Review by Dr. A. Tzouvelekis, v.1

Thank you for giving me the opportunity to review the paper by Vianello et al. This is a seminal study on the use of ECMO and High flow nasal cannula Oxygen therapy in patients with IPF during AEx. While the study presents some interesting data there are major limiations that need to addressed cautisouly.

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
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
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.
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?
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.
6) Among all different demographic, clinical and serological data illustrated in Table 2 they were no significant differences that could rreliably discriminate responders from non-responders 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 non-responders. 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.
7) Comorbidities should be reported in details.
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.