Author’s response to reviews

Title: Stability Across Time of the Neutrophil-Lymphocyte and Lymphocyte-Neutrophil Ratios and Associations with Outcomes in Cardiac Surgery Patients

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Revisions: Stability Across Time of the Neutrophil-Lymphocyte and Lymphocyte-Neutrophil Ratios and Associations with Outcomes in Cardiac Surgery Patients

Dear reviewers and editor,

Thank you very much for the insightful comments that allowed us to improve the manuscript. Please find the point-by-point response to your comments below.

Reviewer #1

Q1. Everything is clear in the article; Problem is defined well, it is simple and clear. Their methodology is conducted well. Results were evaluated and illustrated well. However, I have a problem with the structure of your article. It seems the article is gathered from a research report which has been reported before. I mean article has a standard style in writing specially in lecturer review section. The problem is clear but reader wants to know whether any researcher has worked on this problem before or not. If yes, what was their result. Please add a related work section to the article and refer the others endeavors.
A1. Thank you very much for this comment. Related works have been addressed in the Discussion section. This section of the paper has been expanded to provide further context to our paper in relation to the previous literature.

Reviewer #2: The article is interesting and although the findings have been described in the past, I find that this work is of interest for the journal. A few questions and comments. Q1. Did the authors try different cut-off values to separate between highs and lows for NLR and LNR to see if there would be more difference in clinical results? Or was the value of 2.44 selected because it was the value with the best discrimination?

A1. The NLR cutoff value used to dichotomize the group was determined based on the median within our cohort in order to create groups of relatively equal size. We felt this was an objective cutoff useful in operationalizing the analysis. Other cutoff values were not tested and no attempt was made to manipulate this factor in order to maximize statistical significance. In cases where multiple pre-operative CBC values were available prior to the date of surgery, the CBC closest to the date of surgery was always selected for our analysis. This explanation was added to the Statistical Analysis section of the paper.

Q2. Although the longitudinal consistency is rather good, did the authors try to look at values long time before or short time before the surgery? Did they select the highest available value for NLR? This is not well described in the Method section.

A2. There was no attempt to manipulate the number of days between CBC measurements nor the NLR/LNR cutoff value. The acceptable number of days between measurements (up to 100 days) was chosen with consideration of clinical utility and the preservation of sample size for our analysis. In cases of more than 2 measurements, the longest interval within 100 days was chosen. The range used to analyze stability was also purposefully selected to extend past the range used to analyze the relationship between NLR/LNR and outcomes (up to 60 days). In terms of clinical utility, we wanted to select a reasonable range that would be potentially useful to physicians in practice. The other studies referenced in the paper used relatively narrow date ranges, which may increase the strength of NLR’s predictive value but it also limits its clinical utility. For example, Durmus et al. and Giakoumidakis et al. used only lab values collected within 24 hours of surgery and Gibson et al. expanded their range up to 3 days. In practice, that limits the use of pre-operative NLR beyond a fairly narrow period prior to surgery. Thus, our study aimed to demonstrate stability over time and expand that range so that labs ordered throughout the extended pre-operative process may be used to estimate risk and make informed decisions.
Q3. Did the authors try to combine some of the other risk factors used in Euroscore or STS database with the NLR or LNR ratios to see if such combinations would be predictive of worse income? Did they look at correlation between their ratios and Euroscore and STS score? The question is basically if NLR or LNR could be of value as a risk factor in these scoring system.

A3. Our analysis, as currently conducted, did not make these assessments. Our dataset was not connected to patient Euroscore values and did not contain sufficient variables to calculate Euroscore. We also did not correlate with other STS factors in this analysis, relying on previous research cited in the manuscript which has previously demonstrated such relationships, as our intent was not to compare NLR or LNR as an alternative prognosticating tool to the STS model, which is much more extensive in its development and validation.

Q4. Maybe there should be some discussion about why these ratios are important, meaning how can the importance of NLR be explained. Is it an independent risk factor or just a factor reflecting other risk factors. I assume it would be reasonable to look at other risk factors as well to evaluate the potential independence of NLR and LNR.

A4. Thank you for this comment. The importance of these ratios is now mentioned in the introduction and the discussion. Based on the literature, it is hypothesized that NLR integrates the detrimental effects of both neutrophilia, reflecting inflammation, and lymphopenia, a marker of poorer general health and physiologic stress. Thus, the NLR combines both ANC and ALC and has potentially greater predictive value than those factors independently. While we did not analyze these factors independently, Gibson et al. and Durmus et al. have previously demonstrated the superiority of NLR over total white cell count, absolute neutrophil count, and absolute lymphocyte count as individual risk factors.

Q5. Figure 2 is at least for me, difficult to evaluate and understand. It should be revised and have a better legend.

A5. Thank you for this point. Figure 2 has been revised to clarify the legends and labels.