

## Peer Review File

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### Reviewer A

The authors have described a retrospective study investigating outcomes of COVID - 19 patients admitted to single center intensive care unit in three different waves based on the admission period. Out of 428 patients who were included in the analysis 102, 169 and 157 were included in the first wave (February 2020-July 2020), second wave (September 2020-February 2021) and third wave (February 2021-April 2021). The authors compared the characteristics of the patients in three waves, overall mortality, and trends in the mortality rate in the three waves.

Although the study found lower crude mortality rate (ICU as well as in hospital) by 7% and 10% in third wave, however adjusted mortality rate showed no difference in the hazard ratio for mortality among the waves. The authors concluded that their study failed to identify significant improvement in mortality but a trend towards reduction in mortality in third wave.

This study addresses the relevant topic of COVID-19 and trend in mortality with different waves during the pandemic. Overall, the manuscript is well written. The authors have added all the relevant details in the methods section to help readers understand the protocols followed and treatments details. The authors have discussed the results and addressed strengths and limitations of their work. This is a single center study and relatively small study compared to the studies discussed in the literature review in discussion section. However, there are some weaknesses in this study mentioned below that should be noted. The authors should further address and revise the data accordingly. This manuscript requires minor revisions as described.

1. Throughout the manuscript as well as in tables, instead of decimal, a comma is used

Example, In Abstract line 21- P value>0,05, p value =0,001, 62,6%

Reply

We corrected as suggested in tables, supplemental material and in the manuscript

2. In abstract, line 21, “ICU and hospital free days at day 90 were larger” not clear if it should be “more” compared to use of word “larger”, this may be addressed in the result section of main manuscript

Reply

We reformulated the sentence in the abstract at lines 30-31 and we addressed this finding in the ‘Results’ section at lines 171-172 as suggested.

3. In abstract, in result section line 23 the author use “therefore” which does not seem to fit and may be explained the way it was explained in the result section of manuscript. “In the 290 matched patients ...in the third wave”.

Reply

Reformulated as suggested in the abstract at lines 32-33

4. Conclusion in the abstract may be improved if word count allows

Reply

We improved the ‘Conclusion’ section in the abstract at lines 37-39 as suggested.

5. It is hard to understand the importance of the propensity matched analysis which showed reduction in the mortality wave by 11%. Can authors explain this briefly?

Reply

We performed the propensity matched analysis to minimize confounding factors and strengthen the relevance of our findings, as this study was underpowered to detect mortality reduction. We considered relevant that this trend of mortality reduction was confirmed in the propensity matched population analysis.

6. In the discussion section, Line 198 – “Furthermore, bacterial infection .... appears to limit” seems incomplete.

Reply

We completed the sentence in the ‘discussion’ section at lines 214-215 as suggested.

7. In the discussion section, Line 201- “In contrast to dexamethasone, the

development of bacterial infection during ICU stay in our patients was associated with increased risk of death throughout pandemic [29].” It is not clear if the authors are commenting on their study population, or they are saying that in general and using a reference to support the statement.

Reply

We were commenting the results in our population and underlying that they are consistent with the cited metanalysis. We better formulated the sentence as suggested in ‘Discussion’ section at lines 218-221.

## **Reviewer B**

Regarding "Critical Covid-19 Patients Through First, Second and Third Wave:2 Retrospective Observational Study Comparing Outcomes In ICU "

The COVID-19 pandemic poses an indescribable burden for patients and their families worldwide. Every effort to alleviate this burden is of extreme value. The authors' effort to analyse the effects of implemented therapies is highly appreciated.

There are a few important points that I think need to be addressed in order to make the paper's results comparable to other outcomes internationally.

Major corrections

1) Study design

a) Decision to admit to the ICU

The authors state that they excluded from the analysis the data of patients with the decision to withhold life-sustaining treatments because too sick to benefit.

It means that all results of this study are to be understood as applying not for all critically ill COVID-19 patients, but for the sub-population of pre-selected patients for whom the decision has been made that they could benefit from ICU treatment (or had a realistic potential to survive COVID-19 with ICU treatment).

1. The authors refer to the WHO guideline in the Process of care section but the question of ICU admission is a major point that has to be addressed in the Study design section more specifically: - The number and proportion of patients not admitted to ICU should be retrospectively documented. Does the "Patients excluded because of limitation of care" in Table 1 refer to this? If yes, please write the main percentages in the text of the Study design since this is a major issue, at least as important as the

subsequent details in the Process of care section.

- The major lines of making this decision should be outlined briefly but precisely: who made this decision? What were the main factors taken in account? Did admission criteria change over the course of the pandemic (as the authors rightly allude to in the Discussion)? If yes, how?

Reply

"Patients excluded because of limitation of care" in Table 1 refers to patients with the decision to withhold life-sustaining treatments because too sick to benefit. This does not refer to ICU admission, but to the inclusion in the study: these patients were patients admitted to ICU and excluded in the analysis. We reformulated in Table 1 and added the proportion of patients excluded in 'Results' section at lines 163-165.

We outlined the decision-making process in 'Methods' section at lines 76-79.

We applied the same criteria through the three waves to select patients destined to ceiling of care, as shown in the table below.

Table: number of patients excluded from analyses because destined to withhold life-sustaining measures in each wave with median age and mortality rates.

	<b>Numer of excluded patients (%)</b>	<b>Median age (median, IQR)</b>	<b>In-hospital mortality (n,%)</b>
<b>1<sup>st</sup> wave (n=102)</b> February 25 <sup>th</sup> , 2020- July 6 <sup>th</sup> , 2020	7 (6,9)	74 (67-78)	6 (85,7)
<b>2<sup>nd</sup> wave (n=169)</b> September 20 <sup>th</sup> , 2020 - February 13 <sup>th</sup> , 2021	13 (7,7)	76 (73-79)	11 (84,6)
<b>3<sup>rd</sup> wave (n=157)</b> February 14 <sup>th</sup> , 2021 - April 30 <sup>th</sup> , 2021	11 (7,0)	77 (62-82)	9 (81,8)
<b>P value</b>		<b>0,709</b>	<b>0,653</b>

2. In clinical practice, admission to ICU can become a very difficult, sensible issue that may be to a certain extent dependent on the cultural context.

While the boundaries are not sharp, depending on the cultural context, approaches to ICU treatment as a whole could be located on a spectrum. Some may consider ICU more as a "therapeutic modality" (a mode of treatment that includes several invasive procedures, with a delicate balance between potentially life-saving treatments and potentially life-threatening side-effects). Some others may see ICU more as an "ultimum refugium" (a last chance for survival that must be given definitely, when all other treatment modalities fail). Could this also result in significant differences in what "best practice" means exactly, on a local level, and what the society in general expects from the ICU physician? In addition to the differences in ICU availability, level of technical equipment, availability of human resource, degree of practice and knowledge, could differences in cultural expectations from ICU have had an additional impact on COVID-19 statistics? These issues were especially amplified during the dramatic situation of the COVID-19 pandemic - even the more so, that COVID-19 patients appeared to be even above average vulnerable to any invasive ICU procedure - and will need further consideration in the future; in the meantime, the current article has to address this question by being more specific on ICU admission. The authors of the current paper report an overall mortality of 31.8% for all patients who required ICU (with 47% for those requiring IMV). The paper also refers to relevant literature from Wuhan to Washington with a wide interval of 30%-80% for the same parameter. Since differences in overall approach to ICU as a treatment may also contribute to these differences, the issue of ICU admission needs to be addressed in a thorough and sensible way. A few sentences in the study design and/or a Supplementary file could help to fix this question.

Reply

We completely agree on this point, but as indicated in the 'Methods' section, lines 78-79, we never experienced shortage of ICU beds during the pandemic and admission criteria to ICU had remained the same during the pandemic.

b) Saturation of beds

3. The authors state in the Discussion that their ICU capacity was upgraded to 35 beds, following which their beds were not saturated. Many statistics from other hospitals

were distorted by overloaded wards in the third wave, so the strength of this study of not being over-saturated is a major point that has to be highlighted right from the start, in the Study design too.

Reply

We outlined this feature in the 'Methods-Study design' section at lines 78-79 as suggested.

2) Process of care

a) Treatments given during 3rd wave

4. Some treatments mentioned by the authors were under investigation by the time of the third wave, and some that the authors did not mention in this article were used by other hospitals. Unavailable evidence regarding these therapies (including timing and dosage) by the time of the third wave could have significantly affected the results of this study.

For instance,

- ventilation: supplementing with high-flow nasal oxygen therapy was widely used in some centers (1, 2) - please comment on whether it was used in the current hospital or not. If not, why? if it was used, please report the number of these patients since some studies include this sub-population in the ICU statistics, some not. Was it used under the sub-ICU setting, as shown in Figure 1?

Reply

In our hospital, high-flow nasal oxygen was used in the current practice, mainly in the sub-ICU setting. Only 20 of the included patients admitted to ICU were treated only with HFNC, respectively 1 patient in the first wave (1%), 11 patients in the second wave (6,6%), 8 patients in the third wave (6,1%) ( $p>0,05$ ). We decided not to analyze this sub-population because of the small number of patients and the equality in the distribution among the waves.

- iv tocilizumab seems to be beneficial for only a tiny portion of patients, those who present symptoms and lab signs of cytokine storm (3) - please comment on why the current hospital used it in a wider indication.

Reply

We started early in the use of Tocilizumab in patients with signs of cytokine storm

because we were participating to a open observational study on the use of cytokine - blocking agents in those patients (Guaraldi G, Meschiari M, Cozzi-Lepri A, et al. Tocilizumab in patients with severe COVID-19: a retrospective cohort study [published correction appears in Lancet Rheumatol. 2020 Oct;2(10):e591]. Lancet Rheumatol. 2020;2(8):e474-e484. doi:10.1016/S2665-9913(20)30173-9)

- therapeutic LMWH seems to be beneficial before patients become critically ill (4) while the harmful aspects of this dosage become more marked once invasive modalities are initiated - please comment on that the dosage question was addressed later in the pandemic (5)

Reply

We completely agree with the reviewer comment, in fact we had used LMWH at standard dosages not as therapeutic attempt but only for prophylaxis (better specified in ‘Methods – Process of care’ section at lines 129-130). The use of unfractionated heparin was considered in case of pulmonary embolism documented by CT-scan or strong clinical suspicion.

- iv remdesivir given early in the course of the disease was proved to improve the outcomes (6,7) - please comment on whether it was used in this setting, if not, why?

In general, it appears that the importance of timing and dosage in COVID-19 is paramount; the same treatment in a given dose that is life-saving at a certain stage of the disease could well become useless or even harmful at another stage of the disease.

Reply

We completely agree with the reviewer comment, but in Italy Remdesivir was provided only in patients with proper clinical indications and could be routinely prescribed accordingly to the recommendations of regulatory agencies (Farmaci utilizzabili per IL trattamento DELLA malattia COVID-19 | Agenzia Italiana del Farmaco. Available: <https://aifa.gov.it/aggiornamento-sui-farmaci-utilizzabili-per-il-trattamento-dellamalattia-covid19> [Accessed 15 Apr 2021]).

The article in its current version could give the impression that the treatments given at the time of the third wave were mostly ineffective (with the exception of dexamethasone); however, in line with the above, it may also be possible that it is their

timing and their dosage that need adjustments in order to become effective. There may also be other explanations.

Reply

We have the real suspicion that something different from steroids and tocilizumab, as antiviral agents, may reduce mortality rate in covid-19 patients, however, there is currently no strong evidence that the use of remdesivir or others are effective on critically ill patients, and the right timing for administration play certainly a pivotal role.

5. Please also do address this issue in the Discussion, since the purpose the study is to promote the quest for best practice. What do the authors think? How do they explain their findings? Please address this in the discussion, i.e., that - according to later studies - a better timing of the same treatments could have resulted in better survival, or add any other explanation you may have for your findings.

Reply

We added some lines to address this issue in 'Discussion' section at lines 240-242

6. Please also underline this issue in the Abstract,  
- by using in Background, line 9, the term "development" instead of "improvement":  
Indeed, new approaches were being developed, and it is the current study's aim to investigate whether it resulted in fact in improvement. The proposed sentence is:  
"During these periods, progressive knowledge of the disease led to the development of specific therapeutic strategies. This retrospective study investigates whether this led to improvement in outcomes of COVID-19 patients admitted to intensive care unit".

Reply

We corrected the sentence as suggested in the background at line 18.

- by stating in Conclusion, that unfinished protocols could have influenced the results:  
For ex, start the conclusion with saying: "With application of best practice as known by the time of the first three waves of the pandemic, our study failed to identify" ...etc etc.

Reply

Conclusion in the abstract was reformulated as suggested at line 35.

b) Vaccination rates as possible confounding factor?

7. Vaccines were on the way of becoming available to the wider public by the time of the third wave.

This is an important point in an article examining the effects of different therapies.

If possible, please address this issue by showing the proportion of patients vaccinated and if it is relevant, see if the subgroup of these patients differed from the unvaccinated. According to the proportion of vaccinated patients, did the vaccination represent a reasonable confounding variable to deal with, in the geographic area of the study and by the time of the third wave? If yes, since vaccinated patients can still become critically ill, the article has to address whether they presented to the ICU in smaller proportion and whether they had better survival rates.

Reply

Unfortunately, we have no data regarding duration or characteristics of pre-hospital symptoms.

We seek for vaccination, but none of patients admitted to ICU until 30t April 2021 was vaccinated. In Italy, with exception of health-care personnel, the vaccination started at the end of February 2021 with population aged > 80 years.

3) Conclusion

8. At the end of the conclusion the authors allude to the role of dexamethazone and bacterial infection as two major factors explaining their results.

As these two factors are inter-related, and of opposite effect on mortality, please consider ending your conclusion with a short elaboration on this issue. This is very relevant to clinical practice, this could be one of the main conclusions drawn from your data, for the clinician. For example, you could say: "From this perspective, a major factor that our study could underline is that dexamethazone as a life-saving first-line therapy in COVID-19, is also a strong immune-suppressant predisposing to potentially life-threatening secondary infections. Early recognition and abrupt empiric treatment of secondary bacterial sepsis appears of paramount importance in order to keep the benefits of dexamethazone among critically ill patients recovering from COVID-19."

Reply

We completely agree and added some lines at the end of our conclusions at lines 249-252

Minor corrections

9. In Abstract, for better understanding please consider to correct

"notwithstanding, in sub-analyses was found a trend in mortality reduction in the third wave" to: "notwithstanding, the sub-analyses showed a trend in mortality reduction in the third wave"

Reply

Reformulated in the abstract at line 37.

10. In Results,

- line 158 please be more specific for better understanding: "The Cox regression multivariable analysis for all the study population who was admitted to the ICU"...

Reply

Corrected as suggested in the 'Results' section at line 175

- line 162 please be more specific for better understanding: "The sensitivity analysis conducted for the subgroup of the patients who also underwent IMV during their stay at the ICU (268 patients - 78 in the..."

Reply

Corrected as suggested in the 'Results' section at line 180

- line 167 please correct typo: "Tables S4, S5, S6)"

Reply

Corrected as suggested in the 'Results' section at line 185

11. In Discussion, please consider the following corrections for better understanding:

- line 174 "Key findings from our cohort study showed a difference in crude mortality during the three pandemic waves. In detail, the third wave had a lower death rate than the first. " correct to: "Key findings from our cohort study showed a difference in crude mortality during the three pandemic waves, with the third wave having a lower death rate than the first"

Reply

Corrected as suggested in the 'Discussion' section at lines 193-194

- line 191 "But the decrease found in this study in the unadjusted analysis was not confirmed in the adjusted one." What does "this study" refer to? Does it refer to the large European multicenter study? in this case please delete "Whereas" line 189. Or does it refer to the current study? Please clarify.

Reply

'This study' refers to the large European study. 'Whereas' was deleted at line 207 as suggested

- line 220 "considering the mean mortality rate of the population 24,1%" Where does this data come from? Please clarify.

Reply

This data comes from the results in table 2, showing in the first line a ICU mortality rate in the whole study population ('All patients', first column) of 24,1%.

12. In the Conclusion,

- line 226: please consider changing "therefore" to "however" to make it less confusing. Did you mean to say: "Our study failed to demonstrate a significant improvement in survival rate when comparing the different waves in both the whole population and in invasively ventilated patients, however, a trend in mortality reduction in the third wave was identified when propensity score-matched population was considered".

Reply

Corrected as suggested in the 'Conclusions' section at line 244

- line 227: please consider deleting "Rather". Better to say, simply: "We intercepted the possible protective effect of dexamethasone on mortality and the increased risk of death related to bacterial infections in the three waves. " or, "We think to have intercepted" ...etc.

Reply

Corrected as suggested in the 'Conclusions' section at line 247

13. In Tables

- In Tables 1, 2, S1, S2, S4 and S5, giving the p values in the last column can be

confusing since some readers may not be familiar with p values in descriptive statistics. Please explain in the legends what p values exactly mean in this table, or maybe better delete these columns to help understanding.

Reply

Added in each legend of the tables indicated at page 6-7 of the manuscript, lines 300-327

- In legend of Table 1, please be more specific: "of all ICU study population" (Figure 1 mentions study populations outside ICU, that's why it is better to emphasize that Tables are for ICU only). Same for Table 2 and also specify this in legend of Table 3.

Reply

Corrected as suggested in the legends of table 1, 2, 3

- In legend of Table S3, please correct "no survived" to "not survived"

Reply

Corrected as suggested in table S3

- Please add legends for Tables S4, S5, S6 (for ex. "Propensity matched analysis for 290 patients of the ICU study population")

Reply

Added in the manuscript at lines 297-303 in the 'Supplementary materials' section.

Overall, this article investigates an extremely important issue, the findings are interesting, timely and relevant.

COVID-19 is a major overwhelming tragedy like not many that has been seen since generations, unusually burdening health care systems and especially ICU-s worldwide, and an open dialogue on the role and possibilities of ICU is of paramount importance. In addition to the findings on treatment effectiveness, this paper contributes to enhance such gap filling dialogue.

After the above issues are solved, this paper will certainly get my support for publication.

The reviewer has no competing interests to declare.

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