

Peer Review File

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Reviewer A

In this study, the authors have assessed the value of serum albumin (SA) levels as a prognostic factor among elderly patients with diffuse large B-cell lymphoma in China. The study design is sound, and the results seem to duplicate those of several previous reports. There are, however, a few weak points:

Dear Reviewer,

Thank you very much for your time involved in reviewing the manuscript and your very encouraging comments on the merit.

Major corrections:

1) For the multivariate survival analysis, it is unclear why the co-variables assessed (age, gender, NLR and aCCI) were selected for the analysis, as none of them were significantly associated with survival on univariate analysis. The IPI/NCCN-IPI +/- the presence of B-symptoms should be included in this analysis.

Reply1: Thank you for the detailed review. This is an especially important issue. In the multivariable analysis, confounding factor is an important issue. Serum albumin was analyzed as a continuous and categorical variable, with model I adjusting for age and gender and model II adjusting for variables from model I as well as clinical indications including aCCI and NIR. Although NLR is meaningless on univariate analysis, it has significance for the prognosis of lymphoma through literature review.

eg:

1) One research(1) enrolled 11 studies with a total of 2515 patients for meta-analysis, drawing a conclusion that patients with higher NLR were more likely to have poorer prognosis than those with lower NLR.

2) A meta-analysis(2), which aggregated data from 9 studies including 2297 patients. The results demonstrated that NLR has a strong association with worse OS and PFS in patients with DLBCL.

Considering that the study population belongs to the elderly population, the patients had a median age (years) of 78 years (range, 70–100 years), approximately 55.0% (53/96) of the patients combined chronic diseases. Patients with comorbidities are more prone to treatment-related toxicity and experience dose reductions, which might contribute to the lower rates of complete remission in elderly patients. A limited number of small studies (3-7) have shown the association between comorbidities, as assessed by Charlson Comorbidity Index (CCI), and adverse outcome in DLBCL, so NLR and aCCI were selected for the analysis. In addition, due to the small sample size, it is limited by the number of model adjustments.

Why are IPI/NCCN-IPI +/- the presence of B-symptoms not included in the model? The IPI was specified when the patient received only the chemotherapy regimen, its ability to discriminate patients with a poor outcome in suboptimal (8). NCCN-IPI was specified when the newly diagnosed patient received the R-CHOP regimen, the prognostic value of the NCCN-IPI may be diminished in elderly patients (>60 years) because the low-risk category is excluded due to the high impact of age (9) . Another point is that the NCCN-IPI does not take other important clinical parameters into account (in addition to the five factors considered in the IPI). Compared to the aCCI and NLR indicators, B symptoms were subjective, and the medical record writing bias, so we did not include this index. Variables with $p > 0.05$ can be selected if they have clinical significance.

2) The authors state that the question of SA levels in adult patients with DLBCL has not been fully explored (line 68), but have cited at least 7 articles which have addressed this question, and there are several more which they have not mentioned (eg Ochi, Y., Kazuma, Y., Hiramoto, N. et al. Utility of a simple prognostic stratification based on platelet counts and serum albumin levels in elderly patients with diffuse large B cell lymphoma. *Ann Hematol* 96, 1–8 (2017)., Seok-Hyun Kim, Se-Il Go, Jangho Seo, Myoung Hee Kang, Sung Woo Park, Hoon-Gu Kim, Gyeong-Won Lee. Prognostic impact of pretreatment albumin to globulin ratio in patients with diffuse large B-cell lymphoma treated with R-CHOP, *Leukemia Research*, Volume 71, 2018 (100-105)., Gupta A, et al. *Indian J Med Paediatr Oncol* 2019; 40(02): 232-239., Luigi Marcheselli, Alessia Bari, Samantha Pozzi, Raffaella Marcheselli, Maria Christina Cox, Luca Baldini, Stefano Luminari, Stefano Sacchi, Prognostic Role of Serum Albumin Level in DLBCL before and during the Rituximab Era. *Retrospective GISL Study over 738 Cases*, *Blood*, Volume 124, Issue 21, 2014, Page 5411., etc). It would perhaps be more accurate to say that this question has not been fully explored in China?

Reply2: Thank you for the detailed review. Indeed, we cited many references on the prognosis of albumin on diffuse large B cell lymphoma. However, It should be noted that the median age of patients included in those studies were younger (less than 60 years old), meanwhile these studies in the onset time earlier, some patients without chemotherapy or without Rituximab use, and our target population is greater than or equal to 70 years old this part of the special population. In addition, the median age of the study patients was 78 years (range, 70–100 years) next to the median age of the other 2 studies. We have also consulted the literature you mentioned. Thank you for your valuable suggestion, we have cited related literature in the proper place of the revised manuscript.

Changes in the text:

“However, the prognostic value of the SA level in adult patients has not been fully explored.” have corrected into “However, there is limited literature evidence of the role of albumin levels in prognosis in elderly patients with DLBCL.” (See Page3, line 69-71)

We have cited related literature in the proper place of the revised manuscript. (See Page11, line 344-346, line 347-349, line 357-359)

Minor corrections:

1) In line 56, the following: “the c-MYC gene, and B-cell lymphoma 2 double expressor or translocation, have been examined in relation to DLBCL prognosis “ should be rephrased as follows: “ and c-MYC gene rearrangement or co-expression with B-cell lymphoma 2 protein (double expressor) have been examined in relation to DLBCL prognosis”.

Reply1: Thank you for your valuable suggestions to improve the quality of our manuscript. We have modified our text as advised.

Changes in the text: “and c-MYC gene rearrangement or co-expression with B-cell lymphoma 2 protein (double expressor) have been examined in relation to DLBCL prognosis” (See Page2, line59-61)

2) In line 113-116, the meaning of the following sentence is not clear: “In the subgroup analysis, we also explored the potential effect modifications of the association between SA and OS. The following variables were assessed: gender, age...”etc.

Reply2: Thank you for the valuable suggestions. This is an especially crucial issue. Based on your suggestions, we have changed our expression.

Changes in the text: “Potential effect modification was evaluated by stratified analyses and interaction testing. We conducted subgroup analyses of the covariates’ gender, age, aCCI and LDH to further explore the effects of the covariates on outcome events. ” (See Page4, line126-129)

3) In line 127, it is stated that Low SA levels were significantly correlated with several factors. What correlation analysis was performed? This was not mentioned in the statistical methods.

Reply3: Thanks for your suggestion. This is a particularly important question that we ignored. We have been added related statistical methods in the “Method” section.

Changes in the text: Chi-square or Fisher’s exact test was performed for categorical variables, and the Mann–Whitney U test for continuous variables, to compare the baseline characteristics between the high and low SA groups. (See Page4, line121-124)

4) In line 135-136, it is stated that “However, gender, age, ECOG, LDH level, COO, and the Ki-67 index percentage were not found to have any significant prognostic value in predicting the OS of patients in this study ($P>0.05$; Table 2)”. This would be better phrased: “However, gender, age, ECOG, LDH level, COO, and the Ki-67 index percentage were not found to have any significant association with the OS of patients in this study ($P>0.05$; Table 2)”.

Reply4: Thank you again for your valuable suggestions to simplify our expressions. We have corrected the sentence into “However, gender, age, ECOG, LDH level, COO, and the Ki-67 index percentage were not found to have any significant association with the OS of patients in this study ($P>0.05$; Table 2)”.(See Page5,line147-149)

5) The meaning of the Subgroup analysis presented in lines 149-158 is unclear.

Reply5: Thank you again for your detailed review. I am sorry this part was not clear in the original manuscript. We have revised the contexts to address your concerns and hope that it is now clearer.

Changes in the text: We have corrected the sentence into “To detect whether the association between SA levels and prognosis was stable in different subgroups, stratified and interactive analyses were stratified according to the gender, age, aCCI, LDH. The results show that high SA levels was a favorable factor for OS of participants aged < 80 years (HR, 0.45; 95% CI, 0.21-0.96) and aCCI (5-7) (HR, 0.38; 95% CI, 0.18-0.8). We did not observe any significant interaction in the subgroups (p-value for interaction >0.05 for all, Figure2).” (See Page5, line162-167)

6) In lines 156-157, the following: “Compared to the low SA group, the high SA group showed a significant increase in OS” would be better phrased: “Compared to the low SA group, the high SA group showed a significantly higher OS rate”.

Reply6: Thank you again for your valuable suggestions to improve the quality of our manuscript. We have changed the sentence “Compared to the low SA group, the high SA group showed a significant increase in OS” to “Compared to the low SA group, the high SA group showed a significantly higher OS rate”. (See Page6, line170-171)

7) In line 194-195 it is stated that “Older patients with lymphoma, a poor nutritional status, and state of disease progression also routinely have hypoproteinemia.” This statement cannot be made categorically. Not all older patients with lymphoma have hypoproteinemia for instance. Please rephrase.

Reply7: Thank you for the valuable suggestions. Based on your suggestions, we have modified the sentence “Older patients with lymphoma, a poor nutritional status, and state of disease progression also routinely have hypoproteinemia.” to “Some elderly patients with lymphoma who present hypoalbuminemia may be due to old age or poor nutritional status or disease progression.” (See Page7, line 207-208)

8) There are several instances in the Discussion where findings are discussed that were not presented in the results. This is not good practice in academic writing. Examples include the association between B-symptoms and lower SA levels (line 193-193), the relationship between hypoproteinemia and survival (lines 200-201) and the outcomes according to both treatment received and SA levels (lines 217-218).

Reply8: Thank you again for your detailed review. I am sorry this part was not clear in the original manuscript .We have revised the partial contexts to address your concerns and hope that it is now clearer. In addition, in table2, table3, the relationship between albumin levels and lymphoma prognosis clarified our view.

We have modified “Lower ALB levels were also shown to be associated with B symptoms” to “Presence B symptoms were also shown to be associated with inferior prognosis”. (See Page7, line204-205)

We have corrected the sentence “Interestingly, our study did not find a direct relationship between chemotherapy and SA” into “Interestingly, hypoalbuminemia was associated with high tumor burden, but not with the number of chemotherapy cycles.” (See Page7, line229-230)

9) In line 202, it is stated that “the clinical significance of SA levels in other Asian populations and young patients needs to be explored.” Please take note of references listed above which include studies from Japan and South Korea.

Reply9: Thanks for your suggestion. As suggested by the reviewer, we have corrected the sentence “the clinical significance of SA levels in other Asian populations and young patients needs to be explored.” into “the clinical significance of SA levels in young patients needs to be explored.” (See Page7, line214-215)

Reviewer B

This manuscript evaluated the clinical value of serum albumin in patients with diffuse large b-cell lymphoma. The manuscript is well written, it is easy to read, and to understand. There are enough tables and figures. This type of lymphoma is heterogeneous, and the series is limited to 100 cases. Nevertheless, the IPI kept the prognostic value. Therefore, the results are of interest. Low levels associated to poor prognosis.

Dear Reviewer,

Thanks for your positive advice. We hope we can be better. Thank you.

Additional comments:

(1) In the Introduction. Could you please add a more detailed description of the current classification of DLBCL?

The International Consensus Classification of Mature Lymphoid Neoplasms: a report from the Clinical Advisory Committee.

<https://doi.org/10.1182/blood.2022015851>

The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms.

<https://doi.org/10.1038/s41375-022-01620-2>

Reply1: Thanks for your suggestion. We have added the relevant classification of diffuse large B cell lymphoma in the text.

Changes in the text: 5th edition of the WHO Classification of Haematolymphoid Tumours (WHOHAEM5) recognizes 17 specific entities as “large B-cell lymphomas” other than DLBCL, NOS (not otherwise specified) and refined the previous DLBCL subtypes. (See Page2, line47-49)

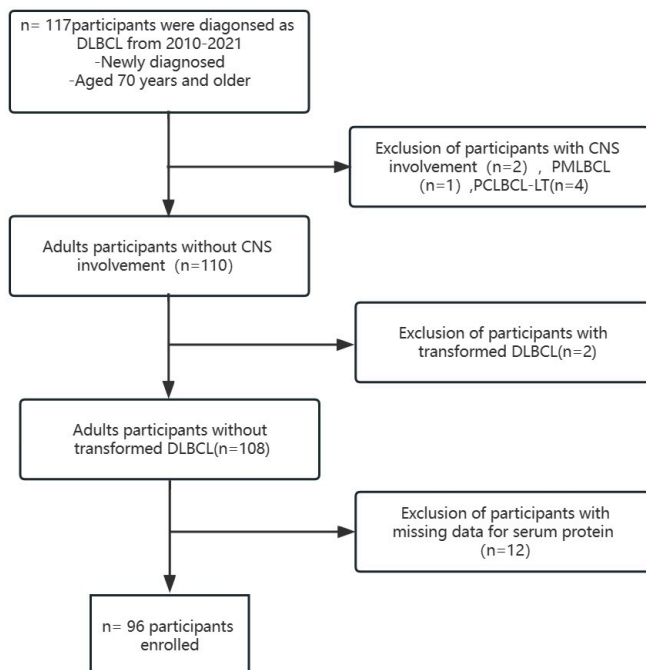
(2) In your series, CNS DLBCL was excluded. This is fine. But, what about the other subtypes of DLBCL?

In the previous classification (2016) the different subtypes were also important. For example, EBV (EBER+), TCHRLBCL, PMLBCL, FISH for MYC/BCL2/BCL6, etc.

The 2016 revision of the World Health Organization classification of lymphoid neoplasms.
<https://doi.org/10.1182/blood-2016-01-643569>

You may use the word "large b-cell lymphoma" or "NOS", if adequate for your series.

Reply2: Thank you for your detailed review. We think this is an excellent suggestion. We have been checked the original data again, and during the inclusion of the study population, we indeed excluded Primary mediastinal large B-cell lymphoma, Primary cutaneous diffuse large B-cell lymphoma, leg type. Of the 96 patients, 4 patients were combined EBV-positive. Due to the long time span of the population included in the study, and some patients did not have relevant FISH for MYC / BCL 2 / BCL 6 tests for economic reasons, no further description was made. This is a regret of our study. Secondly, due to the limitations of retrospective studies many patients could not meet the classification of the 2016 revision of the World Health Organization classification of lymphoid neoplasms. We adjusted our flow chart and modified the population inclusion process in the flow chart. (See Figure1-revised)



(3) Line 86. Do you have IRB number?

Reply3: Thanks for your suggestion. We have add the IRB number in the "Method" section of Main Text and the "Ethical Statement" section of Footnote.

Changes in the text: The study was approved be ethics board of Shaanxi Provincial People's Hospital (NO, 2018ZDXM-SF-065). (See Page4, line106-107 and See Page8, line264-265)

(4) Could you please explain how the Ki67 was evaluated?

Reply4: Thanks for your suggestion. Ki67 was assessed by immunohistochemistry in pathology specimens. We use MIB-1 antibody in our center and count positive cells by manually in the hotspot region. The Ki67 index was reported as an average percentage.

(5) Line 96. Could you please add in the appendix, information about the Charlson comorbidity index?

Reply5: Thanks for your suggestion. As suggested by the reviewer, we have provided appendix, information about the Charlson comorbidity index in the supplementary material.

(6) Regarding the biochemical parameters such as the SA, were they taken during the same time of the diagnostic biopsy (are all pre-treatment)?

Reply6: Thank you for the detailed review. All the albumin levels were test before treatment. As we used the retrospective data, these SA levels were not measured at the same time.

(7) Lin 107. In the COX model, did you use the method "enter" (all variables at the same time, in "one go")?

Reply7: Thank you for the detailed review. We used forward stepwise regression. In the final model adjustment, all covariates were not included due to the limitation of the study sample size.

(8) The liver is the major site where serum proteins are synthesized. These include albumin and the coagulation factors. Albumin is quantitatively the most important plasma protein. Approximately 300 to 500 g of albumin is distributed in the body fluids, and the average adult liver synthesizes approximately 15 g per day (200 mg/kg per day). The serum albumin concentration reflects the rate of synthesis, rate of degradation, and volume of distribution. Albumin synthesis and function are regulated by a variety of factors, including nutritional status, serum oncotic pressure, cytokines, and hormones. Hypoalbuminemia does not always reflect the presence of hepatic synthetic dysfunction since a variety of other conditions may be responsible including systemic inflammation, the nephrotic syndrome, and malnutrition.

Could you please confirm that other diseases associated with low albumin and poor prognosis of the patients were included in the multivariate analysis?

Reply8: Thank you for the detailed review. Indeed the level of albumin is influenced by multiple factors, and among the limitations of the article, we have clarified the absence of other indicators affecting albumin levels. Specific inflammatory markers (e.g., C-reactive protein, the white blood cell count, fibrinogen, and IL-6) were not measured in this study. Thus, no adjustments were made for these potential confounders. However, in the multivariable analysis,

we included albumin as a continuous variable or a categorical variable, suggesting that hypoalbuminemia was associated with poor prognosis, and the results were all robust.

(9) Could explain with more detail and/or clarify the “subgroup analysis” as shown in the lines 149-153?

Reply9: Thank you again for your detailed review. I am sorry this part was not clear in the original manuscript. We have revised the contexts to address your concerns and hope that it is now clearer.

Changes in the text: We have corrected the sentence into “To detect whether the association between SA levels and prognosis was stable in different subgroups, stratified and interactive analyses were stratified according to the gender, age, aCCI, LDH. The results show that high SA levels was a favorable factor for OS of participants aged < 80 years (HR, 0.45; 95% CI, 0.21-0.96) and aCCI(5-7) (HR, 0.38; 95% CI, 0.18-0.8). We did not observe any significant interaction in the subgroups (p-value for interaction >0.05 for all, Figure2).” (See Page5, line162-167)

(10) In Table 3. In the adjusted model, do you mean that for example in Model I in the COX the covariates were albumin, age, and sex?

The only limitation is the number of cases of the series, and the "subclassification" of Diffuse large b-cell lymphoma. Nevertheless, the results are of interest.

Reply10: Thank you for the detailed review. This is an especially important issue. In the multivariable analysis model, we used forward stepwise regression. Serum albumin was analyzed as a continuous and categorical variable, with model I adjusting for age and gender.

Thanks for your positive advice. The number of cases is indeed a deficiency of our study, and in the subsequent studies, we hope to find out by increasing the sample size or in larger multicenter clinical study should be conducted to confirm our findings. Meanwhile, we adjusted our flow chart and modified the population inclusion process. (See Figure1-revised)

Reviewer C

This paper overviews the prognostic implications of a low serum albumin level in elderly patients with DLBCL. Although there is limited literature evidence in elderly patients with DLBCL, there is some published literature. This should be overviewed in the introduction as the current paper provides corroborative evidence to strengthen the value of this literature. Suggest look at the following articles:

1) Liu H, Zhang CL, Feng R, Li JT, Tian Y, Wang T. Validation and Refinement of the Age, Comorbidities, and Albumin Index in Elderly Patients with Diffuse Large B-Cell Lymphoma: An Effective Tool for Comprehensive Geriatric Assessment. *Oncologist*. 2018 Jun;23(6):722-729. doi: 10.1634/theoncologist.2017-0361. Epub 2018 Jan 9. PMID: 29317552; PMCID: PMC6067934.

2) Ochi Y, Kazuma Y, Hiramoto N, Ono Y, Yoshioka S, Yonetani N, Matsushita A, Imai Y, Hashimoto H, Ishikawa T. Utility of a simple prognostic stratification based on platelet counts and serum albumin levels in elderly patients with diffuse large B cell lymphoma. *Ann Hematol*. 2017 Jan;96(1):1-8. doi: 10.1007/s00277-016-2819-3. Epub 2016 Sep 19. PMID: 27641425.

3) Kaneko H, Shimura K, Yoshida M, Matsumoto Y, Kobayashi T, Uchiyama H, Kuroda J, Taniwaki M. Serum Albumin Levels Strongly Predict Survival Outcome of Elderly Patients with Diffuse Large B-Cell Lymphoma Treated with Rituximab-Combined Chemotherapy. *Int J Hematol Oncol Stem Cell Res*. 2022 Jan 1;16(1):1-8. doi: 10.18502/ijhoscr.v16i1.8433. PMID: 35975118; PMCID: PMC9339123.

6) Gang AO, Pedersen M, d'Amore F, Pedersen LM, Jensen BA, Jensen P, Møller MB, Mourits-Andersen HT, Pedersen RS, Klausen TW, de N Brown P. A clinically based prognostic index for diffuse large B-cell lymphoma with a cut-off at 70 years of age significantly improves prognostic stratification: population-based analysis from the Danish Lymphoma Registry. *Leuk Lymphoma*. 2015;56(9):2556-62. doi: 10.3109/10428194.2015.1010078. Epub 2015 Feb 17. PMID: 25629994.

Reply1: We sincerely appreciate the valuable comments. We have checked the literature carefully and overviewed in the INTRODUCTION part.

Changes in the text:

“However, there is limited literature evidence of the role of albumin levels in prognosis in elderly patients with DLBCL. Albumin, alone or together with other clinical indicators, such as age, platelet, globulin, and comorbidity index, can serve as an effective tool to predict the prognosis of elderly DLBCL by forming the conformity index or calculating the integral index.”
(See Page3, line 69-74)

We have cited related literature in the proper place of the revised manuscript.(See Page10, line 301-303, Page11-12, line 350-367)

Other minor corrections:

1) Page 3: Line 101. “A cut-off value of 4.0 g/dL for the SA level was adopted in our study”. Suggest include a rationale for choice of this cut-off value.

Reply1: Thank you for your suggestion. According to the research of A.O. Gang et al.(10) We used the same cut off values of hypoalbuminemia in the present study.

Changes in the text: According to the research of A.O. Gang et al. (See Page4, line111)

2) Page 5: Lines 149-153

“##Subgroup analysis

A subgroup analysis was conducted to detect any association between the subgroup SA levels and OS in DLBCL. The results showed that there was no interaction between the SA level (low group vs. high group) and OS in the DLBCL patients (P value for the interaction >0.05; Table 4)”

Relook at the wording of this paragraph to clarify the meaning, as it is unclear currently.

Reply2: Thank you again for your detailed review. I am sorry this part was not clear in the original manuscript. We have revised the contexts to address your concerns and hope that it is now clearer.

Changes in the text: We have corrected the sentence into “To detect whether the association between SA levels and prognosis was stable in different subgroups, stratified and interactive analyses were stratified according to the gender, age, aCCI, LDH. The results show that high SA levels was a favorable factor for OS of participants aged < 80 years (HR, 0.45; 95% CI, 0.21-0.96) and aCCI(5-7) (HR, 0.38; 95% CI, 0.18-0.8). We did not observe any significant interaction in the subgroups (p-value for interaction >0.05 for all, Figure2).” (See Page5, line162-167)

3) Table 1: page 15

Correct typographical error: ECOF PS – ECOG PS

There is limited literature evidence of the role of albumin levels in prognosis in elderly patients with DLBCL. This paper provides corroborative evidence to strengthen the value of this literature.

Reply3: Thank you for the detailed review. We are very sorry for our careless mistake and it was rectified. Thank you very much for your very encouraging comments on the merits.

Changes in the text: ECOF PS-ECOG PS (See Table 1: page 14)

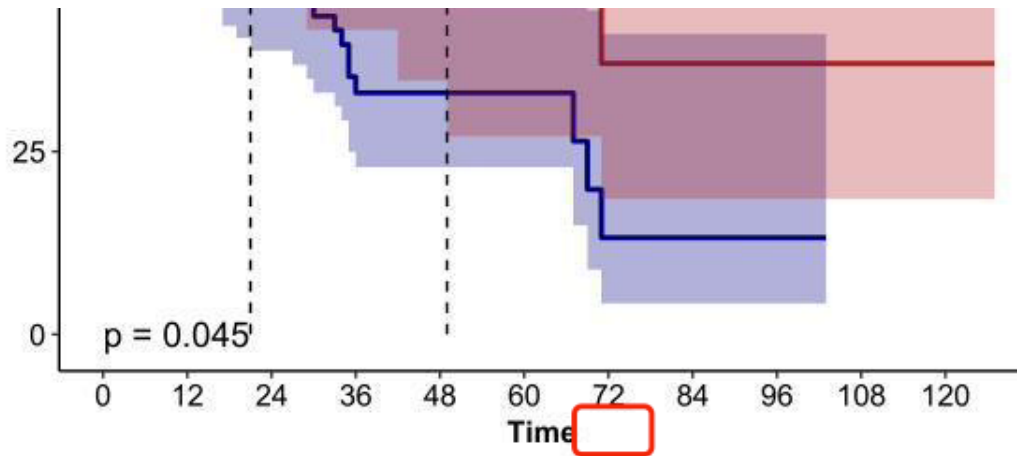
Reviewer D

1. Wei is not the first author of Ref.41, please check and revise.

259 nutritional status, but also poor responsiveness and tolerance to treatment (50) Wei et
260 al. examined the dynamics of SA levels over time and showed that a low SA level both
261 at the time of diagnosis and after the end of transmission were associated with
262 undesirable outcomes, and better survival rates were recorded when the SA levels
263 returned to normal (41). Interestingly, hypoalbuminemia was associated with high

Reply: Thank you for the detailed review. We are very sorry for our careless mistake and it was rectified.

2. Please add unit for X-axis in Figure 3.



Reply: Thank you for the detailed review. I have provided the Figure 3-revised with higher resolution.

3. Please define “*” in Table 1 footnote.

Table 1. Clinical characteristics of patients with DLBCL older than 70 years according to serum albumin level

Characteristics	Total	Serum albumin		P-value*
		Low (n = 76)	High (n = 20)	

Reply: “*” in Table 1 means High Serum albumin group vs. low Serum albumin group.

4. Please define “*” in Table 2 footnote.

Reply: “*” in Table 2 means Cox analysis.

5. Please define ALL abbreviations in Tables footnotes.

Reply: In the process of revise the manuscript, we found that the abbreviation of the footnote in table1 was incomplete. So I have define ALL abbreviations in Table1, Table2 and Table 3 footnotes.

Changes in the text:

Table 1 Abbreviations:

GCB, germinal center B-cell-like; ECOG PS, Eastern Cooperative Oncology Group performance status; IPI, International Prognostic Index; NCCN-IPI, National Comprehensive Cancer Network-IPI; AGR, albumin to globulin ratio; NLR, neutrophil-to-lymphocyte ratio; ALB, albumin; aCCI, age-adjusted Charlson Comorbidity Index; LDH, lactate dehydrogenase

Table 2 Abbreviations:

GCB, germinal center B-cell-like; ECOG PS, Eastern Cooperative Oncology Group performance status; IPI, International Prognostic Index; NCCN-IPI, National Comprehensive Cancer Network-IPI; AGR, albumin to globulin ratio; NLR, neutrophil-to-lymphocyte ratio; ALB, albumin; aCCI, age-adjusted Charlson Comorbidity Index; LDH, lactate dehydrogenase; HR, hazard ratio; CI, confidence interval.

Table 3 Abbreviations:

aCCI, age-adjusted Charlson Comorbidity Index; NLR, neutrophil-to-lymphocyte ratio; ALB, albumin; HR, hazard ratio; CI, confidence interval.

References

1. Mu S, Ai L, Fan F, et al. Prognostic role of neutrophil-to-lymphocyte ratio in diffuse large B cell lymphoma patients: an updated dose-response meta-analysis. *Cancer Cell Int.* 2018;18:119.
2. Wang J, Zhou X, Liu Y, et al. Prognostic significance of neutrophil-to-lymphocyte ratio in diffuse large B-cell lymphoma: A meta-analysis. *PLoS One.* 2017;12:e0176008.
3. Kobayashi Y, Miura K, Hojo A, et al. Charlson Comorbidity Index is an independent prognostic factor among elderly patients with diffuse large B-cell lymphoma. *J Cancer Res Clin Oncol.* 2011;137:1079-84.
4. Lin TL, Kuo MC, Shih LY, et al. The impact of age, Charlson comorbidity index, and performance status on treatment of elderly patients with diffuse large B cell lymphoma. *Ann Hematol.* 2012;91:1383-91.
5. Jelacic J, Todorovic Balint M, Sretenovic DA, et al. Enhanced International Prognostic Index (NCCN-IPI), Charlson Comorbidity Index and absolute lymphocyte count as predictors for survival of elderly patients with diffuse large B cell lymphoma treated by immunochemotherapy. *Neoplasma.* 2015;62:988-95.
6. Wieringa A, Boslooper K, Hoogendoorn M, et al. Comorbidity is an independent prognostic factor in patients with advanced-stage diffuse large B-cell lymphoma treated with R-CHOP: a population-based cohort study. *Br J Haematol.* 2014;165:489-96.
7. Miura K, Konishi J, Miyake T, et al. A Host-Dependent Prognostic Model for Elderly Patients with Diffuse Large B-Cell Lymphoma. *Oncologist.* 2017;22:554-60.
8. Ziepert M, Hasenclever D, Kuhnt E, et al. Standard International prognostic index remains a valid predictor of outcome for patients with aggressive CD20+ B-cell lymphoma in the rituximab era. *J Clin Oncol.* 2010;28:2373-80.
9. Melchardt T, Troppan K, Weiss L, et al. A modified scoring of the NCCN-IPI is more accurate in the elderly and is improved by albumin and beta2 -microglobulin. *Br J Haematol.* 2015;168:239-45.
10. Gang AO, Pedersen M, d'Amore F, et al. A clinically based prognostic index for diffuse large B-cell lymphoma with a cut-off at 70 years of age significantly improves prognostic stratification: population-based analysis from the Danish Lymphoma Registry. *Leuk Lymphoma.* 2015;56:2556-62.