

Dear Editor

Thank you very much for your email of December 17, 2021, informing us of tentative acceptance of the above referenced paper. Attached please find the revised manuscript. Our point-by-point responses to the reviewers' comments are as follows.

Responses to Reviewer 1's critiques

1. Critique "I struggled to follow the grammar and hence easily understand the paper. Even though the authors provided a grammar certificate, the poor use of tenses and sometimes difficulty in understanding what is being discussed was a concern. E.g., this entire section of the key results o "The 3-year and 5-year cumulative survival rate was significantly lower in patients with high (n=26) than with low(n=56) NLR (19.1% vs. 67.2%, $P<0.001$) (0.0% vs. 48.3%, $p<0.001$).” is difficult to follow.”

Reply: Thank you for your careful read and thoughtful comments on previous draft. We have re-written this sentence according to the reviewer's suggestion. "The 3-, 5-year cumulative survival rates of high NLR group ($NLR\geq 3$ patients) were 19.1% and 0.0%, respectively, which were lower than low NLR group ($NLR<3$ patients) (67.2% and 48.3%).”

2. Critique "In the methods section, the groups they mention are not defined”

Reply: Thank you for your suggestion. According to the referee’s suggestion, the relevant content has been added. Line 98 "According to their NLR values, patients were grouped into a high NLR group ($NLR\geq 3$ patients) and a low NLR group ($NLR<3$ patients).”

3. Critique "Use of tenses e.g., is instead of was o This sentence line 126 which reads: The average POS was 27.03 ± 21.31 months should read: The average time POS was 27.03 ± 21.31 months o Starting a sentence with a number is not acceptable in scientific writing, line 139 o What is $NLR>3$ group? o Lots of formatting errors hear and there. Commas in the wrong place and double full stop at one point. -Abbreviations in the abstract that are not defined are difficult to make out as these are not standard. -Let the reader know in the abstract already the setting of the study i.e., hospital name.”

Reply: Thank you for your careful read. We have made correction according to the reviewer’s comments.

4. Critique "-Methods section both in abstract and body should specify how NLR was obtained. No formular is mentioned and no clear indication how the neutrophil and lymphocyte count was obtained by the hospital is alluded to. -The background/introduction is not elaborative enough/hypothesis driven.”

Reply: According to the referee’s suggestion, the relevant content has been added. "According to the blood routine examination, NLR was calculated from the absolute number of neutrophils, and lymphocytes. Calculated by the number of neutrophils divided by the number of lymphocytes.”

5. Critique "I wondered how treatment could have influenced NLR since most of the patients were treated. I know the authors say there was no significant difference.”

Reply: NLR is easily interfered with other factors. Such as the increase of white blood cells and neutrophils after surgery or trauma; Leukocyte and lymphocyte decrease

caused by myelosuppression after chemotherapy. For patients with other infectious diseases or those who are using certain drugs, the values from the peripheral blood are not completely accurate.

6. Critique “Exact time or an estimate of the last follow up visit should be provided. -Authors do not explain what operation the patients got. It will be helpful to the reader. -Provide company name of statistical packages in brackets.”

Reply: Thank you for your good comments and the relevant content has been added. “ The average follow-up period of 82 patients was 27.03 ± 21.31 months(range, 0.25-84 months)” “^aThe soft-tissue mass extended resection or partial rib resection;^bIntralesional resection and filling with polymethylmethacrylate bone cement in long bone of limbs metastases or incomplete metastasectomy in spinal metastases; ^cPercutaneous biopsy.” “(IBM SPSS Statistics 19.0)”.

7. Critique “This sentence: “There was no significant difference in preoperative chemotherapy regimens ($P=0.216$), time from a diagnosis to surgery ($p=0.321$).” I am not sure if it is with reference to the regimen or the time?”

Reply: There are two Characteristics, one is “preoperative chemotherapy regimens”, another is “the time from a diagnosis to surgery”. This “time” refers to the time from diagnosis of MM to surgery.

8. Critique “Abbreviation used that were not defined before e.g., AST - Please provide exact p values and not just $p>0.05$ or $p<0.05$ - Lots of tables for data that is already reported in text. Consider consolidating some of the tables. The same apply to a good number of figures e.g., figures 1-4 should be consolidated into one figure with A-D and Figures 5 and 6. - The A and B in figures 5 and 6 are not explained. Consider revising the legends to be more explicit. - Table 9 and 10 don’ t really belong in the table. Those belong to the discussion and should be discussed.”

Reply: According to the referee’s suggestion, the relevant content has been added.

Responses to Reviewer 2's critiques

1. Critique “1. Several investigators have reported that many blood markers such as monocyte-lymphocyte ratio and platelet-lymphocyte ratio have the prognostic impact in patients with MM. However, the authors focused on NLR alone in the present study. The authors should indicate about this issue.”

Reply: Thank you for your thoughtful comments on previous draft. We also considered analyzing the influence of NLR and PLR on MMBD patients at the same time before the start of this study. However, considering the limited sample size in this study, if the related factors affecting platelets need to be included in the simultaneous analysis of PLR, the results of multivariate analysis may be affected. On the other hand, this study not only aim to evaluate whether NLR can be used to predict the prognosis of MMBD patients after operation, but also to evaluate the immune status of MMBD patients in different time periods, which mainly included neutrophils and lymphocytes. Therefore, we only focus on NLR only in this study.

2. Critique “Many investigators have demonstrated the prognostic significance of NLR in patients with MM. What is the new finding in this study”

Reply: As a marker of systematic inflammation, the neutrophil-lymphocyte ratio (NLR) has been used to diagnose infectious diseases. Although some retrospective studies have initially explored the influence of NLR on the prognosis of MM in recent years, these studies didn't report on whether there is any change in the immune status of MM patients before and after the operation.

Our study showed that postoperative chemotherapy and preoperative peripheral blood NLR were independent risk factors affecting the POS of MMBD patients. We also found that MM patients had a high NLR before the operation, which significantly increased 1 week after the operation. In the second week after the operation, the absolute neutrophil count significantly increased while the absolute lymphocyte count declined; in the second month, the NLR declined while the absolute neutrophil count and absolute lymphocyte count returned to levels before the operation. At the last follow-up visit, the NLR returned to a high level while the absolute neutrophil count significantly increased and the absolute lymphocyte count significantly declined. Such change indicates that a high preoperative NLR, which may be the result of the imbalance of inflammatory reaction between anti-tumor and pro-tumor effects, can be used to predict poor prognosis in MM patients.

ROUND 2

Dear Editor

Thank you very much for your email informing us of tentative acceptance of the above referenced paper. Attached please find the revised manuscript. Our point-by-point responses to the reviewers' comments are as follows.

Responses to Reviewer 1's critiques

9. Critique “I struggled to follow the grammar and hence easily understand the paper. Even though the authors provided a grammar certificate, the poor use of tenses and sometimes difficulty in understanding what is being discussed was a concern. E.g., this entire section of the key results o “The 3-year and 5-year cumulative survival rate was significantly lower in patients with high (n=26) than with low(n=56) NLR (19.1% vs. 67.2%, $P<0.001$) (0.0% vs. 48.3%, $p<0.001$).” is difficult to follow.”

Reply: Thank you for your careful read and thoughtful comments on previous draft. We have re-written this sentence according to the reviewer's suggestion. **Line56-59**

“The 3- and 5-year cumulative survival rates of the high NLR group ($NLR\geq 3$ patients) were 19.1% and 0.0%, respectively, which were lower than those of the low NLR group ($NLR<3$ patients) (67.2% and 48.3%).”

10. Critique “In the methods section, the groups they mention are not defined”

Reply: Thank you for your suggestion. According to the referee’s suggestion, the relevant content has been added. **Line 159-161** “According to their NLR values, patients were grouped into a high NLR group ($NLR\geq 3$ patients) and a low NLR group ($NLR<3$ patients).”

11. Critique “Use of tenses e.g., is instead of was o This sentence line 126 which reads: The average POS was 27.03 ± 21.31 months should read: The average time POS was 27.03 ± 21.31 months o Starting a sentence with a number is not acceptable in

scientific writing, line 139 o What is NLR>3 group? o Lots of formatting errors hear and there. Commas in the wrong place and double full stop at one point. -Abbreviations in the abstract that are not defined are difficult to make out as these are not standard. -Let the reader know in the abstract already the setting of the study i.e., hospital name.”

Reply: Thank you for your careful read. We have made correction according to the reviewer’s comments.

12. Critique “-Methods section both in abstract and body should specify how NLR was obtained. No formular is mentioned and no clear indication how the neutrophil and lymphocyte count was obtained by the hospital is alluded to. -The background/introduction is not elaborative enough/hypothesis driven.”

Reply: According to the referee’s suggestion, the relevant content has been added.

Line 157-159 “According to routine blood examination, the NLR was obtained using the absolute number of neutrophils and lymphocytes, calculated by the number of neutrophils divided by the number of lymphocytes.”

13. Critique “I wondered how treatment could have influenced NLR since most of the patients were treated. I know the authors say there was no significant difference.”

Reply: NLR is easily interfered with other factors. Such as the increase of white blood cells and neutrophils after surgery or trauma; Leukocyte and lymphocyte decrease caused by myelosuppression after chemotherapy. For patients with other infectious diseases or those who are using certain drugs, the values from the peripheral blood are not completely accurate.

14. Critique “Exact time or an estimate of the last follow up visit should be provided. -Authors do not explain what operation the patients got. It will be helpful to the reader. -Provide company name of statistical packages in brackets.”

Reply: Thank you for your good comments and the relevant content has been added.

Line 193-195 “The average follow-up period of 82 patients was 27.03±21.31 months(range, 0.25-84 months)” **Table 1 Note** “^aThe soft-tissue mass extended resection or partial rib resection;^bIntralesional resection and filling with polymethylmethacrylate bone cement in long bone of limbs metastases or incomplete metastasectomy in spinal metastases; ^cPercutaneous biopsy.” **Line 180-181**“(IBM SPSS Statistics 19.0)”.

15. Critique “This sentence: “There was no significant difference in preoperative chemotherapy regimens (P=0.216), time from a diagnosis to surgery (p=0.321).” I am not sure if it is with reference to the regimen or the time?”

Reply: There are two Characteristics, one is “preoperative chemotherapy regimens”, another is “the time from a diagnosis to surgery”. This “time” refers to the time from diagnosis of MM to surgery.

16. Critique “Abbreviation used that were not defined before e.g., AST - Please provide exact p values and not just p>0.05 or p<0.05 - Lots of tables for data that is already reported in text. Consider consolidating some of the tables. The same apply to a good number of figures e.g., figures 1-4 should be consolidated into one figure with A-D and Figures 5 and 6. - The A and B in figures 5 and 6 are not explained.

Consider revising the legends to be more explicit. - Table 9 and 10 don' t really belong in the table. Those belong to the discussion and should be discussed.”

Reply: According to the referee’s suggestion, the relevant content has been added.

Figure 1

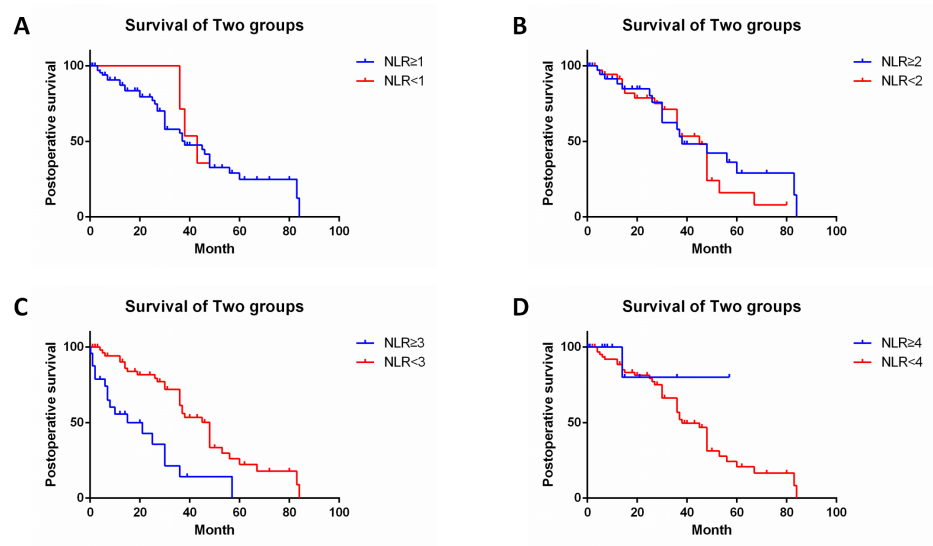


Figure. 1 A Comparison of POS in patients within the $NLR \geq 1$ group and $NLR < 1$ group, among which the POS of patients in the $NLR \geq 1$ group and the $NLR < 1$ group showed no significant difference ($p > 0.05$). B The POS of patients in the preoperative peripheral blood $NLR \geq 2$ group and the $NLR < 2$ group showed no significant difference ($p > 0.05$). C The POS of patients in the preoperative peripheral blood $NLR < 3$ group was significantly longer than that in the $NLR \geq 3$ group ($p < 0.05$). D The POS of patients in the preoperative peripheral blood $NLR < 4$ group was significantly longer than that in the $NLR \geq 4$ group ($p < 0.05$).

Figure2

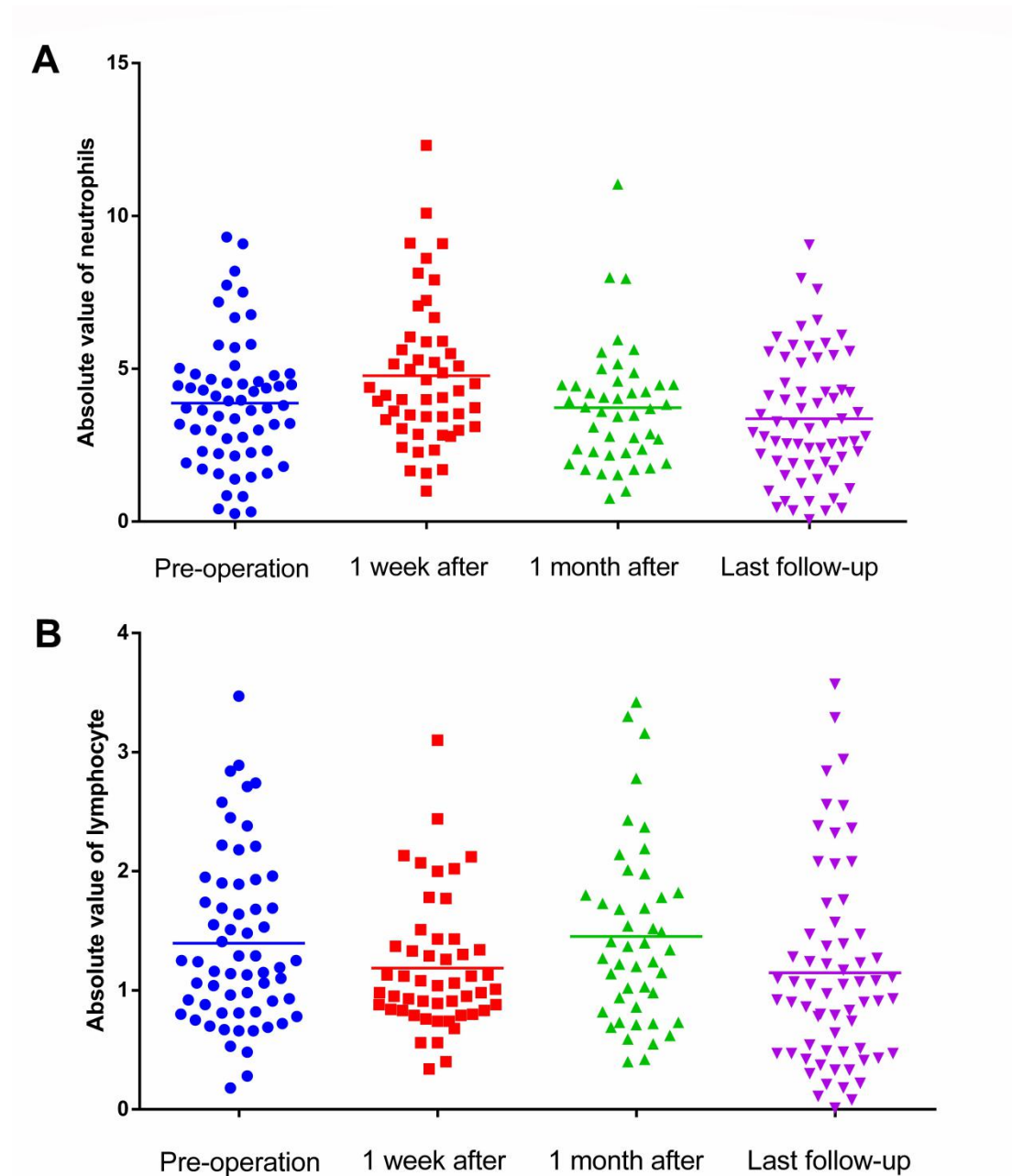


Figure. 2 Comparison of absolute neutrophil count and lymphocyte count between preoperation, 1 week after the operation, 1 month after the operation and the last follow-up visit in multiple myeloma bone disease patients. A The absolute neutrophil count increased significantly 1 week after the operation and returned to that before the operation 1 month after the operation. B The peripheral blood absolute lymphocyte count declined after the operation, returned to that before the operation 1 month after the operation, and returned to a low level at the last follow-up visit.

1. Critique For this response below, the authors should make amendments in the article and specify that this has been done.

Critique “This sentence: “There was no significant difference in preoperative chemotherapy regimens ($P=0.216$), time from a diagnosis to surgery ($p=0.321$).” I am not sure if it is with reference to the regimen or the time?”

Reply: There are two Characteristics, one is “preoperative chemotherapy regimens”, another is “the time from a diagnosis to surgery”. This “time” refers to the time from diagnosis of MM to surgery.

Reply: Thank you for your careful read on previous draft. We have corrected it in our paper. **Line 224-225 “the time from diagnosis of MM to surgery”.**

2. Critique Authors seem to have removed p values even in the abstract e.g $P<0.001$. This was not the request. It is understandable if very low values are reported as such but sometimes, the values can be provided as was the case in the critique above

Critique “Abbreviation used that were not defined before e.g., AST - Please provide exact p values and not just $p>0.05$ or $p<0.05$ - Lots of tables for data that is already reported in text.

Reply: Thank you for your precious opinion. We have corrected it in our paper.

Line 59 Results “The 3- and 5-year cumulative survival rates of the high NLR group ($NLR\geq 3$ patients) were 19.1% and 0.0%, respectively, which were lower than those of the low NLR group ($NLR<3$ patients) (67.2% and 48.3%) ($P=0.000$)”

Line 233-235 “Differences in preoperative Hb and AST were found between the high NLR group and the low NLR group ($P = 0.047$, $P = 0.007$), while no difference was found for PLT and pre/postoperative CRP (Table 5). ”

Abbreviations

NLR: Neutrophil-lymphocyte ratio

MM: Multiple myeloma

MMBD: Multiple myeloma bone disease

POS: Postoperative survival

ISS: International staging system

CT: Computed tomography

MRI: Magnetic resonance imaging

BMI: Body mass index

ASCT: Autologous stem cell transplantation

OS: Overall survival

PFS: Progression-free survival

DFS: Disease-free survival
Hb: Hemoglobin
PLT: Platelet
ALb: Albumin
AST: Aspartate transaminase
ALT: Alanine transaminase
 Γ -GT: Glutamyl transpeptidase
 β 2-MG: β 2-microglobulin
Cr: Creatinine
CRP: C-reactive protein

3. Critique I don't see the consolidated figures from the attachment and hence cannot confirm the below

Consider consolidating some of the tables. The same apply to a good number of figures e.g., figures 1-4 should be consolidated into one figure with A-D and Figures 5 and 6. - The A and B in figures 5 and 6 are not explained. Consider revising the legends to be more explicit. - Table 9 and 10 don't really belong in the table. Those belong to the discussion and should be discussed."

Reply: The full text is polished in native language. Tables 9 and 10 have been removed.

Figure 1

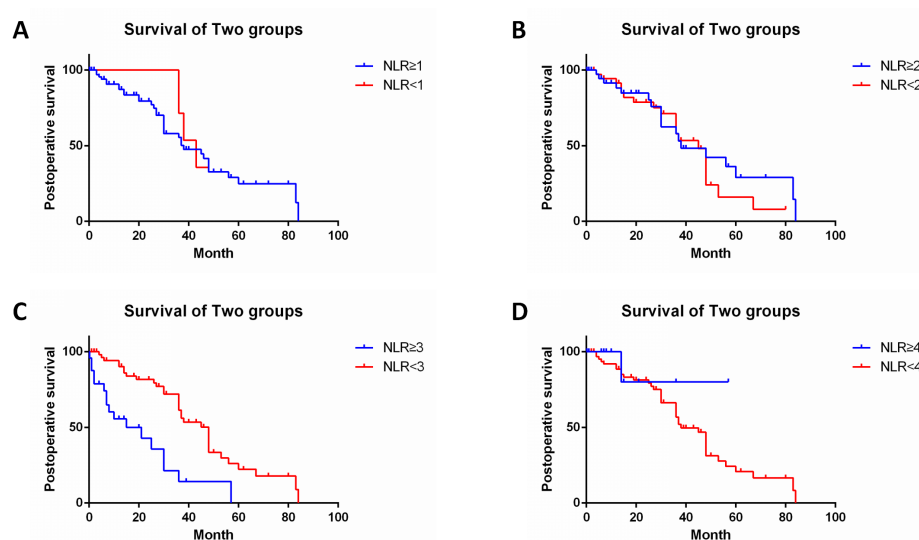


Figure. 1 A Comparison of POS in patients within the NLR ≥ 1 group and NLR < 1 group, among which the POS of patients in the NLR ≥ 1 group and the NLR < 1 group showed no significant difference ($p > 0.05$). B The POS of patients in the preoperative peripheral blood NLR ≥ 2 group and the NLR < 2 group showed no significant difference ($p > 0.05$). C The POS of patients in the preoperative peripheral blood NLR < 3 group was significantly longer than that in the NLR ≥ 3 group ($p < 0.05$). D The

POS of patients in the preoperative peripheral blood $\text{NLR} < 4$ group was significantly longer than that in the $\text{NLR} \geq 4$ group ($p < 0.05$).

Figure2

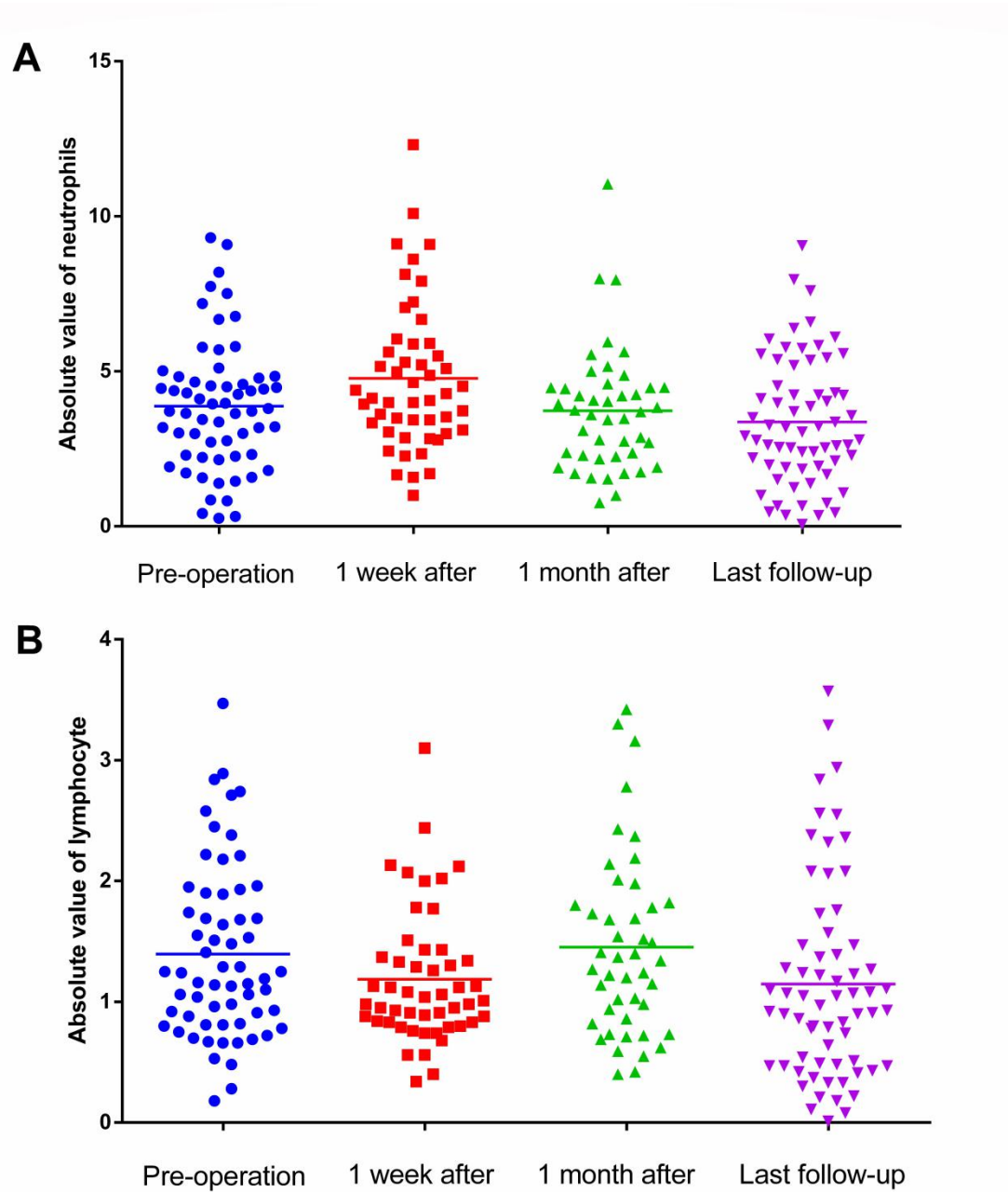


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