Dear editor,

Here enclosed is the revised version of our manuscript: “High flow nasal cannula (HNFC) oxygen therapy to treat acute respiratory failure in patients with acute exacerbation of Idiopathic Pulmonary Fibrosis”.

We have made every effort to take all of the reviewers’ comments and suggestions into consideration and to modify the text accordingly. We hope that the revised version that we are now forwarding you will satisfy the reviewers’ concerns, and we trust that in its present form the paper will be considered suitable for publication in your journal.

The revisions/corrections are outlined in detail here below. We would like to take this opportunity to thank you and the reviewers for helping us to formulate a clearer, more articulate work, and it goes without saying that we will be anxiously looking forward to hearing from you at your convenience.

Kind regards,

Andrea Vianello, MD

Reviewer #1:

Major limitations:

1) The study is hampered by its retrospective and descriptive nature as well as limited number of patients which is further diluted by different subgroup analyses.

We agree with the reviewer that both the retrospective design and the limited number of patients enrolled are important drawbacks of our study. We mentioned these limitations in the “Discussion” section.

2) Title is misleading as it refers to a treating algorithm that has been applied in a minority of patients. What authors are implying is to apply HFNC, and if after correction of hypoxemia the patient has developed fatigue and hypercarbia they suggest application of NIV. And if NIC is unsuccessful then they suggest to apply EcMO. However, authors have applied this algorithmic therapeutic approach in only 1 patient. In addition, in 6 patients who responded poorly to HFNC, EcMO was not applied due to severe comorbidities and thorough discussion with family members. Thus, I would suggest to change the title with one relevant to HFNC considering that the majority of patients were subjected to this intervention. Otherwise I would suggest author to further enrich their cohort

The title has been changed according to the reviewer’s auggestion.

3) I am also a bit confused on the nature of IPF AEx. Median NT proBNP levels were markedly elevated (1700), and in one patient NT-proBNP levels were 6309. If that is the case then at least this patient, potentially more, did not experience an AEX of IPF but a cardiogenic pulmonary edema which has to be excluded in order to set the diagnosis of AEX of IPF based on the latest criteria in 2016 by Collard et al.

Although the influence of left ventricular dysfunction cannot be excluded in the development of acute decompensation, elevated plasma NT-proBNP levels in our patients could – we hypothesize -

correspond to RV pressure overload caused by profound hypoxemia and pulmonary hemodynamic derangement associated to acute IPF.

Vianello A, et al. Noninvasive ventilation in the event of acute respiratory failure in patients with idiopathic pulmonary fibrosis. J Crit Care. 2014 Aug;29(4):562-7.

4) I am a bit concerned on the diagnostic criteria used to set the diagnosis of IPF. Authors state that out of 17 patients admitted to ICU only 11 were on anti-fibrotic treatment while 4 patients were under immunomodulatory therapeutic regimens. That means that there were at least 3 patients which were under no treatment and 6 patients in total that were not under standard of care, meaning pirfenidone or nintedanib.How do authors explain this discrepancy? Were these true IPF cases or cHP or IPAF cases requiring immunomodulatorry treatment?

IPF patients who were not under standard of care had not been prescribed anti-fibrotic agents due to the following reasons: the drugs were not yet on the market (3 cases; Pirfenidone and Nintedanib were, in fact, approved for IPF treatment by the regional health authority on August 1, 2013 and April 1, 2016, respectively); scarce compliance (2 cases); the indications for the drug did not include the age group into which the patient fell (1 case). This information has been added in the "Results" section. Immunomodulatory treatment was only utilized before anti-fibrotic agents were on the market.

5) Frequency of discharge was the same between the two groups : Conventional O2 therapy with HFNC. Differences in mortality were noticed ;2/8, vs 6/9. How do authors explain these differences. Kaplan meier curves should be drawn for both treatment groups.

This question is not completely clear: in fact, the proportion of patients discharged alive in the conventional oxygen therapy group, also including subjects receiving combined NIV and/or ECCO2R treatment, was higher, although not significantly, compared to that in the HFNC group (5/8 vs 4/10; p=0.637). Conversely, mortality rate was higher in the HFNC group, perhaps due to more severe comorbidities. Kaplan-Meier estimates of survival function, stratified according to the type of supplemental oxygen therapy has been illustrated in fig.4.

6) Among all different demographic, clinical and serological data illustrated in Table 2 they were no significant differences that could reliably discriminate responders from nonresponders in the HFNC group. Thus on what basis should clinicians apply this algorithm? Surprisingly in the PAO2 row, responders seem to have lower PaO2 levels than nonresponders. This kind of oxymorous . However, a closer look on the CI values shows that in one patients PAO2 was 258.7 which does not correspond to a real value unless the patient on MV.

Patients with CPR levels above 100 ug/ml were found to have a substantially higher risk of HFNC failure (approximately 4-fold) with respect to their counterparts with lower levels. This result has already been commented in the "Discussion" section. We could argue that HFNC treatment should be preferred for patients whose CRP level is below this cut-off value; in the event of higher values, correction of severe hypoxemia is likely to require the application of ECMO. PaO2 was measured during supplemental oxygen therapy: for this reason, its absolute value cannot be considered a reliable index of the degree of blood gas exchange abnormalities.

7) Comorbidities should be reported in details.

Details on comorbidities have been added in the "Results" section.

8) From the laboratory exams it seems to the reviewer that at least 4 patients had an infection – related AEx (leukocytosis, elevated CRP and PCT levels). Authors reported that these patients did not respond satisfactorily to HFNC.

We agree with the reviewer that 4 patients could have developed an infection – related AEx. In an attempt to confirm the diagnosis of respiratory tract infection, BAL could only be carried out in 4 out of 17 cases, due to the severity of clinical status. 2 patients were positive for type A and B influenza viruses according to viral culture carried out on nasopharyngeal swab. This data has been added in the "Results" section.

Reviewer #2:

1) As a result, a total of 17 patients were enrolled in this study. The enrolment process should be mentioned more clearly, even part of it can be seen in Method part.

More information about the enrolment procedure has been included in the "Methods" section.

2) The authors described in Discussion part that the lower RICU mortality rate was obtained in this study, compared with published studies (i.e. Reference No 23) with conventional oxygen therapy. However, the difference of other treatments including high-dose corticosteroid therapy among studies should also be considered in the context.

According to ref 23, a short sentence on positive impact of avoiding steroids on survival has been added in the "Discussion" section.