# Peer Review File

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## Reviewer A

This is a retrospective study on the use of high flow nasal cannula (HFNC) in COVID-19 pneumonia which also investigates the predictors of HFNC failure (defined as a composite of intubation and death) in such patients.

I have several reservations and recommendations for the authors.

Comment 1:Are there any exclusion criteria? Are patients who received non-invasive ventilation (NIV) or those with DNR status excluded?

Reply 1: No, there are no exclusion criteria. All patients with COVID-19 pneumonia, treated with HFNC during the defined period were included in the study. No patients received non-invasive ventilation (NIV) as mean to avoid intubation and mechanical ventialtion. In general, at that time, our strategy of non invasive suppor tof COVID-19-induced severe respiratory failure did not include NIV. The same was true for the ICU of our hospital. NIV was applied in four of them after extubation as part of post-extubation respiratory support.

Changes in the text: 1) At the Methods section we added the phrase “All patients with COVID-19 pneumonia and respiratory failure treated with HFNC during the defined period were included in the study.” (page 7, line 83) 2) At the Results section we also added the phrase “Non-invasive ventilation was not used as pre-intubation mean of respiratory support in any of the patients.” (page 9, line 112-113).

Comment 2: Did any of these patients included receive NIV in their treatment? I am aware that NIV and HFNC has been used in the management of acute hypoxemic failure in COVID-19 patients.

Reply 2: Please see reply to the comment 1.

Changes in the text: See above at the response of comment 1

Comment 3: The authors should state clearly what is the primary outcome in the abstract and methods section. I gather that the primary outcome is a composite one i.e comprising of intubation and death. In addition, what does death refer to in this study; hospital death; death at 28 days, all-cause death or COVID-19 related death?

Reply 3: The primary outcome of this study was treatment failure, i.e. the composite of intubation or death during hospital stay. Success was considered discharge from the hospital without the need for intubation and mechanical ventilation.

Changes in the text: 1) At the Abstract section, we added the phrase: "The primary outcome of this study was treatment failure, i.e. the composite of intubation or death during hospital stay." (page 3, lines 31-32). Furthermore the phrase "The association between outecomes…." was modified to "The association between treatment failure…" (page 3, line 32). 2) At the Methods section we added the sentences: "The primary outcome of this study was treatment failure, i.e. the composite of intubation or death during hospital stay. Success was considered discharge from the hospital without the need for intubation and mechanical ventilation.", (page 7, line 84-86).

Comment 4: I gather that the authors also did a logistic regression analysis on the outcome of intubation alone (Table 5). I think the authors should state this in the Methods section to include this as a sensitivity analysis.

Reply 4: It is true that logistic regression analysis was performed to look for predictors of intubation. We have now removed this analysis to comply with the recommendation made by reviewer#2 in order to make the manuscript more simple by avoiding repetition (findings of the two analyses do not practically differ).

Changes in the text: See bellow at the response of comment 1 of Reviwer's B.

Comment 5:Any loss of data and incomplete data? How did the authors deal with it if it is present?

Reply 5: There was no loss of data.

Changes in the text: No

Comment 6 The major flaw of this study is the methodology of the logistic regression (LR) model. I think this LR model suffers from multiple comparisons with confounding or collinearity effects not accounted for as well as insufficient power needed for this LR analysis. The specific issues are:

a. The predictors of HFNC failure (death and intubation) determined a priori or post-hoc; this is not clear. Ideally, the predictors should be determined a priori based on existing literature and sound clinical reasoning. I am not sure why important predictors of intubation in COVID-19 use like dexamethasone use is not studied.

Reply 6a: Data acqusition and analyisis was done retrospectively and non of the parameters analysed as possible predictors of the outcomes in this study was used to guide clinical decisions according the intubation need. For the purpose of adjusted regression analysis we had initially treated some of the parameters, typically connected with worse patients' outcome, (gender, age, race, different comorbidities and Charlson Comorbidity Index) as confounders. However, to adopt the reviewer's comment 6c, we changed the model of adjusted analysis (see below). The following

parameters are now used as confounders: age, gender, CCI, ARDS severity and NEWS2, on admission and PaO2/FiO2 ratio at the time of HFNO initiation. They have chosen based on the literature wich demonstrate that male sex, older age, comorbidities NEWS2 score and sevirity of lung disease are closely associated with poor outcomes of COVID-19 patients.

Dexamethasone use was not included in our analysis, because at the time of the study, dexamethasone was administrated in every patient who needed supplementary oxygen therapy, according to international and national guidllines, thus in every patients included in our study.

Changes in the text: See below, at the response of comment 6c.

b: The authors should also state; beside the reasoning for the selection of predictors of HFNC failure; the type of variables these predictors are (categorical vs continuous and if categorical what are the categories). I think most of the predictors shown in Table 4 and 5 are treated as continuous variables. However, ARDS severity (per unit) in these tables; what does it mean? ARDS severity as many know are graded as mild, moderate and severe using Berlin classification and why there is a per unit measurement?

Reply 6b: Data were treated as categorical (i.e., sex, racial origin, presence of a symptom or presence of a comorbidity, grade of ARDS severity) or continuous. We thank the reviewer for helping as to clarify that the ARDS severity is presented by grade (mild/moderate/severe), according to the Berlin definition.

Changes in the text: 1) The following phrase was added at the Methods section: “Data were treated as categorical (i.e., sex, racial origin, presence of a symptom or presence of a comorbidity, grade of ARDS severity) or continuous (the rest of them)” (page 8, line 96-97) 2) At the table 2, the ARDS severity is now presents as “per

grade" instead of "per unit". At the legend, the numbers 1,2 and 3 were deleted (page 27).

c: I think the sample size for the LR model is likely to be insufficient and hence. There will possibility of insufficient sample size, multiple comparisons and false positive results. There is no sample size consideration for LR model in this manuscript. The study recruited 132 patients and there is a 50.7% rate of HFNC failure (intubation or death); i.e. 67 patients with this outcome. This can allow for maximum 7 degrees of freedom for the variables in the LR model; using a requirement of 10 events per degree of freedom rule of thumb. Table 4 shows that there are already more than 7 degrees of freedom in the predictors which show an association. Furthermore, there is likely to be more variables which have been explored but showed no association. Besides, some of these predictors in Table 4 like Charleson Comorbidity Index and NEWS score are composite scores with many variable components and might involve a larger sample size for the LR analysis to be credible and robust.

Reply 6c: We thank the Reviewer for this comment. We replaced our previous analysis, so now in the adjusted analysis, we adjusted for the 6 important confounders, i.e. age, gender, CCI score and NEWS2 score on admission and PaO2/FiO2 ratio and ARDS severity at the time of HFNO initiation, so that if we account for the exposure as well, we will have up to 7 degrees of freedom, as the Reviewer suggested.

Changes in the text: 1) At the Abstract we replaced "comorbidities, age, gender and race" with "age, gender, CCI score and NEWS2 score on admission and PaO2/FiO2 ratio and ARDS severity at the time of HFNO initiation" and then modified the rest of the sentence as follows: "it was significantly associated with the presence of dyspnea [adjusted OR 2.48 (95%CI, 1.01-6.12) and higher Urea serum levels [adjusted OR 1.25 (95%CI, 1.03-1.51), by mg/dL] (page 4, lines 36-44). We also replaced the sentence "Patient's features on hospital admission and severity of

respiratory involvement at the time of HFNC initiation offer predictive potential" with the sentence: "The presence of dyspnea and high serum Urea levels on admission are closely related to HFNC failure" (page 4, lines 46-48).

2) At the Methods section we replaced the phrase "comorbidities, age, gender and race" with "age, gender, CCI score and NEWS2 score on admission and PaO2/FiO2 ratio and ARDS severity at the time of HFNO initiation" (page 8, lines 98-99) 3) At the Results section the sentence "When adjusted logistic regression analysis was used…" was modified as follows: "However, when adjusted logistic regression analysis was used, only the presence of dyspnea and high Urea serum levels on admission, were found to be significantly associated to the failure of HFNC." (page 9, lines 117-118). 4) At the Discussion section the following changes were made: a) The sentence noted as "i)" was modified as "HFNC treatment succeeded (discharge without intubation) in 49.3 % of the patients and after adjustment for age, gender, CCI score and NEWS2 score on admission and PaO2/FiO2 ratio and ARDS severity at the time of HFNO initiation, this was significantly associated with the presence of dyspnea [adjusted 2.48 (95%CI, 1.01-6.12) and higher Urea serum levels [adjusted OR 1.25 (95%, 1.03-1.51), by mg/dL] on admission" (pages 10-11, lines 136-143) b) The sentence "After adjusting for…." was modified as "After adjusting for age, gender, CCI score and NEWS2 score on admission and PaO2/FiO2 ratio and ARDS severity at the time of HFNO initiation, we found that the presence of dyspnea and higher urea serum levels on admission are associated with increased risk of HFNC failure." (page 12, lines 164-168). c) The words "both in adjusted and" (page 12, line 170) have now been removed. d) The sentence "We demonstrated that…" was modified as follows: ". We demonstrated that other physiological features, such as PaO2/FiO2 ratio (on admission and after HFNC initiation), grade of ARDS severity and the NEWS2 score (on admission), were not linked with treatment failure" (page 12-13, lines 172-174). d) In the sentence "Interestingly…" the word "creatinine" was replaced from the word "urea" and the word "mainly" was removed (page 13, line 175). e) The sentence "Taken together…" was modified as follows: "Taken together

the above demonstrate that the presence of dyspnea and abnormal renal function on admission can predict failure or the method." (page 13, lines 175-177). f) We added the sentence: "It is very challenging to interpret the observed associations as causal because we may have unmeasured confounding, despite controlling for i) all the significant variables from the univariate analysis and ii) the 6 most important confounders, i.e. age, gender, CCI score and NEWS2 score on admission and PaO2/FiO2 ratio and ARDS severity at the time of HFNO initiation, in the adjusted analysis" (page 13, lines 179-182). g) The sentence "Patient's features on admission…" was replaced by: "The presence of dyspnea and high serum Urea levels on admission are closely related to HFNC failure" (page 14, lines 191-192).

d: There is minimal mentioning of the accounting for confounding effects of the predictors. Some of these are obviously related like PaO2/FiO2 ratios and ARDS severity. Did the authors do further sensitivity analysis or use variance inflation factor?

Reply 6d: To comply with the reviewers' reccomontation, PaO2/FiO2 ratios and ARDS severity have now been used as confounders in the adjusted analysis (See reply 6c).

Chenges in the text: See changes in the text for comment 6c

**Reviewer B**

This manuscript describes a cohort of adult patients with COVID 19 who received non-invasive ventilation and sought to investigate outcome and identify factors associated with failure. it is an interesting study as NIV may prevent intubation in these patients and prove to be helpful. it is well written.

Major points:

Comment 1:Authors talk about group of full treatment, no definition of which group is that. My guess it is the group excluding patients with DNI orders (5 patients). I think this added an unnecessary repetition in results as it showed same. I would recommend excluding the patients with DNI condition and present the data without these patients as they may present a bias.

Reply 1: We are grateful to the reviewer for his/her remark on the repetition issue. We think it is absolutely. We however thought that testing the clinical impact of HFNC would better take into account patients with DNI order. This is because upgrading respiratory support of patients with a DNI order, from low flow oxygen systems to HFNC is not just a palliative act, but suggests that every effort is still made to achieve the main therapeutical intention, to save lives, even though care is provided up to a certain limit, since it has been just that is highly unlikely to survive if intubated. In fact, in some instances, people requiring support with HFNC, finally survive (unfortunately not in the present cohort). For these reasons our primary end-point, HFNC failure, included, not only intubation, but also death without intubation. Thus, to adopt the reviewer suggestion, and avoid repetition, we believe that it would be better to delete the analysis on intubation.

Changes in the text: 1) At the Methods section the phrase "or intubation alone" has now been removed (page 7, line 92). 2) At the Results section the sentences "Un-adjusted logistic regression analysis, demonstrated that increased risk of intubation was associated with advanced age, low P/F ratio, presence of dyspnea, high Urea and Creatinine levels on admission, as well as low P/F ratio soon after HFNC initiation and ARDS severity (table 5). Using an adjusted logistical regression model, presence of dyspnea, low systolic blood pressure, high Urea and Creatinine levels on admission, as well as low P/F ratio on admission and soon after HFNC initiation and ARDS severity, predicted intubation." have now been removed (page 9, line 121-126). 3) At the Discussion section the phrase "and after adjustment for comorbidities, age, sex and race, intubation risk was found to increase in the presence of dyspnea [adjusted OR 2.96 (95%CI, 1.19-7.37)], lower systolic blood pressure [adjusted OR

0.73 (95%CI, 0.55-0.96) by 10 mmHg], high Urea [adjusted OR 1.39 (95%CI, 1.11-1.74), by mg/dL] and Creatinine [adjusted OR 4.65 (95%CI, 0.97-22.22), by mg/dL] levels on admission, as well as low P/F ratio on admission [adjusted OR 0.95 (95%CI, 0.91-1.00) by 10mmHg] and soon after HFNC initiation [adjusted OR 0.70 (95%CI, 0.59-0.82) by mmHg] as well as high ARDS severity, [adjusted OR 10.71 (95%CI, 3.87-29.61), by severity grade (see legend on table 5)]" (page 11, lines 144-150), as well as the words "and intubation" (page 12, line 170) have been removed 4) table 5 has now been removed (page 28-29).

Comment 2: Tables: table 1, there is no median values as presented in table description so would eliminate. Also table 2 and 3 don't present any important information and make the manuscript lengthy without adding importance, would recommend to remove.

Reply 2: We totally agree with the reviewer'e comment.

Changes in the text: 1) the phrase "or median (Interquartile range)" has now been removed from the legend of table 1 (page 22). 2) The sentence: "The clinical, laboratory and imaging characteristics of the patients are presented at tables 2 and 3." from the results section has now been removed (page 8, lines 104-105). 3) tables 2 and 3 have now been removed (pages 22-25).

Comment 3: I would add data about proning as proning may have affected outcome

Reply 3: At that time, awake proning has not been routinely used. It was only used occasionaly, for very short periods of time and data were not avaliable at the medical records.

Changes in the text: No

Comment 4: Any of patients were switched from high flow O2 to BIPAP?

Replay 4: As stated above (reply on the first reviewer's comment), no patients received non-invasive ventilation (NIV) as mean to avoid intubation and mechanical ventialtion. In general, at that time, our strategy of non invasive suppor tof COVID-19-induced severe respiratory failure did not include NIV. The same was true for the ICU of our hospital. NIV was applied in four of them after extubation as part of post-extubation respiratory support.

Changes in the text: We added the phrase "Non-invasive ventilation was not used as pre-intubation mean of respiratory support in any of the patients." (page 9, line 108-109)

Comment 5: In discussion, I would add a recent study very similar to what the authors did: Noninvasive ventilation for acute hypoxemic respiratory failure in patients with COVID-19 by Sergey N. Avdeev et al.

Reply 5: We thank the reviewer for this comment. We now comment on the results of that study.

Changes in the text: We reffered to this study in the disscussion section in the sentense "In agreement with others……", so we added the phrase "and similarly to an observation made with the use of NIV in COVID-19-related severe respiratory failure (25)" (page 12, lines 168-169) and we also added the reference at the References section (page 20, lines 283-284).

Additional changes in the text:

1) At the Footnote section we added an "Funding/Aknowledgment" statement, where we wrote: "Funding/Aknowledgment: The publication of the present article was

funded by the National & Kapodistrian University of Athens, Greece (Special Research Fund Account).” (page 16, lines 215-216).

2) At the Results section and at the sentence: “Un-adjusted logistic regression analysis revealed…..” the words “low systolic blood pressure” have now been removed as systolic blood pressure was not significantly associated with HFNO failure in the unadjusted analysis.

3) Tables: a) All references to “Table 4” where modified to “Table 2”. b)The row which reffers to “Systolic blood pressure” was removed because it was not significantly associated with HFNO failure nor in the unadjusted, neither in the adjusted analysis. c) The word “significantly” has now been removed from the legend of Table 2

4) The name of the author “Michalis Katsoulis” was changed to “Michail Katsoulis” after his kind request.

5) The word count, was revised after the changes that were made.