Peer Review File

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Reviewer A:

The authors have made retrospective study concerning the predictive factor for selecting candidate of adjuvant therapy for patients with stage I NSCLC with use of SEER database. Indeed, they conducted retrospective study among large scale patients' cohort and with use of sophisticated statistical method, propensity-score matching analysis. However, I consider the database they used in their analyses lacks much important data concerning to the indication and efficacy of adjuvant chemotherapy, and results from their study may result in misleading conclusion to the readers.

In the SEER database, patients' performance status (pre- and/or post-operative) and co-morbidities of each patient are not recorded. Both data are influence on the indication of adjuvant chemotherapy and postoperative outcome. In clinical practice, patient who have severe and/or many number of co-morbidity or patients with low performance status likely to be avoided to administer adjuvant chemotherapy even if they have progressive disease such as p-stage II-III NSCLC. In addition, each of these (co-morbidity and performance status) are the independent prognostic factor. Thus, naturally, group of patents who don't receive adjuvant chemotherapy should include many patients whose prognosis is poor irrespective of the administration of adjuvant chemotherapy. Under such circumstances, a lot of studies concerning the efficacy of adjuvant chemotherapy have conducted as prospective setting or with much consideration of balancing the factors affecting to the postoperative outcomes. In this study, they could not control the influence of these important factors affecting to the indication of adjuvant chemotherapy and postoperative outcome, thus, their results have little reliability. In their study, the significant difference in LCSS and/or OS between patients who received adjuvant therapy and patients who did not may be not due to the administration of adjuvant chemotherapy but due to the patients' background itself, even after PS matching was conducted. If so, their results can be misleading conclusion to the readers, and it must be avoided.

As referred above, SEER database does not have the data concerning patients' performance status and co-morbidities, thus the authors cannot revise their study adequately.

Reply: Thank you for your advice and criticism. While our efforts have enabled us to conduct thorough analysis based on available data sets, it's important to acknowledge the inevitable limitations inherent in the database, which may have influenced our research findings to some extent. Consequently, we anticipate future studies that take a forward-looking approach to address these data gaps and offer a more comprehensive understanding. Additionally, we understand the significance of juxtaposing our research outcomes with real-world conditions to elucidate the constraints and potential biases of database research. We eagerly await further

exploration of these issues in future research endeavors, aiming to provide more profound insights and practical solutions.

Changes in the text: We have added the shortcomings of the research in the discussion and started the next research plan. (see Page 14 line 369-373) Although we have conducted an in-depth analysis based on the available data set, it is undeniable that the limitation of the database may affect the robustness of the results of this study. Therefore, we expect that more real-world studies or prospective clinical trials can improve the above data and conduct a more comprehensive analysis to further verify the results of this article.

Reviewer B:

This study delves into the crucial topic of identifying high-risk clinicopathologic features that can significantly impact the decision-making process for chemotherapy in stage I non-small cell lung cancer (NSCLC). The primary predictor, visceral pleural invasion (VPI), and the secondary predictor, the examination of an insufficient number of lymph nodes (LNs), along with high histologic grade, are highlighted as key factors influencing the prognosis.

Strengths:

Identification of Primary and Secondary Predictors: The study effectively pinpoints VPI as the primary predictor, shedding light on its importance in assessing the need for chemotherapy. The recognition of an insufficient number of LNs as a secondary predictor adds depth to the understanding of high-risk features.

Independent Risk Factors: The study establishes high-risk clinicopathologic features, including high histologic grade, VPI, insufficient LNs examination, and limited resection, as independent risk factors for a poor prognosis in stage I NSCLC. This provides valuable insights for clinicians in risk assessment.

Stratification and Variability: The stratification of patients based on pathologic stage and high-risk clinicopathologic features is a notable strength. The identification of varied benefits of chemotherapy depending on specific factors challenges the one-size-fits-all approach, emphasizing the need for individualized treatment plans.

Implications:

Informed Decision-Making: The study underscores the importance of considering individual patient characteristics and high-risk features when deciding on chemotherapy for stage I NSCLC. This nuanced approach ensures that treatment decisions are tailored to the unique circumstances of each patient.

Challenging Universal Benefit: By highlighting the variability in the benefits of chemotherapy, the study challenges the notion of a universal benefit for all stage I NSCLC patients. This calls for a reevaluation of existing treatment guidelines to incorporate a more personalized and targeted approach.

Recommendations for Improvement:

Clarification on Limited Resection: The study mentions limited resection as an independent risk factor, but further clarification on its significance and impact on prognosis would enhance the comprehensibility of the findings.

Long-Term Follow-Up: Including information on the long-term follow-up of patients would strengthen the study's credibility by providing insights into the durability of the observed effects.

External Validation: The findings would benefit from external validation to confirm the robustness of the identified predictors and their implications across different patient populations.

In conclusion, this study contributes significantly to the understanding of high-risk clinicopathologic features in stage I NSCLC and their influence on the decision-making process for chemotherapy. The emphasis on individualized treatment plans and the reevaluation of the universal benefit of chemotherapy make this research a valuable resource for clinicians and researchers in the field.

Reply: Thank you very much for your comment. Because this study is only a database-based study, the next step is to explore the impact of limited excision on the prognosis of patients through real-world research. Next, we will use the data of our center to further verify the existing high-risk factors and follow-up observation of patients to verify the reliability and credibility of the corresponding conclusions.

Changes in the text: We have added the shortcomings of the research in the discussion and started the next research plan. (see Page 14 line 369-373) Although we have conducted an in-depth analysis based on the available data set, it is undeniable that the limitation of the database may affect the robustness of the results of this study. Therefore, we expect that more real-world studies or prospective clinical trials can improve the above data and conduct a more comprehensive analysis to further verify the results of this article.

Reviewer C:

Comment 1: Summary: The authors investigated if chemotherapy has an associated survival benefit in stage I NSCLC when stratifying by pathologic stage and high-risk clinicopathologic features. They queried the SEER database and identified 26,160 eligible patients (primary lung cancer only, tumors 4cm. The authors should comment on the similarities/differences of their study compared with Pathak et al in the discussion.

Reply 1： Pathak et al. is based on the chemotherapy efficacy of patients with stage I and II lung cancer based on the NCDB database. This study is based on the chemotherapy efficacy of patients with stage I lung cancer on the SEER database.

Changes in the test: None

Comment 2： Line 331 – reference the two recently published randomized trials on sublobar vs. lobar resections (JCOG0802, CALGB 140503).

Reply 2: It's a great honor to receive your comments. We have inserted relevant references COG0802, CALGB 14050. Segmentectomy is significantly better than lobectomy in terms of OS and lung function.

Changes in the test: We add Segmentectomy is significantly better than lobectomy in terms of OS and pulmonary function in Page 13 line 343-344.

Comment 3 The authors acknowledge several limitations of their study. One limitation that should be included is the quality of chemotherapy data in the SEER database. Previous investigations comparing SEER data with Medicare claims data found that the sensitivity for SEER data to identify individuals who received chemotherapy was only 68% (Noon et al. Med Care2016).

Reply 3: We have inserted relevant references.

Changes in the test: We add "Finally, the quality of chemotherapy data in the SEER database was unknown. Previous investigations comparing SEER data with Medicare claims data found that the sensitivity for SEER data to identify individuals who received chemotherapy was only 68%." in Page 14 line 366-369.

Comment 4： This study concludes with indications for the administration of chemotherapy in stage I NSCLC. The data also highlight patients who should not receive chemotherapy. For stage IA NSCLC, patients receiving adjuvant chemotherapy had worse survival in isolation and when stratified by high-risk features. This warrants further comment in the discussion and the authors should consider this in their conclusion.

Reply 4: This study is only a database study and requires multi-center large-scale research to explore the stratification of the problem.

Changes in the test: We add "For stage IA NSCLC, patients receiving adjuvant chemotherapy had worse survival in isolation and when stratified by high-risk features." In Page 13 line 349-350.

Reviewer D:

Comment 1. We are pleased to have the opportunity to review this paper.

The authors use a large database to analyze prognostic risk factors and the effect of adjuvant chemotherapy in stage I non-small cell lung cancer, which is an important study. However, there are several issues that need to be corrected for publication.

Major comments

1. Adjuvant chemotherapy may be selected based on the patient's general condition and comorbidities; the poor prognosis of the non-chemotherapy group in stage I may be due to selection bias. Therefore, performance status and Charlson's comorbidity index should be added as factors for propensity score matching.

Reply 1: Thank you very much for your comments!

Due to the limitations of the database, we can't obtain the relevant data of the patient's performance status and Charlson's comorbidity.

Changes in the test: None

Comment 2. The conclusion that chemotherapy should be administer because the examination of an insufficient number of LNs is dangerous. If the examination of an insufficient number of LNs is a poor prognostic factor, we should probably do adequate lymph node dissection.

Reply 2: If the number of lymph node resections is insufficient, the patient's prognosis may be poor, and auxiliary treatment may be considered. However, due to the limitations of the database, we will confirm it in the next study.

Changes in the test: We add the "It is recommended to perform adequate LNs dissection. And the adjuvant chemotherapy may be required for the patients with an insufficient number of LNs removed." see Page 12, line 324-326.

Reviewer E:

This is good work done on a big cohort of patients. Well done!

A few minor comments:

Comment 1: Figure 1 should be extended downwards to 4285 patients and not end at 26160. ultimately the figure should be improved to show only the patients that were analysed.

Reply1: It's my pleasure to accept to your comments. We revised the Figure 1.

Changes in the test: We revised the Figure 1.

Comment 2: Where should further studies and direction be headed to base on the limitation of the study? Pls include that in your conclusion.

Reply: The presence of VPI in stage IA patients is the main indicator of postoperative chemotherapy, and the insufficient number of LN is a secondary indicator. if the patient has the high pathological grades，it is a potential indicator that chemotherapy is required. So, we will conduct prospective clinical trials for patients with these high-risk clinicopathologic features.

Changes in the test: We add the "More multi-center prospective clinical trials and real-world studies with large samples are needed to further verify the results in this study." In Page 14 line 378-379.

Comment 3: Please check through the discussion to ensure each paragraph only focuses on one topic / result from the study followed by comparison with what is known in literature. Some paragraphs are bulky with 2 topics within the paragraph.

Reply: We have revised.

Changes in the test: We have paragraphed on page 14 line 348-349.