Reviewer 2 v.1

Comments to the Author

In this manuscript, Dr Chen et al. describe the characteristics, risk factors and outcome of NLRTI in 250 patients with Influenza-related ARDS.

The question addressed is relevant and the paper is overall well written, however I have several major methodological concerns.

1. Bacterial co-infections associated with Influenza have already been investigated, and the novelty of the present study is that it addresses NLRTI, excluding bacterial CAP. The authors state that they followed the guidelines to exclude CAP, however it is in my opinion very difficult sometimes to exclude CAP in a patient admitted with Flu. For instance, in patients who required intubation only several days (>2) after admission and who had at the time of intubation a positive culture of respiratory sample, how could the authors determine whether it was a CAP (not yet diagnosed) or NLRTI ?

I think the authors should give much more details about that part of the methods as it is crucial.

2. In my opinion, Kaplan Meier curves are not appropriate to assess the impact of time-dependent variables (like ECMO) on NLRTI.

3. Some data would require more clarity :

- laboratory data are reported 'upon initial presentation', is that on hospital admission ? ICU admission ? intubation ?

- in table 1, 21 patients in the NLRTI had ECMO, 20 of them before NLRTI. If the goal is to address risk factors for NLRTI, I think authors should report in the table data before NLRTI, not only for ECMO but also vasopressors, etc…

- the number (%) on vasopressors in non-NLRTI group is erroneous

- I am surprised that only about 80% of patients received sedatives ; most patients had moderate to severe ARDS which usually requires heavy sedation, do the authors have any explanation for this finding?

- I don`t think the mean steroid dosage is an adequate variable unless authors also report the number of patients who received steroids in each group ; and again only steroids received before NLRTI (and not within 14 days as currently in the manuscript) should be included in the analysis if the goal is to address their impact on NLRTI.

4. I think again that the analysis of risk factors for NLRTI is difficult to interpret due to the time-dependence of multiple variables. On the other side, the authors only described the mortality in the

2 groups but did not address in a multivariate analysis (or other) the independent effect of NLRTI on mortality, which would be much more interesting.