Peer Review File

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**Reviewer A**

1. Please provide insights incorporating the findings from the paper below.
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The study presents intriguing findings regarding the association between thymic density changes and the efficacy of immune checkpoint inhibitors (ICIs) in patients with non-small cell lung cancer (NSCLC). Building upon the established knowledge from the NEJM study, which highlighted adverse outcomes associated with thymectomy, this research delves into the potential implications of thymic density alterations on immunotherapy response.
The observation that decreased thymic density correlates with prolonged overall survival (OS) in NSCLC patients receiving ICIs is particularly noteworthy. It suggests a possible link between thymic function, immune response, and treatment outcomes in the context of immunotherapy. However, it's essential to acknowledge potential confounding factors and limitations, such as the retrospective nature of the study and the need for further validation in larger cohorts.
Moreover, while the NEJM study emphasized the adverse effects of thymectomy on immune-related outcomes, this study offers a contrasting perspective by suggesting a beneficial association between thymic density loss and treatment response. Integrating these insights, it becomes imperative to explore the nuanced interplay between thymic function, immune modulation, and therapeutic outcomes comprehensively. Further investigations elucidating the mechanistic underpinnings of thymic density changes and their impact on immune surveillance and response to ICIs could pave the way for personalized treatment approaches in NSCLC.
In summary, this study contributes valuable insights into the complex relationship between thymic density alterations and immunotherapy efficacy in NSCLC patients. It prompts further research to elucidate the underlying mechanisms and clinical implications, ultimately aiming to optimize treatment strategies and improve patient outcomes in the era of immune-based therapies.

**Response:** We thank this reviewer for his/her constructive comment.
We complemented our research background section with the NEJM study.
Changes in the text: 1.Introduction, paragraph 2, line 72-75

**Reviewer B**

I think this study very interesting as it suggests a relationship between the thymus and immune checkpoint inhibitors.

It is known that thymus density increases with infection and steroids in previous studies. I think it would be better to indicate how many patients in the “no-loss” group had increased density, as well as their history of steroid use, if known.
**Response:** We thank this reviewer for his/her constructive comments. We reviewed the clinical records of all enrolled patients and added to the manuscript information on progression of thymic density and history of steroid use.
Changes in the text: Table 1; 3.1. Patients , paragraph 1, line 175-177

It would be better to indicate the percentage of patients in each group who experienced immune-related adverse events (irAEs) such as myasthenia gravis, and whether there is any relationship between the change in density and irAEs. This would be a better discussion of the relationship between the safety of ICI and thymus and the relationship between thymus and ir AEs.
**Response:** We were unable to collect all data on myasthenia gravis and immune-related adverse events (irAEs) due to the limitations of a retrospective study with some missing data. We supplemented this limitation in the "Limitations" section.
Changes in the text: 4. Discussion, paragraph 6, line 305-307

**Reviewer C**

This study suggests that a loss of thymic attenuation during a course of immune checkpoint therapy for NSCLC may indicate a better prognosis (perhaps because of thymic cell deployment).

While the results are very interesting and make intuitive sense, they are currently not well communicated. In addition, the methodology, as described, is suboptimal, making the results less credible and jeopardizing the conclusion.

The writing of this paper is confusing and hampers successful communication of ideas and results. It requires improvement re: grammar, word choice, and clarity. Misplaced clauses make some sentences are nonsensical.

It is not clear whether patients were on immunotherapy, chemotherapy, or both. The investigators must provide specific information about the therapy of all included patients in the study. If various patients were on one of these 3 treatment regimens, subgroup analyses are needed.
**Response:** Many thanks for the reviewer's suggestion. This is indeed a point of significant interest. Although this is of great concern, given the characteristics of retrospective studies, we have included only patients who were first undergoing immunotherapy, and it is possible that they may have received further treatment at other medical institutions. However, we are unable to ascertain the subsequent treatments of these patients, which has been newly included in the limitations section of the study.
Changes in the text: 4. Discussion, paragraph 6, line 305-307

It appears that ROI standard deviations were not recorded. To determine whether a drop or increase in attenuation of the thymus is significant, provision and examination of standard deviations would be useful.

**Response:** We appreciate the constructive suggestions provided by this reviewer. We have conducted a thorough re-examination of the ROI regions in the medical images of all patients, extracted the standard deviations for these ROI areas, and meticulously analyzed them.
Changes in the text: 3.1. Patients, paragraph 6, line 175-178

The authors must be more specific about their ROI placement methodology—how, where why?
**Response:** Thanks to the reviewer for his/her careful reading and inspection. In response to the reviewer's queries, we have augmented the text with details regarding the placement of ROIs. Region of interest (ROI) were selected from the relatively homogeneous areas within the anterior mediastinum to assess the overall CT values. The size of the ROIs was approximately 100 mm2, and their positions were determined by the observers. The first observer assessed the images twice, with measurements taken after a 4-week washout period, while the second observer conducted a single assessment. Neither was aware of the other's results. Any discrepancies were resolved through consensus, with the final CT values of the thymic region being jointly determined by both observers. To ensure reproducibility, The intra- and inter-observer reliability for measurement of thymic density was excellent at 0.96 (95%CI, 0.89-0.99) and 0.97 (95%CI, 0.91-0.99). Furthermore, to address artifacts, we excluded patients who exhibited issues related to poor image quality during the study, and "Poor image quality of chest CT scans" has been included in the exclusion criteria.
Changes in the text: 2.2. Data acquisition and analysis, paragraph 2, line 123-130

Obtained thymic attenuation values are a matter of timing. While the thymus is deploying, its cell population can deplete, only to re-constitute in the thymus later, after a suitable time interval. The authors must be more specific about the window of study analysis in relationship to therapy.
**Response:** We are grateful to the reviewer for this valuable insight and attention to our research. However, as far as we know, a paper in Nature Communications suggests that, except at very advanced ages, thymic lymphocytes in an atrophied thymus remain essentially unchanged, while the age-related changes primarily manifest in stromal cells, especially in the cortical area[1]. Therefore, it can be basically concluded that the density of the thymus in a natural environment is relatively constant.
Changes in the text: None.

The Methodology section states that: "Patients were followed via telephone every 6 months"—by whom, to learn what, etc.? If the study was retrospective, how could patients be followed (prospectively) by telephone?
**Response:** In light of the reviewer's constructive suggestions, we have provided additional clarification regarding the follow-up aspect of our study. We conduct telephone follow-up assessments every six months with patients, focusing primarily on disease progression and mortality information until the patient's death. In addition, the study was conducted largely on the basis of preexisting clinical data, which were collected before the research question was established. Although we introduced a prospective follow-up element by contacting participants by telephone or other means of communication to obtain their current vital status later in the study, the study as a whole remained retrospective in nature.
Changes in the text: 2.2. Data acquisition and analysis, paragraph 2, line120-121

Please consult a statistician regarding if statistical tests were selected and employed properly.

**Response:** Thank the reviewer for his/her sincere suggestion. We consulted our colleague, Lingli Li, who is well versed in statistics regarding the use of statistical methods and expressed our gratitude to her in the acknowledgments section of the article.
Changes in the text: Acknowledgments

ABSTRACT
Purpose: "There is increasing evidence that the thymus can be associated with immunotherapy." Please be more specific regarding which aspect of the thymus is "associated" with immunotherapy, Size? Weight? Density/Attenuation? Thickness? Germinal centers? Etc.
**Response:** We are grateful to the reviewer for this valuable insight and attention to our research. We have carefully considered his/her suggestion regarding the wording of this sentence and have made the appropriate revisions. Now, we explicitly state in the text that "There is increasing evidence that thymic function may be related to immunotherapy."
Changes in the text: Purpose, line 15

Methods, Results, and Conclusion of Abstract: Very confusing as stated.Please re-write for clarity and understanding by someone not involved in this study. Please see more detailed comments below.
**Response:** We thank this reviewer for his valuable comments on the Methods, Results, and Conclusions section of our abstract. We agree with you that the original wording may have caused confusion, and we appreciate your concern. We have carefully reviewed and revised these sections to enhance their clarity and coherence.
Changes in the text: Abstract

INTRODUCTION
"Thymus density can be identified in chest computed tomography (CT), but its clinical value is not optimistic because of its anatomical characteristics." The word choice "optimistic" doesn't make sense in this context. Please choose a more appropriate word.
**Response:** We are grateful to the reviewer for this valuable insight and attention to our research. We have carefully considered his/her suggestion regarding the wording of this sentence and have made the appropriate revisions. Now, we explicitly state in the text that "...its clinical utility is limited due to the anatomical nature of the thymus."
Changes in the text: 1.Introduction, paragraph 3, line 75-76

P.2, Lines 53-4: The introduction is not the place for un-referenced conjecture: "Perhaps it is involved in building the link between the thymus and immune checkpoint inhibitors."
**Response:** Thank the reviewer for his/her sincere suggestion. We have revised this imprecise sentence and added some relevant references to prove it.
Changes in the text: 1.Introduction, paragraph 2, line 58-62

P.2, Line 56—Please correct this statement. The thymus in an infant may be large, relative to the baby's size, but it reaches maximal weight at puberty, not infancy.
**Response:** We are grateful to the reviewer for his/her genuine suggestion. We have amended the imprecise statement and cited a relevant reference for proof.
Changes in the text: 1.Introduction, paragraph 2, line 64

P.2, Line 72—The word “optimistic” is not the correct word here/does not make sense. Please choose the correct word to convey what you mean.
**Response:** We are grateful to the reviewer for this valuable insight and attention to our research. We have carefully considered his/her suggestion regarding the wording of this sentence and have made the appropriate revisions. Now, we explicitly state in the text that “...its clinical utility is limited due to the anatomical nature of the thymus.”
Changes in the text: 1.Introduction, paragraph 3, line 75-76

METHODS

It is not clear whether patients were on immunotherapy, chemotherapy, or both. If various patients were on one of these 3 treatment regimens, subgroup analyses are needed. The investigators must provide specific information about the therapy of all included patients in the study.
**Response:** Many thanks for the reviewer's suggestion. This is indeed a point of significant interest. Although this is of great concern, given the characteristics of retrospective studies, we have included only patients who were first undergoing immunotherapy, and it is possible that they may have received further treatment at other medical institutions. However, we are unable to ascertain the subsequent treatments of these patients, which has been newly included in the limitations section of the study.
Changes in the text: 4. Discussion, paragraph 6, line 305-307

It is not clear where in the thymus the ROIs were placed to measure thymic attenuation. It is also not clear how ROIs were placed. How was the decision made as to where to place the ROI and how was ROI size determined? How were CT artifacts superimposed over the thymus navigated/managed?
**Response:** Thanks to the reviewer for his/her careful reading and inspection. In response to the reviewer’s queries, we have augmented the text with details regarding the placement of ROIs. Region of interest (ROI) was selected from the relatively homogeneous areas within the anterior mediastinum to assess the overall CT values. The size of the ROIs was approximately 100 mm2, and their positions were determined by the observers. The first observer assessed the images twice, with measurements taken after a 4-week washout period, while the second observer conducted a single assessment. Neither was aware of the other’s results. Any discrepancies were resolved through consensus, with the final CT values of the thymic region being jointly determined by both observers. To ensure reproducibility, The intra- and inter-observer reliability for measurement of thymic density was excellent at 0.96 (95%CI, 0.89-0.99) and 0.97 (95%CI, 0.91-0.99). Furthermore, to address artifacts, we excluded patients who exhibited issues related to poor image quality during the study, and “Poor image quality of chest CT scans” has been included in the exclusion criteria.
Changes in the text: 2.2. Data acquisition and analysis, paragraph 2, line 123-130

It appears that ROI standard deviations were not recorded. To determine whether a drop or increase in thymic attenuation is significant, provision and examination of standard deviations would be useful.
**Response:** We appreciate the constructive suggestions provided by this reviewer. We have conducted a thorough re-examination of the ROI regions in the medical images of all patients, extracted the standard deviations for these ROI areas, and meticulously analyzed them.

Changes in the text: 3.1. Patients, paragraph 6, line 175-178

P.3, Line 110—Please specify the type of "CT value." If it is attenuation measurement in Hounsfield units (HU), please state this here and anywhere else relevant in this paper.
**Response:** Many thanks for the reviewer's suggestion. We clarify that the "CT values" refer to attenuation measurements in Hounsfield Units (HU), and we have provided this clarification throughout the text where relevant.
Changes in the text: Many in the article.

P.3, Line 114: Please provide more detail re: "Patients were followed via telephone every 6 months"—by whom, to learn what, etc.. If the study was retrospective, how could patients be followed (prospectively) by telephone?
**Response:** In light of the reviewer's constructive suggestions, we have provided additional clarification regarding the follow-up aspect of our study. We conduct telephone follow-up assessments every six months with patients, focusing primarily on disease progression and mortality information until the patient's death. In addition, the study was conducted largely on the basis of preexisting clinical data, which were collected before the research question was established. Although we introduced a prospective follow-up element by contacting participants by telephone or other means of communication to obtain their current vital status later in the study, the study as a whole remained retrospective in nature.
Changes in the text: 2.2. Data acquisition and analysis, paragraph 2, line120-121

P.3, Line 115: "plotted" (i.e. on a graph during data acquisition) or recorded?
**Response:** We strongly agree with the reviewer and have revised the wording.
Changes in the text: 2.2. Data acquisition and analysis, paragraph 2, line122

P.3, Lines 118-119—Why were age and sex data made available to the observers/data acquirers?
**Response:** We thank the reviewer for his/her attention to this point. Age and gender were used as basic information to distinguish different patients and avoid repeated delineation. Although this will not affect the results of ROI delineation, this sentence may cause misunderstanding, so we have deleted it.
Changes in the text: 2.2. Data acquisition and analysis, paragraph 2, line130

P.3, Line 126: The term "thymic area density" is not standard and is confusing. Is attenuation/Hounsfield unit measurement by region-of-interest (ROI) meant here? If so, please use this standard terminology.
**Response:** Thanks to the reviewer for his/her careful reading and inspection. We have changed the use of this term to ensure the professionalism and accuracy of the article.
Changes in the text: Many in the article.

P.3, Line 132: The OS definition to date of death makes sense, but OS defined as survival to end of last follow-up does not.
**Response:** Thanks to the reviewer for his/her careful reading and inspection. We modified the description of the OS definition to avoid creating ambiguity.
Changes in the text: 2.3. Patient outcomes, paragraph 2, line 142

RESULTS

Please re-write more clearly. For example: P.5, Lines 200-203—please state these associations/negative or positive correlations more clearly.

**Response:** Thanks to the reviewer for his/her careful reading and inspection. We have revised the wording in the subgroup analysis section to more clearly articulate our results and to more intuitively illustrate the level of risk.

Changes in the text: 3.2 Effect, paragraph 3, line 216-221

DISCUSSION

Please shorten/be much more concise and organized, beginning by briefly summarizing the key study findings and then explaining their significance in a broader clinical context.

**Response:** Thanks to the reviewer for his/her careful reading and inspection. We have added some description of our results in the discussion section and cut some unnecessary content.

Changes in the text: 4. Discussion, paragraph 2, line 242-251

P. 5, Lines 209-211: please back up this "viewpoint" further. Palmer's finding neither supports nor contradicts this viewpoint.

**Response:** We wholeheartedly agree with your perspective and have revisited the literature. I believe our original expression was indeed ambiguous, and thus we have rewritten that sentence.

Changes in the text: 4. Discussion, paragraph 1, line 226-228

P. 5, Line 225—What is a "surface" chest CT scan?

**Response:** Thanks to the reviewer for his/her careful reading and inspection. We intended to convey "chest-level CT," and the previous expression may have caused confusion; therefore, we have revised the relevant sentences.

Changes in the text:4. Discussion, paragraph 1, line 239

P. 5, Line 230—Please explain/elaborate on what is meant by "thymus detection rate." This reviewer knows what is meant, but many readers will not. They may wonder how ROIs were placeable on the thymus if it wasn't detectable!

**Response:** We appreciate the constructive suggestions provided by this reviewer. Due to the excessive content in the discussion section, we have made deletions to the sentences that include this particular phrase.

Changes in the text: The sentence was deleted.

P.5: Lines 235-40—Does the referenced literature in variance with your results refer to static evaluation of the thymus, as opposed to evaluation of the thymus over time? Please analyze the research referenced further to determine if its findings are truly at odds with your own.

**Response:** Thanks to the reviewer for his/her careful reading and inspection. We have augmented the relevant explanations in compliance with your suggestions. Additionally, we opine that the dynamic alterations in thymic density during immunotherapy may yield more comprehensive information regarding the mechanisms of immunotherapy than the thymic density observed prior to treatment.

Changes in the text: 4. Discussion, paragraph 3, line 260-270

P. 5, Line 232--What is meant by "dense hypodense areas"?

**Response:** Thanks to the reviewer for his/her careful reading and inspection. “Dense hypodense areas” refers to the thymic region in the anterior mediastinum, which in most elderly individuals, appears as a uniform low-density area resembling fat density. We have revised our description to enhance clarity.
Changes in the text: 4. Discussion, paragraph 3, line 253

P. 6, Line 265--The words “Of course” are not necessary.
**Response:** Thanks to the reviewer for his/her careful reading and inspection. We quite agree with your proposal. We have corrected this.
Changes in the text: This word was removed.

TABLES
Please better explain in the column headings and footnotes how the information in the table is depicted, to facilitate understanding and interpretation by the reader.
**Response:** Thanks to the reviewer for his/her careful reading and inspection. We have checked and confirmed that the column headings and footnotes for each table are easily understandable.
Changes in the text: Table

**Reviewer D**

The authors investigated how changes in thymic density are related to response to immunotherapy in patients with NSCLC through CT imaging assessment, including RECIST evaluation and overall survival as clinical outcomes.

The study was characterized by its simplicity and well-executed methodology, featuring a straightforward yet robust approach. Its findings have yielded valuable insights and have stimulated hypotheses for future research endeavors. In that context, efforts aiming to elucidate the immune landscape within the context of NSCLC are highly appreciated and welcomed.

However, certain aspects warrant consideration. Firstly, the introduction section, particularly the second paragraph, could benefit from improved clarity and conciseness. Additionally, in the methodology section, it is suggested to include measures taken to control for other factors influencing thymus density, such as rebound hyperplasia due to steroid use, radiation therapy, and other severe systemic stresses.
**Response:** Thanks to the reviewer for his/her careful reading and inspection. Firstly, we have streamlined the introduction. Secondly, due to the limitations of a retrospective study, we were unable to collect all data on radiation therapy, and other severe systemic stresses. We supplemented this limitation in the "limitation" section. However, we added a history of steroid use at baseline.
Changes in the text: Table 1; 3.1. Patients , paragraph 1, line 188-190

Regarding the discussion section, there appears to be redundancy and lengthiness. Some portions could be condensed, while reasonable explanations for the presented results could be strengthened. Notably, it is recognized that PD-1 is expressed in T cells, B cells, and macrophages, while its ligand, PD-L1, is present in

tumors and normal tissues, including the thymus. It is recommended to incorporate this underlying pathophysiology to explain certain results.
**Response:** We thank the reviewer for his/her attention to this point. We have made modifications to the Discussion section and have incorporated the potential pathophysiological mechanisms you mentioned to explain our findings.
Changes in the text: 4. Discussion, paragraph 4, line 279-283

Furthermore, justification for the disparate outcomes related to immunotherapy response is warranted, particularly considering the negative results for RECIST assessment but positive outcomes for overall survival prediction. Clarification on these discrepancies would enhance the comprehensibility and impact of the study's findings.
**Response:** We are grateful to the reviewer for his/her genuine suggestion. Concerning the negative results of RECIST assessment and the positive prognosis for overall survival, we have added relevant explanations in the Discussion section. Our study results indicate that patients with reduced Hounsfield Unit values in the thymus region after immunotherapy exhibit better OS, whereas there were no differences in PFS, ORR or DCR between the two groups. Some immunotherapy trials have also yielded similar conclusions[2]. PFS, ORR and DCR have been implemented as early clinical endpoints and are widely used for the assessment of antitumor therapies [3, 4], but the association between short-term efficacy and long-term efficacy has not been confirmed. Among the population that benefits from immunotherapy, they have not achieved significant short-term efficacy but have shown benefit in long-term efficacy. This result may support the long-tailed effect of immunotherapy, with the observation that the longer the duration of immunotherapy, the greater the benefit for patients[5].
Changes in the text: 4. Discussion, paragraph 2, line 242-251

**Reviewer E**

In this manuscript the Authors analyze the correlation between the changes in thymic tissue density and oncological outcome in patients with non-small cell lung cancer submitted to immunotherapy. The results of the study show that stable thymic density was associated with a higher risk of progression-free survival, and that patients with a reduction in thymic density after immunotherapy had a better prognosis. The Authors concluded that the change of thymic density may be related to the efficacy of immunotherapy.

The topic of the manuscript is certainly of interest. However, since according to previous reports a higher thymic density may theoretically be associated with a higher T-cell mediated immunocompetence, there are no data to adequately support the conclusions of the study.
**Response:** We thank the reviewer for his/her attention to this point. We fully concur with the reviewer's perspective that higher thymic density may be associated with increased T cell-mediated immune activity. However, our study focused on the changes in thymic density, which may reflect a dynamic process related to the migration of T cells between tumor cells and the bloodstream. Although this is speculative, it may provide direction or insights for future research. Consequently, we believe that the dynamic changes in thymic density may be more sensitive and reliable than the baseline.
Changes in the text: 4. Discussion, paragraph 3, line 260-270

In particular, the Authors fail in giving a conclusive discussion on the correlation between variation in thymic density and response to immunotherapy.
**Response:** Thanks to the reviewer for his/her constructive suggestions. We conducted a Logistic regression analysis to assess the correlation between changes in thymic density and immunotherapy response, and the results indicated no correlation between the two (OR = 1.13 95%CI, 0.77-1.66, $p$ = 0.549). This finding was further discussed in the Discussion section, where possible reasons for the lack of correlation were presented.
Changes in the text: 3.2. Effect, paragraph 3, line 199-203; 4. Discussion, paragraph 2, line 242-251

**Reviewer F**

The authors investigated the association between changes of thymic density on CT images after immunotherapy and prognosis in patients with lung cancer. The authors found that non-loss of thymic density after immunotherapy was related to poor OS and PFS. While the results are interesting, there are several issues to be addressed.

Major comments:
As follow-up intervals vary for each patient, the conclusion of this study may be difficult to generalize.
**Response:** We are grateful to the reviewer for his/her genuine suggestion. We fully agree with this because it is indeed a common limitation of many retrospective studies, and therefore we use the Kaplan-Meier survival curve to present data with inconsistent follow-up times.
Changes in the text: None.

The authors proposed a formula for calculating “annualized thymus progression value”, but it is unclear whether this formula accurately represents the true rate of changes.
**Response:** We thank the reviewer for his/her attention to this point. We use the annualization rate to eliminate the impact of time on changes, which is a commonly used and relatively reasonable method. Previous studies have also used annual change rates to assess changes in imaging images. For example, in the journal Circulation, Drobni et al. calculated the annual progression rate based on the volume of plaque changes observed in imaging studies and the time difference, in order to assess the yearly changes in the plaques[6].
Changes in the text: None.

The authors used a two-dimensional ROI to assess thymic density, but the measurements can change depending on where observers set the ROI within the thymus. This could be an obstacle for other researchers to reproduce the results of this study.
**Response:** We are grateful to the reviewer for this valuable insight and attention to our research. We agree with your statement that using two-dimensional ROI to assess thymic density may have some bias. To ensure the reproducibility of the results, we first selected regions with obvious and relatively uniform density during the process of marking the ROI. Secondly, the observations were conducted by two observers separately, and the intra-group and inter-group correlation coefficients were calculated. The observer-intra and inter-group reliability for measuring thymic density were 0.96 (95% CI, 0.89 to 0.99) and 0.97 (95% CI, 0.91 to 0.99), respectively, indicating that our two-dimensional ROI is relatively reliable. Although two-dimensional ROI

may have some bias, it is also relatively accurate and easier to obtain in practical clinical work compared to three-dimensional ROI.
Changes in the text: None.

Other comments:
(Introduction) “The question of whether thymus remodeling is evident on CT images is of interest”: I do not think it is an interesting question. Changes in thymic volume are sometimes experienced after treatment.
**Response:** We are grateful to the reviewer for his/her genuine suggestion. We have noted changes in thymic volume after treatment, and therefore, we were curious about the relationship between the degree of thymic volume change and treatment efficacy, which led us to conduct this study. This forms the basis of this article.
Changes in the text: None.

(Results, p5) “This suggest that the results remained consistent across different subgroups”: This statement is an interpretation of the results by the authors and should be moved to Discussion.
**Response:** We thank the reviewer for his/her attention to this point. We acknowledge that this sentence appeared in the wrong place, and therefore, we have made a correction.
Changes in the text: 4. Discussion, paragraph 2, line 244

The authors also analyzed the chemotherapy cohort, but it is not mentioned in the objective of this study.
**Response:** We thank the reviewer for his/her attention to this point. We incorporated the chemotherapy-only cohort to provide a comparison with the immunotherapy cohort, primarily to demonstrate that thymic changes cannot serve as a prognostic indicator in the context of chemotherapy alone. This was not the main objective of our study, hence it was not explicitly stated in the section on research objectives.
Changes in the text: None.

References

1. Venables T, Griffith AV, DeAraujo A, Petrie HT: **Dynamic changes in epithelial cell morphology control thymic organ size during atrophy and regeneration**. *Nature communications* 2019, **10**(1):4402.
2. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, Chow LQ, Vokes EE, Felip E, Holgado E *et al*: **Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer**. *N Engl J Med* 2015, **373**(17):1627-1639.
3. Merino M, Kasamon Y, Theoret M, Pazdur R, Kluetz P, Gormley N: Irreconcilable Differences: The Divorce Between Response Rates, Progression-Free Survival, and Overall Survival. *J Clin Oncol* 2023, 41(15):2706-2712.
4. Mok TSK, Wu YL, Kudaba I, Kowalski DM, Cho BC, Turna HZ, Castro G, Jr., Srimuninnimit V, Laktionov KK, Bondarenko I *et al*: Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. *Lancet* 2019, 393(10183):1819-1830.
5. Gettinger S, Horn L, Jackman D, Spigel D, Antonia S, Hellmann M, Powderly J, Heist R, Sequist LV, Smith DC *et al*: **Five-Year Follow-Up of Nivolumab in Previously Treated Advanced Non-Small-Cell Lung Cancer: Results From the CA209-003 Study**. *J Clin Oncol* 2018, **36**(17):1675-1684.

6. Drobni ZD, Alvi RM, Taron J, Zafar A, Murphy SP, Rambarat PK, Mosarla RC, Lee C, Zlotoff DA, Raghu VK *et al*: **Association Between Immune Checkpoint Inhibitors With Cardiovascular Events and Atherosclerotic Plaque**. *Circulation* 2020, **142**(24):2299-2311.