Author’s response to reviews

Title: An inflammation-based cumulative prognostic score system in patients with diffuse large B cell lymphoma in rituximab era

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Author’s response to reviews:

Hao Wang (Reviewer 2)’s comments:

1. I am concerned about the statistical methods that the authors used to determine the cut-off threshold of each of the inflammatory markers. First of all, the clinical outcomes were time-to-event PFS and OS, but the ROC analysis the authors applied was appropriate when the outcome one hoped to predict is binary. Second, my guess was that the authors may have used 3-year PFS or 3-year OS as a binary outcome in this analysis. If so, it needed to be stated in the methods. The choice of 3 year milestone time should be justified. Note that survival at a fixed time point may not represent the totality of survival over time. Furthermore, how the patients who did not have PFS or OS events and were censored prior to 3 year were handled needed clarification. The analysis was not efficient if those patients were excluded. Third, it was not clear based on which outcome the cut-off values were determined. Was it PFS or OS? Forth, the authors should describe how they chose the cut-off value from the ROC curve, and be more specific about what they meant by optimal cut-off.
2. The authors should clarify which endpoint ICPS score was developed from. Table 3 should indicate whether it was hazard ratio for OS or PFS outcome. Also, as a convention, the regression coefficient is denoted as $\beta$, while $n$ often stands for sample size.

3. In Table 4 multivariate analysis, the levels of ICPS were combined into two categories ICPS<2 vs. ICPS $\geq$2. What was the rationale? Did the authors recommend two risk groups defined by ICPS, or four risk groups corresponding to 4 levels of ICPS score?

4. The multivariate analysis in Table 4 included ICPS and individual IPI risk factors. It is also informative to do the analysis considering two variables: ICPS and IPI risk score, to further demonstrate the incremental value of ICPS.

5. The number was the exactly same for 3-year OS rates and 3-year PFS rates at every value of ICPS (Page 9). Was it a typo?

Point-by-point response:

Comment 1:

I am concerned about the statistical methods that the authors used to determine the cut-off threshold of each of the inflammatory markers. First of all, the clinical outcomes were time-to-event PFS and OS, but the ROC analysis the authors applied was appropriate when the outcome one hoped to predict is binary. Second, my guess was that the authors may have used 3-year PFS or 3-year OS as a binary outcome in this analysis. If so, it needed to be stated in the methods. The choice of 3 year milestone time should be justified. Note that survival at a fixed time point may not represent the totality of survival over time. Furthermore, how the patients who did not have PFS or OS events and were censored prior to 3 year were handled needed clarification. The analysis was not efficient if those patients were excluded. Third, it was not clear based on which outcome the cut-off values were determined. Was it PFS or OS? Forth, the authors should describe how they chose the cut-off value from the ROC curve, and be more specific about what they meant by optimal cut-off.
Response:

We are sorry that the description of ‘A survival event was used in ROC analysis.’ was vague in the original manuscript. This has been revised to ‘A survival or death event was used for binary in ROC analysis. The cut-off time for judging the state of survival or death is the last follow-up day, and the event referred to death alone’. We selected the OS event for binary analysis in the ROC curve, which we should point out clearly in the text. In the ROC analysis, the maximal Youden index (Youden index = sensitivity + specificity - 1) was chosen to set optimal cut-off value. These details have been added in the revised text. The authors are grateful to the reviewers for pointing out their error.

Main improvement 1:

The original text (page 7, line1): A survival event was used in ROC analysis.

The revised text: A survival or death event was used for binary in ROC analysis. The cut-off time for judging the state of survival or death is the last follow-up day, and the event referred to death alone. In ROC analysis, the maximal Youden index (Youden index = sensitivity + specificity - 1) was chosen to set optimal cut-off value.

Main improvement 2:

The original text (page 6, line57): The optimal cut-off values for six biomarkers (CRP, albumin levels, LMR, NLR, LPR and fibrinogen levels) were determined using receiver operating characteristic (ROC) analysis.

The revised text: The optimal cut-off values for six biomarkers (CRP, albumin levels, LMR, NLR, LPR and fibrinogen levels) for predicting OS were determined using receiver operating characteristic (ROC) analysis.

Main improvement 3:

The original text (page 7, line42): First, we conducted ROC analysis to determine the optimal cut-off values of all inflammatory parameters as described in method above.

The revised text: First, we conducted ROC analysis to determine the optimal cut-off values of all inflammatory parameters for predicting OS as described in method above.
Comment 2:

The authors should clarify which endpoint ICPS score was developed from. Table 3 should indicate whether it was hazard ratio for OS or PFS outcome. Also, as a convention, the regression coefficient is denoted as \( \beta \), while \( n \) often stands for sample size.

Response:

Thanks for your suggestions. The specific content about which endpoint ICPS score was developed from has been listed in Page 8, line 31 as follows: Based on these three independent inflammatory adverse factors (CRP> 8.6mg/L, albumin<41.5 g/L and LMR≤2.7), we constructed a novel inflammatory-based prognostic model by combing these three prognostic variables. Table 3 shows the hazard ratio (HR) and regression coefficient (\( \beta \)) for OS of each significant inflammatory marker. The regression coefficient (\( \beta \)) for OS of each significant inflammatory marker was calculated from the Cox regression equation (HR=\( e^{\beta} \)). Because the HR for OS of each significant inflammatory marker is very close, we put the same weight on each factor in the prognostic-score model. The sum of the points allotted correlates with the following risk groups: group ICPS=0 (n=202, 35.8%), no inflammatory adverse factors; group ICPS=1 (n=144, 25.5%), 1 factor; group ICPS=2 (n=99, 17.6%), 2 factors; and ICPS=3 (n=119, 21.1%), 3 factors. The hazard ratio in table 3 is for OS outcome, so we have added a note ‘for OS’ in the title of table 3 and relevant paragraphs of the revised text. We have changed the symbol of the regression coefficient from ‘n’ to ‘\( \beta \)’ in the revised text.

Main improvement 1:

The original text (the title of table 3): The hazard ratio (HR) and regression coefficient (n) of each significant inflammatory marker

The revised text (the title of table 3): The hazard ratio (HR) and regression coefficient (\( \beta \)) for OS of each significant inflammatory marker

Main improvement 2:

The original text (page 8, line39): Table 3 shows the hazard ratio (HR) and regression coefficient (n) for each significant inflammatory marker. The regression coefficient (n) of each significant inflammatory marker was calculated from the Cox regression equation (HR=\( e^{n} \)). Because the HR of each significant inflammatory marker is very close, we put the same weight on each factor in the prognostic-score model.
The revised text: Table 3 shows the hazard ratio (HR) and regression coefficient (β) for OS of each significant inflammatory marker. The regression coefficient (β) for OS of each significant inflammatory marker was calculated from the Cox regression equation (HR=\(e^{\beta}\)). Because the HR for OS of each significant inflammatory marker is very close, we put the same weight on each factor in the prognostic-score model.

Comment 3:

In Table 4 multivariate analysis, the levels of ICPS were combined into two categories ICPS<2 vs. ICPS >=2. What was the rationale? Did the authors recommend two risk groups defined by ICPS, or four risk groups corresponding to 4 levels of ICPS score?

Response:

In many clinical analysis of diffuse large B cell lymphoma, IPI scores were often divided into two groups (0-2 vs.3-5) in multivariate analyses. In order to verify higher ICPS score (ICPS >=2) is a risk factor independent of higher IPI score (3-5) for OS and PFS, we combined the levels of ICPS into two categories ICPS<2 vs. ICPS >=2. Divided into two groups is to facilitate to do multivariate analysis, similar approach appeared in previous reports about other scoring systems (Kim Y, et al. The modified Glasgow Prognostic Scores as a predictor in diffuse large B cell lymphoma treated with R-CHOP regimen. Yonsei medical journal 2014, 55(6):1568-1575).

Comment 4:

The multivariate analysis in Table 4 included ICPS and individual IPI risk factors. It is also informative to do the analysis considering two variables: ICPS and IPI risk score, to further demonstrate the incremental value of ICPS.

Response:

I am sorry that we had deleted IPI risk score in the multivariate analysis (table 4) in the first revised version according the suggestion of Reviewer 1. He proposed that it was wrong to do multivariate analysis utilizing bi-variate IPI risk factors along with the IPI, because he thought that would undervalued them, and suggested that we should either include the IPI alone or include all the factors in the IPI, but not both. In view of the disagreement between two reviewers, we reviewed the related statistical knowledge and consulted the similar literature. Finally, we tend to agree with Hao Wang (Reviewer 2) to put both IPI risk factors and IPI in
multivariate analysis to further demonstrate the incremental value of ICPS. We decided to write a detailed letter to the editor in chief to explain the situation and at last to get a decision.

Main improvement:

The original Table 4 (In the first revised version):

Table 4 Multivariate analysis of the inflammation-based cumulative prognostic score (ICPS)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OS</th>
<th>PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P-value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Age(&gt;60y)</td>
<td>&lt;0.001</td>
<td>2.493 (1.657-3.749)</td>
</tr>
<tr>
<td>Ann Arbor stage(III,IV)</td>
<td>0.533</td>
<td>1.185 (0.695-2.022)</td>
</tr>
<tr>
<td>LDH(&gt;245 U/L)</td>
<td>0.042</td>
<td>1.690 (1.020-2.800)</td>
</tr>
<tr>
<td>ECOG PS(≥2)</td>
<td>0.411</td>
<td>1.230 (0.751-2.012)</td>
</tr>
<tr>
<td>Extranodal sites(&gt;1)</td>
<td>0.013</td>
<td>1.803 (1.134-2.868)</td>
</tr>
<tr>
<td>ICPS≥2</td>
<td>0.001</td>
<td>2.476 (1.483-4.136)</td>
</tr>
</tbody>
</table>

Abbreviations: OS, overall survival; PFS, progression-free survival; HR, Hazard Ratio; 95% CI, 95% confidence limits; LDH, lactate dehydrogenase; ECOG PS, Eastern Cooperative Oncology Group performance status; IPI, International Prognostic Index; Hi, high-intermediate; H, high; ICPS, inflammation-based cumulative prognostic score.

The revised Table 4:

Table 4 Multivariate analysis of the inflammation-based cumulative prognostic score (ICPS)
Characteristic | OS | PFS
---|---|---
P-value | HR (95% CI) | P-value | HR (95% CI)
Age(>60y) | <0.001 | 2.300 (1.462-3.619) | 0.428 | 1.169 (0.795-1.718)
Ann Arbor stage(III,IV) | 0.821 | 1.075 (0.576-2.006) | 0.456 | 1.195 (0.747-1.911)
LDH(>245 U/L) | 0.079 | 1.640 (0.945-2.846) | 0.043 | 1.594 (1.016-2.502)
ECOG PS(≥2) | 0.411 | 1.230 (0.751-2.012) | 0.044 | 1.565 (1.012-2.422)
Extranodal sites(>1) | 0.078 | 1.620 (0.947-2.772) | 0.429 | 1.207 (0.757-1.922)
IPI (Hi, H) | 0.592 | 1.256 (0.546-2.887) | 0.646 | 1.173 (0.594-2.313)
ICPS≥2 | 0.001 | 2.467 (1.478-4.118) | 0.018 | 1.618 (1.085-2.413)

Abbreviations: OS, overall survival; PFS, progression-free survival; HR, Hazard Ratio; 95% CI, 95% confidence limits; LDH, lactate dehydrogenase; ECOG PS, Eastern Cooperative Oncology Group performance status; IPI, International Prognostic Index; Hi, high-intermediate; H, high; ICPS, inflammation-based cumulative prognostic score.

Comment 5:
The number was the exactly same for 3-year OS rates and 3-year PFS rates at every value of ICPS (Page 9). Was it a typo?

Response:
We are sorry that it’s an error in the original manuscript. This has been rectified. The authors are grateful to the referees for pointing out their error. Thanks for your careful checks. We are sorry for our carelessness.
Main improvement:

The original text (page 9, line 47): The 3-year PFS rates for patients with ICPS=0, ICPS=1, ICPS=2 and ICPS=3 were 95.6%, 88.2%, 76.0% and 62.2%, respectively (Table 4, Fig.2A).

The revised text: The 3-year PFS rates for patients with ICPS=0, ICPS=1, ICPS=2 and ICPS=3 were 86.5%, 82.3%, 71.6% and 54.5%, respectively (Table 5, Fig.2A).

Feng Gao (Reviewer 3)’s comments:

In this paper, Sun and colleagues developed an inflammation based prognostic scoring system for DLBCL and identified 3 independent predictors including CRP, albumin, and Lymph:mono ratio. The authors did a great job in the revision to address comments raised by previous reviewers. In general, this is a well written manuscript. The materials are well organized. The statistical methods are properly used. The strategy for data analysis is clearly outlined and the results are interpreted properly. The limitation of this study is thoroughly discussed.

No major statistical concerns and just a few minor issues on result presentation:

Essential revisions:

1. Methods- Statistical analysis: the authors mentioned "survival event" was used for ROC analysis. It is unclear whether the event refer to death alone, or death/progression.

2. Results - patient characteristics: The number of events (death, progression) was not presented anywhere in the text or Tables.

3. Results - cut-off: Two outcomes (OS, PFS) were involved in this paper. It is unclear whether the resultant optimal cut-offs represent both outcomes.

Optional revisions:

4. In addition to p-values, it is helpful to present summery statistics (e.g., C-statistics or concordance index, which is analogous to the AUC under binary data setting) for the overall predictive ability of the models.
5. It is understandable that it is hard to perform model-validation with an external data. However, an internal validation (10-fold cross validation, bootstrap re-sampling techniques, or calibration, etc.) will be helpful to understand the reliability of resultant models.

Point-by-point response:

Comment 1 of essential revisions:

Methods- Statistical analysis: the authors mentioned "survival event" was used for ROC analysis. It is unclear whether the event refers to death alone, or death/progression.

Response:

Thanks for your compliment and suggestions. We are sorry that the description of “A survival event was used in ROC analysis” was vague in the original manuscript. This has been revised to “A survival or death event was used for binary in ROC analysis”. The event referred to death alone.

Main improvement:

The original text (page 7, line1): A survival event was used in ROC analysis.

The revised text: A survival or death event was used for binary in ROC analysis. The cut-off time for judging the state of survival or death is the last follow-up day, and the event referred to death alone.

Comment 2 of essential revisions:

Results - patient characteristics: The number of events (death, progression) was not presented anywhere in the text or Tables.

Response: We have added data of the number of events (death, progression) in the revised text.
Main improvement:

The original text (page 7, line34): The median follow-up time was 31.5 months.

The revised text: After a median follow-up time of 31.5 months, 139 patients relapsed or progressed in total and 96 patients died during or after first-line chemotherapy.

Comment 3 of essential revisions:

Results - cut-off: Two outcomes (OS, PFS) were involved in this paper. It is unclear whether the resultant optimal cut-offs represent both outcomes.

Response: We feel great thanks for your professional review work on our article. This problem was also plaguing us when we chose optimal cut-off values: If selecting the OS event for binary analysis in the ROC curve, the cut-offs maybe not the best for PFS, and vice versa. Finally, referring to the practice in many other literatures, we chose the OS event for binary analysis in the ROC curve, so maybe the cut-offs were more suitable for predicting OS, which we should point out clearly in the text (have added in the revised version). Still, all cut-offs can also significantly predict PFS.

Main improvement 1:

The original text (page 6, line57): The optimal cut-off values for six biomarkers (CRP, albumin levels, LMR, NLR, LPR and fibrinogen levels) were determined using receiver operating characteristic (ROC) analysis.

The revised text: The optimal cut-off values for six biomarkers (CRP, albumin levels, LMR, NLR, LPR and fibrinogen levels) for predicting OS were determined using receiver operating characteristic (ROC) analysis.

Main improvement 2:

The original text (page 7, line42): First, we conducted ROC analysis to determine the optimal cut-off values of all inflammatory parameters as described in method above.

The revised text: First, we conducted ROC analysis to determine the optimal cut-off values of all inflammatory parameters for predicting OS as described in method above.
Optional revisions:

4. In addition to p-values, it is helpful to present summary statistics (e.g., C-statistics or concordance index, which is analogous to the AUC under binary data setting) for the overall predictive ability of the models.

5. It is understandable that it is hard to perform model-validation with an external data. However, an internal validation (10-fold cross validation, bootstrap re-sampling techniques, or calibration, etc.) will be helpful to understand the reliability of resultant models.

Response to optional revisions:

Thank you for your suggestions. 10-fold cross validation, bootstrap re-sampling techniques, or calibration, etc. are important methods which are used to determine the accuracy of statistics, in order to use existing samples to improve the accuracy of estimates. We agree with the opinion of the reviewers that it’s need to validate the system to enhance accuracy. Previously, we tried to find external data of other hospitals to verify, but as the reviewers said, there was some difficult. We also considered about doing internal validation, but the ICPS is a multilevel survival predicting system, as the survival has time attribute, which is not a binary data. So we think it is difficult to find a quantitative index to judge the accuracy of the system. And we considered that C-statistics is also only suitable for evaluate binary data setting. Still, optimal cut-off of each factor in our ICPS system was set by the maximal AUC in ROC analysis, which was list in results of the text (from Page 7, line 47 to Page 8, line 12).