Author's response to reviews

Title: Elevated Preoperative Neutrophil/Lymphocyte Ratio as a Predictor of Lower Long-term Mortality in Minimal Invasive Compared to Sternotomy Coronary Artery Bypass Surgery

Authors:

BASEM AZAB (basemnady2000@yahoo.com)
MASOOD A SHARIFF (MSHARIFF@SIUH.EDU)
Rana H Bachir (rhp05@mail.aub.edu)
JOHN P NABAGIEZ (JNABAGIEZ@SIUH.EDU)
JOSEPH T MCGINN JR (JMCgin@SIUH.EDU)

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Author's response to reviews: see over
Dear Editor-in-Chief:

Subject: Revision of manuscript on Reviewer Comments.

Thank you for this opportunity for allowing a thorough review of our submission. Please find below our responses to the reviewer comments.

Reviewer 1:

Minor Essential Revisions:

1. I note that the third tertile (NLR > 3.4) is the only group where there is significantly greater IMA use in patients undergoing MICS compared to sternotomy. IMA use is known to improve long-term outcome, therefore this is an important limitation of the study that should be acknowledged and explained.

   Author’s response:

   We agree with the reviewer regarding this observation, which was controlled in the multivariate analysis. Table 5, multivariate analysis including patients with high NLR, demonstrated that MICS was associated with lower mortality after adjusting for other variables including use of IMA. We have acknowledged this point in the limitation section and we suggested further prospective studies to investigate our findings.

2. Mean follow-up period described in Methodology should be stated with standard deviation rather than with range.

   Authors’ response:

   We edited the required data in the results section, standard deviation (±15 months) was added after the mean months of follow up.

Reviewer 2:

1. The total study cohorts are 1030 patients. The authors divided them to 6 small groups. I don’t know how many patients each small group would have, the manuscript didn’t tell. In MICS subgroups, each group would only have few patients in higher NLR category. It is hard to make any meaningful conclusions with few patients in groups;

   Authors’ response:

   We agree with the reviewer and have added the number in each group (please refer to revised table 1 and 2). We have used this categorization to illustrate the difference of baseline characteristics between MICS and sternotomy in each NLR tertile. Although the number of MICS in the subgroups were relatively small (129, 130 and 137 patients in low, middle and highest NLR tertile, respectively), we have achieved power to demonstrate the significance of high NLR in predicting mortality in CABG patients. In table 5, multivariate model including
patients with high NLR, we had 502 patients that demonstrated the positive impact of MICS vs. sternotomy on survival in this group with NLR >3.

2 In table 1, some patients with NLR>3.4 had leukocytes 9.70 ±3.13. I guess if a patient has leukocytes beyond normal range, the surgeons would have to solve the problem first before they operate them;

Authors’ response:

We agree with this comment. Due the retrospective nature of our study, we could not investigate the circumstances lead to proceed with surgery in face of this leukocytosis, we have found 50 patients with leukocyte > 11 in the highest NLR tertile, we hypothesize the reasons could be preop-MI, or other factors. Further studies needed to validate our results.

To satisfy this raised issue, we excluded all patients with WBC >10.9 (161 patients) and ran additional analyses: Among patients with normal WBC, patients in the highest NLR tertile had significant higher mortality than the lowest NLR tertile group (55/278 vs. 27/349, p <0.0001). Similarly, among patients with normal WBC and NLR >3, MICS group had lower mortality compared to the sternotomy group (18/148 vs. 54/241, p =0.0151).

3 The authors included 13 variables in a multivariate cox proportional hazard model to look for risk factors of 5-year mortality in table 4. The whole manuscript didn't tell us how many patients were followed up for 5-year mortality. I think only patients were operated in 2005 were qualified for studying 5-year mortality . 13 variables included in the model means at least 130 patients died who had surgery in 2005. We need to know how many patients had surgery in 2005 and how many of them died before 2011 ? If less than 130 patients died then table 4 is not correct.

Authors’ response:

We added the number of patients who were followed up for 5-year (467 patients which include those done in 2005 and 2006 and follow-up to 2011). Out of these 467 patients, 78 patients died before 2011. We have used in our multivariate model 1126 patients who were followed up to average of 5 years, 154 patients died during this follow up period. We have corrected that in the text (results section regarding the multivariate models) and table 3.

The “5-year mortality” has been changed to “overall survival” within the manuscript.

4 As I said above, the manuscript didn't show how many patients were followed up for 5 year mortality, so we cannot evaluate figure 1 and figure 3.

Authors’ response:

We have added footnotes to both figures stating the number of patients who were followed up to 5 years.
I hope that the reviewing process finds the comments and responses acceptable; once again we thank the committee for reviewing our work. We are willing to comply with further suggestions to improve upon.

Sincerely,

Basam Azab, MD
Staten Island University Hospital-Department of Surgery
475 Seaview Ave
Staten Island, New York 10305
Ph-718-226-1615
Fax-718-226-1633
basemazab5@gmail.com
basemnady2000@yahoo.com