RESPONSE

1. General comments:
   Please review and correct the grammatical errors noted in many parts of the manuscript.

Response: Thanks for pointing out errors. We have now rectified the errors.

Introduction:
- the description of COVID-19 care structure is valuable. Is there any insight into how the demographics of patients admitted with COVID-19 to Nair hospital might differ from other DCHs? For instances, is there a different in public/private payer mix? Is there a difference in socioeconomic strata or ethnicity?
Response:
Our study describes the characteristic of the patients identified in the duration of March 26, 2020, to May 11, 2020. T.N Medical College & BYL Nair hospital. The hospital was the only designated covid-19 care facilities at that time in Mumbai district. This is mentioned on page 4 of the manuscript.

Other DCH's started treating patients only after mid-May -2020. These DCH's include both public and private practices. There might be differences in the social-economic strata of the patients admitted to centres other than T.N Medical College & BYL Nair hospital. A planned study will be required

in understanding the difference in socio-economic status associated with development and progression of COVID-19 infection.

2. Methods:
   - We all patients confirmed at having SARS- CoV2 infection by PCR? If so please clarify this was an inclusion criteria.

Response:

We thank reviewers for this point. All the cases admitted in the hospital were diagnosed by RT-PCR. The study thus included only RT-PCR confirmed COVID-19 cases.

This point is now described in the revised manuscript and on pg. no 5.

3. It is reasonable that informed consent was waived due to the retrospective observational nature of the study. However, a requirement for informed consent should not be waved because of an ongoing health emergency and this line should be removed.

Response:

Thank you for your suggestion. We have removed this line from the revised manuscript. The revised line is on pg.no. 5.

4. Please better describe your multivariate model. Is it true that you only adjusted for age and gender? Co morbidities are already a known contributor to mortality in many other COVID-19 observational studies lack of adjustment for this will confound any analysis of outcomes of treatment.

In addition, patients who died had a very short length of stay, which may have precluded their ability to receive the treatments evaluated in the multivariate analysis. I would consider dropping this analysis altogether (and focusing on Table 1, and perhaps only a univariate analysis of the variables: age, co morbidities, gender, and need for oxygen).

Response:

Thanks for your suggestion. We agree and aware that co morbidities are important variable in predicting outcome. However, we are unable to adjust co morbidities in multivariable analysis because all diseased persons reported co morbidities. In other words, there was no death without history of co morbidties.

In reference to your comments and possible effect of co morbidities as an outcome, we have now provided univariate analysis in the table -3. We have provided multivariate model after adjusting for age, gender and co morbidities (wherever feasible) as a supplementary table 1.

5. Why did you choose an age of 50 as your dichotomous cut-off?

Response:

The median age of study participants was 44 (SD ± 16.91). We therefore decided to choose an age of 50 years as dichotomous cut-off. Further, as 50 years is conventionally considered as the cut-off in

many studies in India compared to higher age (60 years) in the developed countries because life expectancy in India is lower.

6. How did you define severe acute respiratory infection?

Response:

Severe acute respiratory infection was defined as:-
Any patient with clinical signs of pneumonia plus any one of the following
a) Respiratory rate >30 breaths/min
b) Severe respiratory distress
c) SpO2 <90% on room air

We have now defined severe acute respiratory infection in the footnote of Table 1 & 2.

7. Results: As noted above, I don't feel that much of the discussion around therapeutics and outcomes adds value. Instead, it would more valuable to expand on other issues such as ethnicity, socioeconomic status, occupation (health care worker vs. other), severity of kidney disease and heart disease, severity of cancer, and, ideally a composite index (such as the Charlson co morbidity index) to describe the differences between survivors and non survivors.

Response:

Thank you for suggestion. Analysis was performed on variables extracted from Medical case record file. Details of demographic variables as well as details about co morbid chronic conditions (like cancer) were not available. We therefore could not do the analysis as suggested by reviewer.

8. Discussion: I would focus this on how the data differ from those in other areas (as you do in paragraph 5) but with more details. I would de-emphasize the impact of therapies discussed in paragraphs 6 and 7 of the discussion).

Response:

We have now included more recent data to compare similarities and differences with other areas. Following details are included on page 07. And we have now reduce and modify the discussions on therapies as suggested by reviewer.
“The Mortality rate is much lower in India (91.75 death per million of Population)); [8] compared to many Western countries like UK, USA, France or Italy where the mortality rates are in between 600 to 700 per million of population. [9] This is despite of linear and continuous increase in COVID-19 cases in India with cumulative number as on June 4, 2020, is around 150 per million of the population. [10]

9. Tables and graphs: If only 19 of your patients were in the ICU, what care was provided for other patients who died or worsened on the floor? (I may be understanding table 1 incorrectly, if so, please clarify)

Response:

The study centre Nair hospital was recently converted DCH at the initial time when this study was conducted. So because of the limited availability of resources those patients requiring ventilator support or NIV were taken in ICUs. Those patients who had developed other complications like sepsis, Acute Kidney Injury, DIC etc were given the supportive treatment for the same on floor.

10. I don't feel figure 1 is needed.

Response:
Figure 1 provide important information about joint effect of co morbidities and age stratified by gender. It is important to note presence of co morbidities increases hazard of dying with increase in age. The hazard of dying with increase in age and presence of co morbidity is more for females than for males. We have kept the figure as it is.

Reviewer: 2

1. MAJOR: In the second section of the discussion the authors compare mortality rate of the overall population between countries. This is problematic since this rate is highly dependent upon the testing regime and the test rate within the population. The authors state multiple times that the mortality rate is lower in India than in other parts of the world; yet they report an in-hospital mortality of 22.6% (156/689 cases) whereas in the cited study from New York mortality only was 14.2% (373/2634; Richardson et al, JAMA 2020) despite the older population! The authors need to discuss this discrepancy.

Response:
India is testing around 763 per million population compared to 3945 per million and 3128 per million population testing in UK and USA. The testing strategy in India during study period was to test symptomatic and high risk contact individuals. The literature suggests that high patient mortality relates to symptoms at presentation and asymptomatic patients have lesser mortality (Ref). Therefore not testing asymptomatic individuals may not be the reason for lower mortality observed in India.
We have now included the sentence on page no. 7 as “The patients coming to DCH were severely symptomatic; whereas mildly and asymptomatic patients were referred to DCCH. The death rate in our series was therefore higher as cases admitted in hospital were late in their dieses course and thus possibly only severely sick patients were hospitalized leading to high in hospital mortality”.

2. The authors have a mortality of 8% (2/26) of 10-19 year olds which is much higher than expected. Why is the mortality so high?

Response:

The sample size within this age group was very small (n=26), and hence precision of this mortality estimate is very low. Also, only severally sick patients among the young ones were admitted to DCH.

3. The authors state a higher risk for death for all medications analysed, yet they must provide a justification for this: Were only the more severely diseased treated? Or are these medications

causing the death (which is - given the already available evidence from RCT for most of these medications - highly unlikely)? Are there other explanations?

Response: We have discussed this point on page 8 of manuscript as below:
"We observed no change in disease course with all of these treatments of interest when compared with group of individuals who have not received any treatment. These results should be interpreted with caution as none of the no treatment group of patient had any co-morbidity, or required any oxygen support. As no treatment group was asymptomatic or mildly symptomatic, only three of them died while almost all of them were discharged with advice to be quarantined. Thus the treatment of interest was given to selective group of patients which could be responsible for high risk of death we observed with any of the treatment of interest. We therefore cannot conclude that these treatment combination increases risk of death.
Further as suggested by reviewer 1 we have removed the hazard ratio related to the treatment from main table and data related to treatment are provided in supplementary table.

4. Other from mortality, the clinical course is very poorly described. What was the length of stay? Which complications occurred? How long was ventilation on the ICU?

Response:

- What was the length of stay? : The median length of stay for death as well as alive patients was 3 and 4 days respectively. This information is already included in table 1.
- Which complications occurred? How long was ventilation on the ICU?: The various complications which had occurred were a) Pneumonia b) Acute Kidney Injury c) Sepsis d) Acute Respiratory Distress Syndrome etc. The detailed discussion about this was not possible due to limited data available from the medical records. Regarding the length of ventilatory support as mentioned in table 1 2 patients from study population required the support and both the patients had died the median length as 3 days.

5. The way data is presented in the table has to be optimised for clarity. I am missing a total number per category and the fraction for dead should be given row-wise and not as done column-wise.

Response:
We have tabulated proportions of the death according to variables. Similarly. The proportions of alive by different variables are provided. This type of tabulation makes it easier to compare the differences in proportions among dead and alive individuals by available variables. For example, proportion of dying individual is 40% for age group 60 and above.

6. The language, choice of wording and punctuation in the article has to be improved.

Response:

Corrections are made as per suggestions.

7. The ethical statement is unclear. The authors must state clearly in the methods section if their study protocol was reviewed by an ethical committee, if and how data were anonymised, who had access to the primary data and what data were extracted from "Medical record case file". The justification why an informed consent was not necessary is not clear to me.

Response:

We have modify the statement on pg. no.5 for better celerity as below:-
The study was approved by the institutional ethics committee (IEC) of Nair hospital and T.N Medical College, Mumbai. IEC agreed to our request for waive off individual consent as no direct

communication/contact with cases was involved and all data were extracted from medical case records.

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VERSION 2 – REVIEW

REVIEWER	Arentz, Matthew University of Washington
REVIEW RETURNED	23-Dec-2020

GENERAL COMMENTS	In this re-submission, the authors have addressed the majority of the reviewer comments to satisfaction. While COVID-19 data is rapidly changing, I feel most of my recommendations for further changes would be stylistic, and so I will abstain from further. A few spelling errors remain the submission (for instance, on page 8, there is no space between comorbidities.The , and disease is spelled wrong on the last line). In addition, "kidneydisease" and "liver disaese" are grammatical errors in table 1. I would request the authors thoroughly review for grammatical errors and I would recommend accepting after these edits are made.

REVIEWER	Deuel , Jeremy University of Cambridge
REVIEW RETURNED	08-Dec-2020

GENERAL COMMENTS	The authors have tried to reply to all of the reviewer's comments and have revised their manuscript accordingly. The authors have a compelling dataset giving insights into the management and course of severe COVID-19 in Mumbai and thus add novel insights to the current understanding of COVID-19. However, while reporting most findings accurately and providing decent evidence, the claim of lower mortality rate in India is not adequately backed by data. While a part of the answers to the comments are satisfactory and the changes made to the manuscript, some concerns remain: Major comment 1, Reviewer 2: The authors have left their claim "... lower mortality rate in admitted patients in India..." (page 8, Line 23) unchanged. The authors report a higher mortality rate in their collective than in reports of other countries and explain this with a different risk profile of the admitted patients. While this is a possible explanation for the higher mortality rate of their patients (although their population is younger than the ones reported from other countries), this does not substantiate the claim of a lower mortality rate of admitted patients in India. Major comment 1, Reviewer 2: The authors have now added the section: "The enrolled study participants in the study, therefore, provide a representative sample of admitted COVID-19 patient in the city for the initial period." (p7 35-38). Please clarify the word "admitted": Most patients, specially only mildly symptomatic patients, seem to have been admitted to another center (DCHC) as the authors state in the response to this comment. Since patients were segregated by symptomatology into two centers, yet the patients reported in this study are only from one center (DCH). Thus, in my understanding, the enrolled study participants can only be representative for severely symptomatic patients and not,

	as stated in the manuscript, for all admitted COVID-19 patients in the city. Since the authors use the rate of hypertension in their own study (page 7, line 46) to explain the lower mortality rates for COVID-19 in whole india, they assume their sample to be representative for all COVID-19 cases. Please explain this discrepancy. Comment 4, Reviewer 2: Table 1 states: Median length of stay 1 day for patients that died (thus: Half of the patients that died, died on the day of admission?) and 4 days for patients that are alive. In their answer to my question they state the median length of stay for patients that were dead was 3 days. Which is correct? Comment 5, Reviewer 2: The authors chose not to implement the suggested changes in table 1 for reasons of clarity. In the answer to the comment, the authors state: "For example, proportion of dying individual is 40% for age group 60 and above." Yet, table 1 states 64 of 142 (64+78) of the age group of 60 and above have died, that is 45% and not 40%. What table 1 says is, that of all patients that died, 41% where of the age group of 60 and above. Comment 4 to Reviewer 1, the authors state "... all deceased persons reported co morbidities. In other words, there was no death without history of co morbidities" and use this as justification why not to adjust their model for co-morbidities. In table 3 the authors report 98 deaths (and 462 patients alive) with 0 co-morbid conditions. Please explain. Further comments: - The term "DCCH" is not explained. Do the authors mean DCHC? (page 8, line 5) - The english language should still be further improved.

VERSION 2 – AUTHOR RESPONSE

B. Reviewers comments :

1. Dr. Jeremy Defuel, University of Cambridge
   Comments to the Author:
   The authors have tried to reply to all of the reviewer's comments and have revised their manuscript accordingly. The authors have a compelling dataset giving insights into the management and course of severe COVID-19 in Mumbai and thus add novel insights to the current understanding of COVID-19. However, while reporting most findings accurately and providing decent evidence, the claim of lower mortality rate in India is not adequately backed by data. While a part of the answers to the comments are satisfactory and the changes made to the manuscript, some concerns remain:

Response:

Thank you for reviewing the manuscript so articulately and bringing up the points which we had missed. Your suggestions have been helpful in improving the manuscript.

1.1. Major comment 1, Reviewer 2: The authors have left their claim "... lower mortality rate in admitted patients in India..." (Page 8, Line 23) unchanged. The authors report a higher mortality rate in their collective than in reports of other countries and explain this with a different risk profile of the admitted patients. While this is a possible explanation for the higher mortality rate of their patients (although their population is younger than the ones reported from other countries), this does not substantiate the claim of a lower mortality rate of admitted patients in India.

Response:

We agree with the reviewer that study data does not have any substantial evidence to claim lower mortality rate in admitted patients in India. Hence, we have now removed the assertive sentence from the manuscript.

1.2. Major comment 1, Reviewer 2: The authors have now added the section: "The enrolled study participants in the study, therefore, provide a representative sample of admitted COVID-19 patient in the city for the initial period." (p7 35-38). Please clarify the word "admitted": Most patients, specially only mildly symptomatic patients, seem to have been admitted to another center (DCHC) as the authors state in the response to this comment. Since patients were segregated by symptomatology into two centers, yet the patients reported in this study are only from one center (DCH). Thus, in my understanding, the enrolled study participants can only be representative for severely symptomatic patients and not, as stated in the manuscript, for all admitted COVID-19 patients in the city. Since the authors use the rate of hypertension in their own study (page 7, line 46) to explain the lower mortality rates for COVID-19 in whole India, they assume their sample to be representative for all COVID-19 cases. Please explain this discrepancy.

Response:

The above mentioned inconsistent sentence has been now revised as below (Page no 7):-

The enrolled study participants in the study, therefore, provides a representative sample of COVID-19 patients admitted in hospital (DCH facility). The study, however, did not include the mildly symptomatic or asymptomatic COVID-19 affected patients, as this group of patients were admitted in DCCH.

This has been included on pg. no. 7

1.3. Comment 4, Reviewer 2: Table 1 states: Median length of stay 1 day for patients that died (thus: Half of the patients that died, died on the day of admission?) and 4 days for patients that are alive. In their answer to my question they state the median length of stay for patients that were dead was 3 days. Which is correct?

Response:

Please accept our apology for reporting the wrong values in the previous response. The median length of stay for patients that were dead was 1 day as reported in Table 1 of the manuscript.

1.4. Comment 5, Reviewer 2: The authors chose not to implement the suggested changes in table 1 for reasons of clarity. In the answer to the comment, the author's state: "For example, proportion of

dying individual is 40% for age group 60 and above." Yet, table 1 states 64 of 142 (64+78) of the age group of 60 and above have died, that is 45% and not 40%. What table 1 says is, that of all patients that died, 41% where of the age group of 60 and above.

Response:

We apologize for the discrepancy in the previous response. We are thankful to the reviewer for pointing out the error. The correct figures are reported in the table 1. The proportion of dying individual in the age group 60 and above is 41.03% and not 45% as drafted in the previous response.

1.5. Comment 4 to Reviewer 1, the authors state "... all deceased persons reported co-morbidities. In other words, there was no death without history of co- morbidities" and use this as justification why not to adjust their model for co-morbidities. In table 3 the authors report 98 deaths (and 462 patients alive) with 0 co-morbid conditions. Please explain.

Response:

All the patients receiving any kind of treatment had co-morbidity. In other words, no patient who received any kind of treatment was without co-morbidity. Therefore, treatment effect on outcome could be adjusted for co-morbid conditions. In table 3 (main text), we have provided univariate analysis of the important variables related to the outcome. The supplementary table 1 provides the multivariate model for all the variables except for treatment variables after adjusting for co-morbidities.

In table 3, 98 deaths with co-morbid conditions are reported in no treatment group of the patients. (Patients who have received neither HCQ or Azithromycin or Oseltamivir or steroids independently or in combination). Hence, we could not study treatment effect adjusting for co-morbid conditions. Hence, we have presented COVID-19 co-morbidity hazard ratios in the supplementary Table 1.

1.6. The term "DCCH" is not explained. Do the authors mean DCHC? (page 8, line 5)

Response: We are extremely sorry for typographical error and have corrected DCCH to DCHC.

1.7. The English language should still be further improved.

Response: We have tried to improvise the English of the manuscript.

Reviewer: 1
Dr. Matthew Arentz, University of Washington
Comments to the Author:

In this re-submission, the authors have addressed the majority of the reviewer comments to satisfaction. While COVID-19 data is rapidly changing, I feel most of my recommendations for further changes would be stylistic, and so I will abstain from further. A few spelling errors remain the submission (for instance, on page 8, there is no space between comorbidities.The , and disease is spelled wrong on the last line). In addition, "kidneydisease" and "liver disaese" are grammatical errors in table 1. I would request the authors thoroughly review for grammatical errors and I would recommend accepting after these edits are made.

Response: We are thankful to you for evaluating the manuscript carefully. Your evaluations have increased the quality of the manuscript and also eliminated errors from our side at the time of previous and current submissions.

We have addressed the grammatical and spelling errors in the manuscript now and revisions are highlighted in yellow.

Reviewer: 2
Competing interests of Reviewer: None declared

Reviewer: 1
Competing interests of Reviewer: None declared

VERSION 3 – REVIEW

REVIEWER	Deuel , Jeremy University of Cambridge
REVIEW RETURNED	07-Feb-2021

GENERAL COMMENTS	The authors have responded to the reviewer's comments and removed the unsubstantiated claim of lower mortality rate from COVID-19 in India. The paper ads value to the field by giving a compelling report of the management of severe COVID-19 in a large center in India. It is quite interesting that more than half of the patients who died of COVID-19 did so without respiratory support or intensive care treatment and on the day of admission. Given the lack of further data on these patients, the authors rightfully do not further comment on this; but further studies are necessary to investigate this unexpected finding. I recommend the correction of three minor issues: - The fourth sentence in the results section of the abstract needs revision - RCTs are now available for most of the treatments they used, showing no efficacy for most of them. Instead of stating that RCTs are ongoing (p. 10, line 10), these refs should actually be added now. - Ref 5 is not a reference, the manufacturer's details can be stated in the text in brackets.

VERSION 3 – AUTHOR RESPONSE

a) The fourth sentence in the results section of the abstract needs revision

Response: Thank you for your matriculate review. We have revised the 4th sentence in the result section of the abstract. The new sentence is framed as –

“Older age (Hazard ratio (HR) 2.88, 95% Confidence interval (CI) 2.09 – 3.98), presence of co-morbidities (HR 2.56, 95% CI 1.84 – 3.55),history of hypertension (HR 3.19, 95% CI 1.67-6.08), presence of symptoms at the time of admission (HR 3.21, 95% CI 1.41-7.26) were associated with increased risk of in hospital mortality.”

b) - RCTs are now available for most of the treatments they used, showing no efficacy for most of them. Instead of stating that RCTs are ongoing (p. 10, line 10), these refs should actually be added now.

Response: Thank you for suggesting this. This has strengthened the findings of the manuscript. We have done the changes in the abstract as advised and also have added the 03 new references supporting it as below:-

1. Tang W, Cao Z, Han M, Wang Z, Chen J, Sun W, Wu Y, Xiao W, Liu S, Chen E, Chen W, Wang X, Yang J, Lin J, Zhao Q, Yan Y, Xie Z, Li D, Yang Y, Liu L, Qu J, Ning G, Shi G, Xie Q. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. BMJ. 2020 May 14;369:m1849. doi: 10.1136/bmj.m1849. PMID: 32409561; PMCID: PMC7221473.
2. Cao B, Wang Y, Wen D, et al. A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. N Engl J Med 2020;382:1787-1799.
3. van Paassen J, Vos JS, Hoekstra EM, Neumann KMI, Boot PC, Arbous SM. Corticosteroid use in COVID-19 patients: a systematic review and meta-analysis on clinical outcomes. Crit Care. 2020 Dec 14;24(1):696. doi: 10.1186/s13054-020-03400-9. PMID: 33317589; PMCID: PMC7735177.

c) Ref 5 is not a reference, the manufacturer's details can be stated in the text in brackets.

Response: We have removed the reference from the revised manuscript and included in the main text.