Peer review file

Article information: http://dx.doi.org/10.21037/jtd-20-2891

Reviewer A

Comment 1: "Many lung diseases including pulmonary emphysema, bronchiectasis, and pulmonary fibrosis, impact pneumonia. However, the authors provided no data on underlying lung diseases in patients with NSCLC in this research. This information should be added to the analysis in this study."

Reply 1: We have pulled the data from our cohort regarding COPD and Idiopathic Pulmonary Fibrosis incidence and have added this under the descriptors.

Changes in the text: Please see updated table 1. Please see page 6 line 5.

Comment 2: Furthermore, smoking status is associated with the pathological mechanism of these lung diseases. In this study, the authors classified the smoking status into three groups; never smoker, former smoker, and current smoker. However, smoking status based on never smoking, light smoking, and heavy smoking is also associated with lung diseases' pathophysiology, including lung cancer.

Reply 2: While we agree with the reviewer that smoking intensity may impact outcome, we have used the traditional nomenclature to classify smokers as never, former and current. The intensity of smoking was not captured uniformly in our database and we have therefor omitted this variable.

Comment 3: The current study suggested the association of the onset of pneumonia with the prognosis of lung cancer, whereas pneumonia can also be life-threatening. Thus, the authors should demonstrate information on pneumonia as the cause of death.

Reply 3: We agree that pneumonia can be life threatening. Unfortunately, we are not able to capture cause of death in our database. Our survival data is based on overall survival not lung cancer specific survival. In patients with pneumonia diagnosed after lung cancer diagnosis we would surmise it would be difficult to discern whether death occurred as a result of pneumonia versus cancer progression as often times progression of lung cancer can cause obstructive pneumonias that lead to patient deaths.

Comment 4: As the authors mentioned, there was an imbalance in the numbers between younger and older patients. This study also demonstrated imbalanced numbers of patients by pneumonia status. The authors should address these imbalances that may have the potential for bias.

Reply 4: We agree that there is an imbalance, but that is what was found. We have noted that only 2 patients with in younger cohort presented with pneumonia. We will further emphasize the potential bias this could result in.

Changes in the text: Please see page 11, lines 8-10.

Comment 5: Furthermore, pathogenic microorganisms causing pneumonia can vary according to environment and institution. A therapeutic strategy may not be the same among institutions. Therefore, a single institution study described as one of the limitations in this article may also yield biased results.

Reply 5: We recognize this single institution study as a source of bias and have included this.

Changes in the text: Please see page 11, line 11-12.

Comment 6: The authors analyzed the differences in clinicopathological characteristics between younger and older patients. However, the critical point is the differences among patients with three pneumonia statuses classified in this study. The authors should provide this information.

Reply 6: We have now revised the title to reflect general clinicopathological differences, including pneumonia to:

Characterization of pneumonia and other factors leading to poorer survival across all age groups in patients with non-small cell lung cancer.
Changes in the text: We have changed the title.

Comment 7: As the authors mentioned, the status of lung cancer influences the onset of pneumonia. In NSCLC, squamous cell carcinoma is prone to obstructive pneumonia, compared to non-squamous cell carcinoma. Furthermore, age at diagnosis showed significant differences in histologic findings. Given the importance of lung cancer histology for pneumonia, multivariate analyses should include histologic findings as potential confounding factors.

Reply 7: We have performed multivariate analysis with regards to histology

Changes in the text: Please see updated table II and III. We have discussed these findings in the text on page 8, line 16 and on page 7 under the heading *"Histology and Survival"*.

Comment 8: Furthermore, the proportion of patients with driver oncogenes and the difference in therapeutic modalities significantly impact patients' outcomes with NSCLC. These data are indispensable for the analysis in this study.

Reply 8: We agree that driver oncogene and therapeutic interventions would add extremely interesting findings to our manuscript. We found information on driver oncogenes to be available in less than 20% of patients, using our EMR This may be due to the fact that many of the patients we analyzed were diagnosed in the early 2010s prior to the routine use of mutational analysis. Given this, we did not feel it would be wise to use these variables.

Reviewer B

Comment 1: In the abstract and introduction, it is necessary to write "non-small cell lung cancer" and then in brackets an abbreviation after the full title (NSCLC).

Reply 1: We have made these changes

Changes to text: See page 2, line 3. See page 3, line 8

Comment 2: Lung adenocarcinoma is the most common histological subtype of NSCLC and should be specifically considered and not classified as non-squamous cell carcinoma.

Reply 2: We initially included adenosquamous and large cell carcinomas along with adenocarcinoma in the group "non-squamous cell carcinoma". We have separated the groups into squamous, adenocarcinoma and other.

Changes to text: Please see updated Table I. We defined these subgroups on page 7 under the heading *"Histology and Survival"*.

Comment 3: The suggestion is that the correlation of these two most common histological subtypes of NSCLC (squamous cell and adenocarcinoma) be considered separately in relation to survival rate.

Reply 3: We have analyzed survival rate of adenocarcinoma and squamous cell separately.

Changes to text: Please see supplementary figure 1 and supplementary table 1. Please see updated survival analysis in Table II and III with regard to histology. We have added a section to discuss these subgroups on page 7 under the heading *"Histology and Survival"*.**Comment 4:** The paper states the clinical stage of the tumour disease, misnamed as the pathological stage, which must be changed.

Reply 4: We have changed "pathologic characteristics" in which we discuss staging and histology to "tumor characteristics".

Changes to text: Please see page 6 line 7

Comment 5: The biggest objection is that there is no discussion. The whole discussion is brought under the conclusion that it should be clearly separated under two subtitles.

Reply 5: We have made these changes.

Changes to text: Please see page 9 line 5 and page 11 line 16

Reviewer C

Comment 1: They described only the facts that pneumonia is associated with a poor prognosis. The etiology had not been clarified. Details such as the possibility of obstructive pneumonia or lymphangitis carcinomatosa were not described. Causing pathogens were not clarified.

Reply 1: Unfortunately, we are unable to capture bacterial, viral, fungal, etc etiology of pneumonia as well as obstruction versus non-obstructive pneumonia in our database. We agree that this information would add further explanation to the types of pneumonia NSCLC patients may be predisposed to.

Comment 2: It is necessary to focus on cases of pneumonia. They apparently should seek the more data concerning pneumonia.

Reply 2: We agree that further information regarding classification, etiology and demographics of pneumonia would be interesting. However, our objective in this paper was to take a cohort of patients, young versus old, and delve into demographic and clinico-pathologic data to see if there were differences between these groups of patients that could potentially impact outcomes. This manuscript is meant to describe these overall differences so that further, in depth, analysis could be performed based on each significant difference for future potential publication.

Reviewer D

Comment 1: The title focuses on the role that pneumonia can have on the evolution of a non-small cell lung cancer in the various age groups but in line 22 it is stated that the objective of the study is to identify the differences in demographics between older and younger patients with lung cancer, to assess their overall survival and to determine potential underlying factors that may contribute to poorer outcomes;

In fact, the article extends the objective stated in the title of the study analyzing demographic factors (such as age, gender, smoking habits), the stage of disease at diagnosis, and the histotype of the cancer of younger versus older patients; only one section is reserved to the role that pneumonia may have in the prognosis of patients with NSCLC.

For this reason, I suggest changing the title of the article, as example "Pneumonia prior ... and other factors that can contribute to a worse prognosis (or a worse survival) across all age groups”.

Reply 1: We agree with the reviewer, to emphasize not only pneumonia as a factor contributing to worse prognosis

Changes to text: We have changed the title. Pneumonia prior to diagnosis and other clinic-pathological factors that contribute to outcomes in non-small cell lung cancer. We have spent more time addressing other factors (ie. histology) that contribute to poor outcomes. Please see page 7 under the heading *"Histology and Survival"*.

Comment 2: However, no mention is made of the etiological agent of the pneumonia from which these patients were affected (if known) and of therapies performed, and about the possibility that these therapies, immunodepressing the patient, could have a role in the onset of the tumor. These are, as the authors say, limitations of the study.

Reply 2: We agree that data regarding etiology and treatment would be interesting data to include in the study. This information was not uniformly captured in all patients, therefore we have not reported these. As mentioned previously, we find the association between pneumonia and lung cancer outcome intriguing and further rigorous studies need to be undertaken to study cause and effect.

Comment 3: In the concluding part the role of the radiographic investigation is introduced in the evaluation of a patient with a history of pneumonia. This evaluation, although interesting, appears unrelated to the study of the enrolled patients, for whom the radiological investigations carried out after the pneumonia event are not mentioned.

Reply 3: We will deemphasize the role of radiological investigations.

Changes to text: Please see page 11, lines 21- page 12, line 3