Dear Reviewer 1

The manuscript has been revised in response to your comments.

Reviewer: 1

Comments to the Author
This retrospective analysis looks to identify factors associated with LRTI as a complication of flu-related ARDS. I have several concerns.

1. The methods section should most clearly show the primary endpoint.
Answer: Thank you for your comment. We have addressed the endpoint measurement in the method section. Please read page 8, line 58, page 10, line 22-28 in the revised manuscript.

2. How were disagreements amongst the 2 reviewers as to the presence of a NLRTI resolved? What info did they review to determine if the pt developed NLRTI.
Answer: Thank you for your comment. Clinical NLRTI should be confirmed by agreement of two intensivists (Dr. Kao KC and Dr. Sheu CC) in the study group after a detailed chart review of symptoms and vital signs, laboratory data, microbiology results and chest images. In addition, newly developed or progressive respiratory symptoms, unstable vitals, elevated white blood cell counts or left shift, C-reactive protein or procalcitonin level, and new infiltrates on chest radiographs were included to determine whether the patients developed NLRTI. Please read page 9, line 55-58 to page 10, line 4-7 in the revised manuscript.

3. How were cultures obtained to determine if an NLTRI evolved (eg sputum, trach aspirate, bronch etc)?
Answer: Thank you for your comment. Due to the retrospective nature of this study, methods of respiratory specimen collection for determination if a NLRTI evolved differed from each sites. Tracheal aspirates are most often used (81.9%) in our study. Please read the page 11, line 40-43 in the revised manuscript.

4. The model needs to include a variable for center effect to look for interactions based on the one of the 8 hospitals that contributed pts.
Answer: Thank you for your comment. The hospital that contributed patients is Hospital No. 4. It contributed 56 patients, including 19 patients with NLRTI. We included this hospital to look for center effect in the logistic regression analysis. Both univariate and multivariate regression analysis showed similar results as original Table. Please read the Table below (Please read the atached file) for more information.

5. The model needs a goodness of fit test.
Answer: Thank you for your comment. The Hosmer–Lemeshow test in our multivariate logistic regression analysis showed it was a good fit (P = 0.189). Please read page 12, line 28-31 in the revised manuscript.

6. How was co-linearity addressed?
Answer: Thank you for your comment. The co-linearity analysis showed that no co-linearity issue in our data. All of the variables had variance inflation factor less than 5. Please read the Table below (Please read the attached file) for further information.

7. The authors need to address the immortal time bias issue -- for example pts on ECMO likely were on it for some time and hence observed for a longer period of time and thus this confounds the analysis. The authors have KM curves and time to event so the more appropriate model would be a Cox proportional hazard model.
Answer: Thank you for your comment. We have revised our survival analysis by using Cox proportional hazard model. Please read page 12, line 31-43, page 24, line 25-52 and Figure 2 in the revised manuscript.

8. Similarly, the crude outcomes should be reported as adjusted to removed from the paper. Also, is the LOS that from time of flu and ARDS? Is it adjusted for pre-ARDS time of hospitalization?
Answer: Thank you for your comment. As above, we have revised our survival analysis by using Cox proportional hazard model. The hospital day was calculated from the time of flu and ARDS to discharge or death. Pre-ARDS time of hospitalization was not included. Please read page 9, line 4-7, page 12, line 31-43, page 24, line 25-52 and Figure 2 in the revised manuscript.

9. The limitations section of the discussion needs to be expanded upon significantly.
Answer: Thank you for your comment. Please read page 16, line 31-37, line 46-49, page 17, line 13-16 in the limitation section of the revised manuscript.

Dear Reviewer 2

Thank you for reviewing our manuscript.

Dear Reviewer 3

The manuscript has been revised in response to your comments.

Reviewer: 3

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.
Answer: Thank you for your comment. Due to the retrospective nature of the study, the

confirmation of CAP is difficult and it is also a limitation of our study. Use of antibiotics upon diagnosis of influenza-related ARDS and for at least 5 consecutive days was viewed as evidence of CAP. Please read page 9, line 37-40 in the revised manuscript.

2. In my opinion, Kaplan Meier curves are not appropriate to assess the impact of time-dependent variables (like ECMO) on NLRTI.
Answer: Thank you for your comment. We have revised our survival analysis by using Cox proportional hazard model. Please read page 12, line 31-43, page 24, line 25-52 and Figure 2 in the revised manuscript.

3. Some data would require more clarity :
- laboratory data are reported 'upon initial presentation', is that on hospital admission ? ICU admission ? intubation ?
Answer: Thank you for your comment. The lab data were reported upon initial diagnosis of influenza-related ARDS. Please read page 8, line 43 in the revised manuscript.

- 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…
Answer: Thank you for your comment. The management of influenza-related ARDS and its complications, including prone position, renal replacement therapy, vasopressors, sedatives, neuromuscular blockade, and steroid were all initiated before NLRTI. Please read Table 1 and its footnote c in the revised manuscript.

- the number (%) on vasopressors in non-NLRTI group is erroneous
Answer: Thank you for your comment. It was a typo. There were 88 (49.4%) vasopressor users in non-NLRTI group. Please read Table 1 in the revised manuscript.

- 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?
Answer: Thank you for your comment. Due to lack of complete medications records, some patients might be treated with pain control or antipsychotics only. Please read page 16, line 31-37 in the revised limitation section.

- 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.
Answer: Thank you for your comment. We reported the number of patients who received steroids in each group. In patients developing NLRTI, we re-calculated steroids use only before NLRTI. Please read page 4, line 55-58, page 5, line 4, page 12, line 19-25, Table 1, footnote e, and Table 3 in the revised manuscript.

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.

Answer: Thank you for your comment. We also added a multivariate analysis of the in-hospital mortality. Please read page 12, line 46-52, and supplementary Table 2 and 3 in the revised manuscript.