Author Response

REVIEWER'S 1 COMMENTS AND RESPONSES

1. Does this study have a specific ethical approval by your hospital committee?

This study was conducted as a part of routine Good Clinical Practice (GCP) and in accordance with the declaration of Helsinki. The retrospective collection of data was approved by the local Ethical Committee of Calabria Region on May 13th, 2020. We added these sentences in the revised text. (See lines 167 to 169, page 6).

2. The abstract should be changed. You haven't found any statistical significance, therefore you can't say "Our findings emphasize the role of HFNC that seems to be a preferable choice for treatment of patients with critical COVID-19". I think you should just say that you describe your experience with HFNC and discuss its role in COVID-19 patients.

We changed the abstract according to your suggestions.

3. Please review the language, there are several typos such as "...plays e crucial role..." in the abstract.

We corrected typos.

4. The introduction should be shorter. Practically, you should discuss the burden of hypoxemic respiratory failure in COVID-19 pandemic. The reasons for using other methods than invasive mechanical ventilation (for example, the lack of ventilation and ICU beds...) and a description of the HFNC device and advantages.

Thanks for your comment. In our revised manuscript, we shortened the introduction, and we also made the other suggested changes. (See lines 59 to 67, page 3; and 92 to 104, page 4).

5. Please use HFNC rather than HFNO, the former is a bit more standard term throughout the literature.

The acronym HFNO was replaced by HFNC.

6. When you discuss the use of HFNC, you should elaborate more about the viral transmission risk. For example, whether to use it only in a negative pressure environment or only where the staff is wearing a full PPE?

We investigated more about the viral transmission risk. Negative pressure rooms were not available, so naturally ventilated hospital rooms were used. The staff wore a full PPE. We added it in the revised text. (See lines: 144, page 5; 165,166 page 6; 309 to 322 pages 11 and 12)

7. You should speak about patient safety. In your case series, one might ask why haven't you intubated a severe hypoxemic patients who failed NIV/CPAP? Please suggest what kind of monitoring should be employed when using HFNC.

The failure of CPAP was mainly due to patient's poor tolerance, so we tried a rescue therapy with HFNC. HFNC decreases the probability of unneeded intubation, thus preserving much-needed critical care ventilators that have been in short supply in some areas.
In any case, patients receiving HFNC should be closely monitored in a setting where intubation can be immediately performed in case of relevant clinical deterioration. In particular, to guarantee patient's safety, healthcare professionals should still pay close attention to changes in oxygenation and respiratory frequency, monitoring the progression from mild/moderate ARDS to severe ARDS. We added it in the revised text. (Please see lines 253 to 256 page 9; 271 to 274, page 10; 323 to 325 page 12).

8. Please change the "...elderly and lonely..." in the discussion. If a patient is lonely, it doesn't mean that he/she is not for full quality of treatments including intubation.

The term "lonely" was replaced by "uncooperative". (See line 263, page 10). According to intensive care specialists there was no indication for intubation, especially for the patient with terminal pulmonary fibrosis, the only one who died because of a bleeding complication.

9. I think that you should use this small case series for a review of the HFNC use in the COVID-19 pandemic.
Thank you.

There are already reviews on the use of HFNC in scientific literature, but we plan to implement it. A discussion of similar cases has been added to the revised text. (See lines 275 to 293 pages 10 and 12).

REVIEWER'S 2 COMMENTS AND RESPONSES

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1. Abstract: the authors described some irrelevant information, such as the symptoms and information of COVID-19, which are the common knowledge now and the authors didn't directly study those issues in their study. Please delete. In abstract, authors need to mainly focus on their findings

In the revised text, the abstract was thoroughly modified according to your suggestions.

2. Introduction
a. Paragraph one is general knowledge about ARDS, the relevance to this study is pretty low, suggest delete it.

The paragraph about ARDS was deleted in the revised manuscript. (See lines 71 to 83 page 3)

b. Likewise, paragraphs 2-4 also described lots of common knowledge about HFNC and CPAP, such as the rationale and indications, please shorten the 4 paragraphs and merge into one.

In the introduction of the revised manuscript, we deleted less relevant information and merged some paragraphs according to your suggestions.

c. There have been at least 4 publications on utilizing HFNC for COVID-19 patients, please review them and put the current study results in the introduction.

The studies about HFNC in COVID-19 patients have been reviewed, summarized in the introduction and more in-depth discussed according to your suggestions. (See lines 126 to 128, page 5; 275 to 293 pages 10 and 11).

2. Methods

a. Study design is unclear, please state the study design as well as IRB approval at the beginning of this section

This was a retrospective observational study and was conducted as a part of routine Good Clinical Practice. The retrospective collection of data was approved by the local Ethical Committee of Calabria Region on May 13th, 2020. We added this information in the revised text. (See lines: 134, page 5; 167 to 169, page 6).

b. The process of changing CPAP/NIV to HFNC is not clear. Did they change from CPAP/NIV to HFNC for whoever met the failure criteria? what's the failure criteria? if it is the criteria listed before this sentence "A single attempt lasting a maximum of one hour was performed when SpO2 was less than 92%, RR higher than 28 acts/min, dyspnoea was present, and contraindications including cardiorespiratory arrest, signs of organ failure, hemodynamic instability, facial trauma, and upper airway obstruction were absent.11" any of the contraindication listed here is definitely contraindication for HFNC, those patients need direct intubation, how can it be possible to switch to HFNC? if this is not the criteria, please list.

The CPAP failure criteria were specified in the methods: "CPAP failure was established on the basis of either insufficient improvement or even worsening of SPO2". We better explained the indications

and contraindications to CPAP/NIV in methods and the process of changing CPAP/NIV to HFNC in the results. The failure of CPAP was mainly due to patient's poor tolerance, so we wanted to try a rescue therapy with HFNC. (See lines 145 to 160, page 6; 201 to 212 page 8).

c. From the description, I don't think it is a pre-planned prospective study

It was a retrospective observational study, as we added it in the revised manuscript. (See line 134,page 5).

4. Results
a. What do you mean by "early HFNC treatment"? b. Paragraph 2 is confusing, did you use HFNC for 2 patients directly and switched from conventional oxygen therapy to HFNC for 3 patients? Then you said "CPAP treatment was tried in all 5 patients", when did you use CPAP? Also, did you use CPAP or BiPAP?

a, b: This concept was better explained in the results. (Please see lines 201 to 214 page 8).

We used CPAP not BiPAP.

d. Flow plays a key role in the HFNC use, please report the flow settings as well.

The flow setting of each patient was specified in table 3. (See line 162,page 6 and Table 3 page 16).

5. Discussion
Please focus on the difference and similarities of your finding versus other studies with HFNC for COVID- 19 patients.

We accepted your suggestions, thus providing a discussion of similar cases in the revised text. (See lines 275 to 293, page 11).

Minor points:

1. When an abbreviation is used in the first time, please list the full name, such as PaCO2, PSV, PEEP, etc.

When required, abbreviations were added in the revised text.

2. PaO2/FiO2 rate is not a "rate"

The term "rate" was replaced by "ratio" in the revised manuscript.