Peer Review File

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Reviewer A

Thank you for the opportunity to review this interesting manuscript. The study addresses the prognostic value of C-CONUT in patients with resected NSCLC, which is a clinically relevant topic. The manuscript is generally well structured and the results are clearly presented. However, several important issues should be addressed before the paper can be considered for publication:

1. Definition of C-CONUT

The definition of C-CONUT is described as "CRP score + CONUT." However, the exact scoring system for CRP (cut-off values, point assignment) is not re-described in the manuscript. Since the authors state that C-CONUT is a newly proposed index, it should be possible for a third party to reproduce the calculation without referring to previous publications. Please provide a clear and reproducible definition of the CRP scoring system in the Methods section.

Response: Thank you for your valuable comment. As you pointed out, the C-CONUT score is a novel index we propose in this study, and we recognize that the lack of a detailed description of its component, the CRP score, in the manuscript is an important issue from the perspective of reproducibility.

In this study, we defined the CRP cut-off values as 0.1 and 1.0 mg/dL, and assigned points as follows:

- CRP < 0.1 mg/dL: 0 points
- CRP 0.1–0.99 mg/dL: 1 point
- CRP ≥ 1.0 mg/dL: 2 points

The CRP score was then added to the conventional CONUT score (0–12 points) to calculate the C-CONUT score, resulting in a range of 1–13 points.

We have added these details to the Methods section **(Lines.130–135)** to ensure that the methodology is transparent and reproducible by other researchers.

2. Clinical Meaning of AUC Values

In the ROC analysis, C-CONUT showed an AUC of 0.654, which is only a modest discriminatory ability. The clinical significance of such an AUC should be discussed. For example, does an AUC in this range provide practical utility in guiding treatment decisions? Please elaborate on the clinical implications and limitations of the AUC results.

Response: As pointed out, the AUC of the C-CONUT score in our study was 0.654, which is classified as "moderate" discriminatory ability from a statistical standpoint. However, this value represents the predictive power of a single indicator and should be interpreted within the broader context of clinical application. We believe it is important to evaluate the clinical utility of such a score not only by its statistical performance but also by considering its simplicity, reproducibility, and potential utility in combination with other clinical factors.

In particular, the C-CONUT score is composed of four routinely available blood test parameters (albumin, cholesterol, lymphocyte count, and CRP), allowing clinicians to assess a patient's nutritional and inflammatory status without the need for additional costs or specialized testing. This makes it a valuable tool in clinical practice. Even with an AUC around 0.65, the score may serve as a practical component of a broader risk stratification model when combined with other clinical indicators, especially for identifying high-risk patients in the preoperative setting.

Furthermore, our study demonstrated that the C-CONUT score is an independent prognostic factor even among relatively younger NSCLC patients (aged ≤75 years). This suggests that subclinical inflammation or malnutrition may impact postoperative outcomes even in younger populations, highlighting the score's potential significance as a modifiable prognostic indicator.

We have revised the manuscript accordingly to incorporate this discussion, clarifying the interpretation of the AUC value as well as the clinical limitations and implications of the C-CONUT score (**Lines 250–258)**.

3. Novelty and Added Value

The novelty and added value of the C-CONUT score remain somewhat limited. In its current form, the study compares C-CONUT mainly against CONUT and GPS. However, other well-established nutritional or inflammation-based prognostic indices, such as ALBI, PNI, or NLR, are not included in the analysis. Without such broader comparisons, it is difficult to determine whether C-CONUT truly represents an advance over existing tools. What is the incremental benefit of C-CONUT over the existing markers? Without a clear advantage, the clinical utility of C-CONUT remains questionable. A stronger discussion on novelty is encouraged.

Response: As you rightly pointed out, in order to clarify the clinical utility of C-CONUT, comparison with other established nutritional and inflammatory markers is essential.

Although the present study primarily focuses on a comparison with the CONUT score, we have separately reported a study (Tamura et al., *Ann Thorac Cardiovasc Surg*. 2024) in which we compared the prognostic performance of several other indices—such as PNI, NLR, CAR, and GNRI—with both CONUT and C-CONUT. In that study, we demonstrated the usefulness of C-CONUT as a prognostic indicator.

Tamura M, et al. Prognostic significance of CONUT score in elderly NSCLC. *Ann Thorac Cardiovasc Surg*. 2024;30(1):24-00009. doi:10.5761/atcs.oa.24-00009.

Because these results were already included in the previous publication (Tamura et al., 2024), we intentionally omitted the detailed data in the current manuscript. Building upon the findings of the prior study—which confirmed the utility of C-CONUT in elderly patients—we extended our investigation in this study to a broader age range to examine whether C-CONUT is also applicable in younger and middle-aged populations. Our results showed that, even in younger age groups (≤75 years, ≤65 years), where the original CONUT score alone was not a significant prognostic factor, C-CONUT remained an independent predictor of prognosis.

These findings suggest that C-CONUT is not limited to use in the elderly, but may serve as a prognostic indicator across a wider age spectrum, thereby providing an additional clinical value.
Furthermore, we have revised the manuscript to briefly mention the comparison with other markers in the *Introduction* section (**Lines 63–70**), in order to clarify the positioning of this study and highlight the unique characteristics of C-CONUT.

4. Limitations of Multivariable Analysis
Although the authors report C-CONUT as an independent prognostic factor, the process of variable selection in the multivariable analysis is not sufficiently described. Without a transparent description of the selection procedure and justification for included or excluded variables, the claim of independence appears insufficiently supported. A more rigorous multivariable framework would be needed to convincingly demonstrate the independent prognostic role of C-CONUT.
Response: As you rightly pointed out, the original manuscript did not sufficiently describe the criteria and process for variable selection in the multivariate analysis, which made our claim that C-CONUT is an independent prognostic factor insufficiently supported. To address this concern, we have made the following revisions:

1. We have added a detailed explanation of the criteria and process for variable selection in the statistical analysis section. Specifically, we clarified that variables with a p-value < 0.05 in the univariate analysis were considered candidates, and we selected variables using a stepwise Cox regression model after evaluating clinical relevance and checking for multicollinearity.
2. We also added descriptions in the main text regarding which variables were included or excluded in the final model, along with the rationale for these decisions.

(**Lines 144–150**)

5. External Validity and Generalizability
The study is retrospective and single-center, based entirely on a Japanese cohort. The applicability of C-CONUT to other populations with different genetic backgrounds, comorbidities, or treatment strategies remains uncertain. Please discuss these limitations explicitly and consider outlining the need for external validation or prospective studies.
Response: We acknowledge that this study was a single-center, retrospective study conducted in a Japanese population, and therefore, the generalizability and external validity of the C-CONUT score may be limited. We have addressed this point in the Discussion and Conclusion sections, and have added a statement emphasizing the need for external validation through multicenter, prospective studies involving different racial backgrounds and treatment strategies. We believe that further research is essential to support broader clinical application of the C-CONUT score.

(**Lines 265–269, 285–286**)

6. Clinical Applicability and Impact
While the statistical significance of C-CONUT is shown, the practical consequences for patient management are less clear. For example, how might clinicians use C-CONUT to adjust perioperative care, surveillance, or adjuvant therapy decisions? Without such a discussion, the clinical relevance may appear limited. Please expand the discussion on how this score could realistically influence practice.
Response: We appreciate the reviewer's insightful comment regarding the lack of a detailed description of practical clinical applications of the C-CONUT score. While our study demonstrated that the C-CONUT score is a more useful prognostic indicator than the conventional CONUT score across all age groups, we agree that further elaboration on its implementation in real-world clinical settings was necessary.
Given that the C-CONUT score can be easily calculated from routine preoperative laboratory tests, we believe it can be integrated into preoperative risk assessments and utilized to support clinical decision-making in the following ways:

1. Perioperative management: Patients with high C-CONUT scores may be at increased risk of postoperative complications. The score can aid in decisions regarding postoperative ICU admission or early initiation of nutritional support.
2. Postoperative follow-up: Since high C-CONUT scores are associated with elevated risk of recurrence or mortality, the score may help guide more intensive imaging schedules and closer follow-up plans.
3. Selection of adjuvant therapy: Even among patients with the same pathological stage, those with higher C-CONUT scores may be considered appropriate candidates for more aggressive postoperative adjuvant therapies.

In response to the reviewer's suggestion, we have revised the Discussion section to include these practical clinical scenarios, thereby enhancing the clarity and clinical relevance of our findings.
(see **Lines 240–249, 274–279**)

In summary, the manuscript addresses an important question but requires clarification of methodology, stronger discussion of clinical implications, and improved presentation of results. Addressing the above points will substantially improve the clarity and impact of the work.

Reviewer
Thank you for the opportunity to review this manuscript. I enjoyed reading it.
The authors investigated the utility of the CONUT and C-CONUT scores as preoperative prognostic indicators in 739 patients with surgically treated NSCLC. They demonstrated that the CRP-augmented CONUT score (C-CONUT) was

significantly associated with worse overall survival (OS) and that it served as an independent prognostic factor for OS. The authors should be commended for their effort to examine whether CRP-augmented CONUT provides superior predictive ability in patients with resectable NSCLC.
However, I have several concerns that I believe should be addressed to improve the clarity and validity of the manuscript. I hope my comments will be helpful.

Methods
•The authors calculated the C-CONUT score by simply adding the CRP score to the conventional CONUT score (C-CONUT = CRP score + conventional CONUT score). Does the "CRP score" refer to the actual CRP value? If so, did the authors round the values, given that CRP is usually expressed with two or three digits?
Response: The "CRP score" used in this study is not the raw CRP value itself, but rather a point-based score derived from actual CRP values according to predetermined criteria. Specifically, CRP values were categorized into defined ranges, and corresponding scores were assigned based on these cut-off values. The CRP score was then added to the CONUT score to calculate the C-CONUT score. While CRP values are usually measured with two decimal places, the scoring was not based on rounding or decimal adjustments, but on fixed cut-off thresholds established in advance. Since the definition and calculation method of the CRP score were unclear in the original manuscript, we have added further explanation to clarify this point in the revised text (**Lines 130–136**).

• In developing a scoring system, weighting of potential relevant factors based on predictive value (e.g., odds ratio, hazard ratio) is usually required. While both CRP and CONUT are established indices, it is unclear whether it is methodologically acceptable to simply add them in a 1:1 ratio. If no validation process was conducted, this should be clearly acknowledged as a limitation.
Response: As pointed out, the C-CONUT score is constructed by simply adding the CRP and CONUT scores on a 1:1 basis, and at this stage, we have not yet conducted any validation using weighting based on odds ratios or hazard ratios.
In this study, we adopted this additive method based on a previous study [5]. However, we recognize the need for future investigations into appropriate weighting methods and statistical validation of the score's robustness.
We have clarified this point in the "Discussion" section of the manuscript (**Lines.261–264)** and have added it as a limitation of the present study.

• The definitions of each cohort are unclear and inconsistent. For example, line 131: "the cohort aged 79 years or younger," line 132: "the cohort under 75 years of age," etc. The inconsistent terminology makes the manuscript difficult to follow. In addition, at line 144 cohort 2 is described as "age 75 years or younger," while at line 146 cohort 3 is also described as "age 75 years or younger." Should cohort 3 be defined as "age 65 years or younger" instead?
Response: We have clarified in the manuscript that:

Cohort 1 includes patients “aged ≤79 years”,
Cohort 2 includes patients “aged ≤75 years”, and
Cohort 3 includes patients “aged ≤65 years”.
We have also indicated in the text that these cohorts are overlapping.
(Revised in **Lines 37, 107–109, and 187–189**)

Statistical Analysis
• The authors used ROC curves to define optimal cutoff values for OS prediction. However, ROC-based cutoffs for survival outcomes depend on the specific time point considered (e.g., 1-year, 3-year, or 5-year survival). The authors should clarify at which time point(s) the ROC analysis was performed.
Response: To evaluate the predictive ability for overall survival (OS) in the ROC analysis, we constructed the ROC curve using 5-year survival as the endpoint. This information has been added to the "Statistical Analysis" and "Results" sections of the manuscript (**L.140–143)**.

Results
• Overall, the presentation of data lacks consistency, which makes the manuscript difficult to read.
Response: We acknowledge that the Results section in the original manuscript lacked consistency in the order of data presentation and terminology, which may have made it difficult for readers to follow. We sincerely appreciate the reviewer’s comments and have made the following revisions to improve the clarity and readability of this section:

- We clarified the structure of each subsection (Patient Characteristics, ROC Analysis, Survival Analysis, and Multivariate Analysis) and added appropriate subheadings.
- The presentation order of each result was standardized to follow the pattern: “Summary → Details → Reference to Figures/Tables.”
- Terminology and numerical expressions (e.g., “high group,” “elevated group,” “poor prognosis”) were unified to ensure consistency throughout the section.
- The corresponding figure and table numbers are now clearly indicated in the main text.

We believe these revisions have significantly improved the readability and consistency of the Results section. We kindly ask for your confirmation.

• In Table 2, CONUT is included as a variable. It would be helpful to also present the results when C-CONUT is used instead of CONUT. Additionally, the cutoff for CONUT is “1” in Table 2 but “2” in Tables 3–4. Please clarify the rationale for these differing cutoff values.
Response: We have added the C-CONUT results to Table 2 and the CONUT results to Table 4. In all Tables 2 through 4, both CONUT and C-CONUT scores are now presented side by side. The cutoff values have been standardized to CONUT (≥2)

and C-CONUT (≥3).
Relevant revisions were made in **Lines 42, 185, 192, 197–200, and 203–207.**

• In moving from univariate to multivariate analyses, the selection criteria for variables should be specified. Based on the values in the tables, it appears that variables with $p < 0.1$ were included, but this should be explicitly stated.
Response: Regarding the criteria for variable selection from univariate to multivariate analysis, we selected variables based on a p-value of < 0.05. Since this was not clearly stated in the original manuscript, we have now explicitly described it in the revised version
(**Lines 147–150**).

• In Tables 3 and 4, pathological stage shows strong prognostic value in univariate analysis but is no longer significant in multivariate analysis. This is inconsistent with prior reports and may be due to multicollinearity from including both CONUT and C-CONUT in the same Cox model. I am afraid that this analysis could yield misleading results. The authors should either report variance inflation factors (VIF) to address multicollinearity or perform separate multivariate analyses for CONUT and C-CONUT.
Response: As pointed out, although pathological stage was a significant factor in the univariate analysis, it lost significance in the multivariate analysis. This may be due to multicollinearity resulting from including both the CONUT score and the C-CONUT score in the same Cox proportional hazards model.
To investigate this issue, we assessed multicollinearity using the variance inflation factor (VIF). The results showed that although the VIFs for the CONUT and C-CONUT scores did not exceed 10, they were greater than 3, indicating a certain degree of multicollinearity between the two variables.
Therefore, as suggested, we performed separate multivariate analyses for the CONUT and C-CONUT scores instead of including them in the same model. In these separate models, the C-CONUT score consistently remained a significant prognostic factor.
These revisions have been incorporated into the manuscript and tables. In the relevant sections, we have clearly stated the potential for multicollinearity and described how it was addressed.
(**L.151–155, 202–214**)

• In Table 4, age is not significant as a prognostic factor, even in univariate analysis. Given that cohort 3 includes patients ≤65 years, it appears that age may have been dichotomized into <65 years vs. 65 years alone. Such dichotomization can be arbitrary. An analysis treating age as a continuous variable should be considered.
Response: We re-evaluated Cohort 3 using an age cutoff of 62 years. However, the univariate analysis still did not show statistical significance. We have revised Table 4 accordingly.
(**L.155–159**)

• Figures 3 and 4 are not directly comparable, which compromises readability. For example, Figure 4 presents survival curves for patients ≤65 years, but Figure 3 does not. I suggest adding the ≤65 subgroup to Figure 3 and also including hazard ratios in both figures.

Response: We have revised Figures 3 and 4 to include the data for (A) Overall, (B) Cohort 1, (C) Cohort 2, and (D) Cohort 3. Corresponding modifications have been made in the manuscript at **lines 185–189, 192–195, and 206–207.**

• To facilitate comparison, I recommend adding overall cohort survival curves stratified by C-CONUT in Figure 4.

Response: We have revised Figure 4 to include panel A) showing the C-CONTUT data for the entire cohort (**Lines 192–195)**.

• Given these concerns, particularly the risk of multicollinearity between CONUT and C-CONUT, the current analyses may not adequately support the conclusion that C-CONUT is superior to CONUT. A thorough re-analysis with appropriate statistical guidance may be required. Without this, the conclusion appears premature. If the authors wish to draw conclusions based on the current data and analyses, they should clearly state that these are just exploratory rather than confirmatory findings.

Response: As you correctly pointed out, this study is a single-center, retrospective analysis, and we acknowledge that there are limitations in definitively concluding the superiority of the C-CONUT score. Therefore, we have revised the expressions in the main text and conclusion to avoid asserting that "C-CONUT is superior to CONUT." Instead, we have rephrased the statements to reflect a more cautious interpretation, such as indicating that this is an exploratory analysis and that further prospective studies are warranted.

Furthermore, in consideration of the statistical limitations, we have adjusted the tone to suggest that "C-CONUT may be a promising prognostic indicator," in order to avoid making overly definitive claims.

The relevant revisions can be found in the following sections:

L.49–51, 283–286

Reviewer C

Thank you for the opportunity to review the article entitled "Preoperative C-Reactive Protein-Augmented CONUT Score as a Better Prognostic Indicator Than CONUT Alone in Non-Small Cell Lung Cancer Across Age Groups."

The study presents potentially valuable insights and may be of interest to readers. However, several concerns should be addressed to enhance the manuscript's academic value and clarity:

Major Revisions:

1. In Tables 2, 3, and 4, the authors performed univariate and multivariate analyses

for the overall population, Cohort 2, and Cohort 3, respectively.
However, only in Table 3 are both CONUT and C-CONUT scores included as variables. What is the rationale for this inconsistency? The authors should clarify or adjust for consistency.
Response: We have presented data for both CONUT and C-CONUT in Tables 2, 3, and 4, and have revised Tables 2 and 4 accordingly.

2. In Table 3, the CONUT score showed a significant impact on OS in Cohort 2 (p=0.006) in the univariate analysis.
However, this result does not appear to align with Figure 3C. The authors should confirm the accuracy of the results and provide an explanation if discrepancies remain.
Response: We have re-evaluated Cohort 3 (≤75 years). A statistically significant difference was observed in the Kaplan-Meier analysis (p = 0.02). In the Cox proportional hazards model, the univariate analysis showed a significant difference (p = 0.011), whereas the multivariate analysis did not reach statistical significance (p = 0.07). Figure 3 has been revised accordingly.
(**Lines 187–189, 203–204**)

3. In Figures 3 and 4, the authors presented OS curves based on CONUT and C-CONUT scores across categories.
However, OS curves for Cohort 3 are missing in Figure 3, while OS curves for the overall population and Cohort 1 are missing in Figure 4.
These data should be presented consistently, and appropriate interpretations should be provided.
Response: We have revised Figures 3 and 4 to present the data for A) Overall, B) Cohort 1, C) Cohort 2, and D) Cohort 3. Please refer to **Lines 184–194** in the revised manuscript.

Minor Revisions:
1. The study objective should be clearly stated in the Background section of the Abstract.
Response: We appreciate the reviewer's comment regarding the lack of clarity in the background section of the Abstract. To clearly convey the objective of our study to the readers, we have revised the text accordingly. Specifically, we have clarified that the aim of this study is to investigate whether the C-CONUT score, which has been shown to be useful in elderly patients, can also serve as a prognostic factor in younger patients with NSCLC (**L.32–34**).

2 The terms "univariate" and "multivariate" should be replaced with "univariable" and "multivariable" for greater accuracy.
Response: We agree with the reviewer that the accurate use of terminology in statistical analysis is important. Accordingly, we have corrected the terms "univariate" and "multivariate" used in the manuscript to the more appropriate

terms “univariable” and “multivariable,” respectively.

3. The methodology of the statistical analysis should be described in more detail, especially the selection criteria for variables in the multivariable analysis.
Response: In the multivariate analysis of this study, factors that showed statistical significance in the univariate analysis ($p < 0.05$) were selected as candidates and then entered into the Cox proportional hazards model using the stepwise method to identify independent prognostic factors. We have clarified this point in the “Statistical analysis” section (**L.145–150**) to ensure that the criteria for variable selection are clearly communicated to readers.

4. The descriptions of lymphatic invasion, vascular invasion, and pleural invasion should be standardized across all tables. If abbreviations (Ly, V, Pl) are used, please provide explanations in the table footnotes.
Response: Abbreviations for Ly, V, and Pl have been added to the footnotes of the table, as suggested

5. Lines 74–76: The definition of the cohorts seems misleading. The authors should explicitly state in the manuscript that there is overlap among the three cohorts and that patients aged 80 or above were excluded from all cohorts.
Modifying Figure 1 for clarity would also be helpful.
Response: We have clarified that the three age cohorts in this study (≤79 years, ≤75 years, and ≤65 years) represent overlapping subgroups. Additionally, we have specified that patients aged 80 years or older were not included in this study, and this information has been added to both the main text and Figure 1. Figure 1 has also been revised to visually clarify the relationships among the cohorts.
(**L.107–109**)

6. In all tables and figures, the period after “Cohort” is unnecessary and should be removed.
Response: The period at the end has been removed

7. Line 93: Since the CONUT score may be unfamiliar to many readers, a brief explanation should be provided within the manuscript rather than only citing references.
Response: We appreciate your valuable comment pointing out that, although the CONUT score is a core indicator in our study, it may be unfamiliar to some readers. In response to your suggestion, we have added a concise and specific explanation of the components and evaluation criteria of the CONUT score in the Introduction and Methods sections. We hope that this addition will help readers better understand the significance and calculation of the CONUT score.
(Lines 73–79, 124–126)