Peer Review File

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Reviewer A

Comment 1: I really appreciate your paper.

This is one of papers that have been trying to find out the predictors for immunotherapy.

Unlike other papers, you made a use of a large-scaled dataset and practically tried to search for predictors among personal and clinical characteristics.

One thing to point out is that there is a limit to interpret precisely because this dataset didn`t have some important factors like smoking status.

Reply 1: Thank you for your comment. We agree that this is a limitation of the dataset and have added the following text to clarify this point at the onset of our discussion of limitations

Changes in the text: "Therefore, **there is a limit to the extent to which these findings can be interpreted and…" (See Lines 312-313, Pg. 14)**

Reviewer B

Comment 1: The study uses a large cohort of IV lung cancer patients and looks into epidemiological parameters that might relate to OS following chemoimmunotherapy vs. chemotherapy treatment. A very well-written manuscript.

The strengths of the study are the large cohort of patients used and the selection of checkpoint inhibitor therapies as "immunotherapy" in the chemoimmunotherapy group. As the authors rightly note, inclusion of all kinds of immunotherapy would not be appropriate.

In my opinion, the overall analyses attempted in this study are limited by the lack of further information about the patients. Treatment response, co-morbidities, etc are hugely important factors that should complement analyses based on OS. Lack of these does not allow accurate conclusions that are of clinical value… It would be of interest to delve into other characteristics of the patients- smoking history, comorbidities, other treatments, treatment response, etc- in case some factors can be correlated with OS.

Reply 1: Thank you for your feedback—this is certainly a valid point and as mentioned under Reply 1, the dataset itself lacks data on smoking status; this is included in the discussion as a limitation.

In terms of comorbidities, we have clarified the role of using the NCI adaptation of the Charlson Comorbidity Index (CCI) as one of the covariates and detailed in the text all of the comorbidities it encompasses, many of which (e.g. COPD, cerebrovascular accident or TIA) are strongly associated with smoking; other conditions like heart failure and diabetes are known to also be determinants of cancer outcomes. CCI was included in all the analyses and adjustment, therefore we feel that some of the limitations inherent to large datasets were addressed with this study.

We believe the size and generalizability of the dataset given its national representation otherwise compensates for this limitation. Moreover, we have added a sensitivity analysis including presence of brain metastasis in the multivariate analysis which corroborated our initial findings as presented. Brain metastasis is a covariate that we had not originally included in the analysis, and provides non-overlapping, distinct characteristics about cancer progression and treatment response. Lastly, it is important to note that other types of treatment like surgery and radiation are not indicated for metastatic NSCLC, thus we felt that stratifying by other treatments type was less of a priority.

Changes in the text: As advised we have modified the text to clarify the comorbidities included within the analysis (Lines 138-143), and Tables S2 and S3 has also been added to the supplement: "**Specifically, the CCI is comprised of the following comorbidities, all of which are associated with treatment response and overall health: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular accident or transient ischemic attack, chronic obstructive pulmonary disease, peptic ulcer disease, paralysis or hemiplegia, diabetes history, liver disease, and kidney disease—the last three of which are further weighted by severity (19, 20).**"

We also added the addition of this sensitivity analysis to our methods section: "**A sensitivity analysis was also performed on the subgroup of patients with available data on brain metastasis at time of diagnosis to further evaluate comorbidities potentially affecting treatment response and survival (n=1402)." (Lines 156-158)**

We have also added a sensitivity analysis (Table S3) to include brain metastasis as a covariate to further adjust for **(Lines 212-222):**

"A sensitivity analyses was performed to further adjust for presence of brain metastasis at diagnosis. Chemoimmunotherapy treatment was still associated with significantly better survival (HR_{adj} [age 70-74 years]: 0.72, 95% CI: 0.63-0.83). **With the addition of this covariate in the multivariable survival analysis, brain metastasis at diagnosis (HR_{adj} [brain metastasis]: 1.41, 95% CI: 1.22-1.63) as well as a Charlson Comorbidity Index ≥3 (HR_{adj} [CCI≥3]: 1.21, 95% CI: 1.01-1.46) and "Other" histology (HR_{adj} [other]: 1.34, 95% CI: 1.10-1.63) were found to be independently associated with shorter OS (Table S3). Otherwise, all other results from the sensitivity analysis were consistent with the original multivariate model. For instance female patients (HR_{adj} [sex]: 0.73, 95% CI: 0.64-0.83) still had significantly better survival with chemoimmunotherapy, and those over age 80 years (HR_{adj} [age ≥80]:1.28, 95% CI: 1.07, 1.54) had lower overall survival with chemoimmunotherapy (Table S3)."**

We also expanded upon this in our limitation paragraph in the discussion section as shown below **(Lines 342-346)**

"The sensitivity analysis on a smaller sample size where information on brain metastasis at diagnosis was available corroborates our primary findings, as this allowed us to adjust more comprehensively for covariates

associated with survival and treatment response, and it still corroborated our primary findings."
Lastly, we also clarified the limitation of this study lacking data as per Reply 1 (see Lines 310-32).

Comment 2: One such conclusion here is that males do better on chemoimmunotherapy than females. This is found to be a marginally statistically significant finding in this study, and I would suggest the authors note in the manuscript that the statistical difference is "borderline significant."
Reply 2: This is a good point and we agree that "borderline significant" is more accurate and precise wording. We have changed it accordingly as below:
Changes in the text:
Lines 46-48: After propensity-score matching, the effect of chemoimmunotherapy was **borderline significant** according to sex (p[interaction]=0.0414), but not age or histology.
Lines 204-208: Chemoimmunotherapy showed a **borderline significant** survival increase over chemotherapy among males, but not females (HR_{male}: 0.59, 95% CI: 0.47-0.74; HR_{female}: 0.85, 95% CI: 0.65-1.12; p[interaction]=0.0414) (Figure S2, Table S2).

Comment 3: Minor correction:
In the abstract you describe cohort numbers for each cohort and have the percentage of patients in the chemotherapy group. Very confusing- can you describe it as in your Results section in the manuscript, i.e. "from a total number of n=1,471 patients, 349 (X%) received chemoimmunotherapy and n=1,122 (X%) received chemotherapy alone.
Reply 3: Thank you for pointing out this discrepancy to us—we have revised the results section as below to reflect your suggestions and increase clarity.
Changes in the text: Lines **40-41 Abstract: From a total number of n=1,471 patients, 349 (24%) received chemoimmunotherapy and n=1,122 (76%) received chemotherapy alone.**

Other Revisions/Additions:

- Added additional results for completeness that were not initially described in the initial text (Lines 190-194):

"Likewise, chemoimmunotherapy treatment among older age groups was associated with significantly better survival (HR_{adj} [age 70-74 years]: 0.67, 95% CI: 0.52-0.88; HR_{adj} [age 75-79 years]: 0.72, 95% CI: 0.54-0.96; HR_{adj} [age ≥80]: 0.55, 95% CI: 0.39-0.80). However, there was no significant interaction between age and receipt of chemoimmunotherapy (p[interaction]=0.2165)."

- Updated citation with relevant findings (Lines 293-298)

"A recent study by Tuminello et al. (2022) analyzed population-level from the national cancer database (NCDB) and found males with squamous cell carcinoma

may derive more benefit from chemoimmunotherapy than females; in turn, they hypothesized that histology likely plays an important role in the modulation of sex on immunotherapy effectiveness."