Author’s response to reviews

Title: Dynamic prediction of long-term survival in patients with primary gastric diffuse large B-cell lymphoma: A SEER population-based study

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Dear editors and reviewers:

We are grateful to you for your valuable comments and suggestions which help us to improve the quality of the manuscript. We have study the comments carefully and have made modifications and corrections which we hope to meet your approval. We revised the manuscript according to your kind advices and detailed suggestions. Here below is our description on revision.
Reviewer reports:

Judith Ann Ferry, MD (Reviewer 1): The authors have evaluated a large series of gastric DLBCL derived from the SEER database. They then identified clinical factors associated with outcome and created a statistical tool for predicting outcome for individual cases.

The authors have excluded patients whose deaths were not tumor related. Does that mean that patients who died of complications of chemotherapy or radiotherapy were excluded? There is almost certainly some long-term impact of survival on patients who received such therapy. What about those who underwent complete gastrectomy? Perhaps the authors should investigate overall survival as well as cancer-specific survival.

Response: In this study, we compared overall survival and cancer specific survival of patients. 5-year CSS (59.3%) was significant higher than 5-year OS (52.4%) (Supplement Figure. 1a). In order to explore the impact of the disease on long-term survival of patients and make the purpose of this study clear, we included CSS as the end point of the study. Therefore, patients who die from complications of chemotherapy or radiotherapy were excluded, which we have added in the method part with red front.

The impact of adjuvant chemotherapy on the survival of patients is similar to the literature report. The study found that 5-year CSS (65.1%) of patients receiving chemotherapy was significantly better than that of patients without chemotherapy (38.1%) (Supplement Figure. 1b).

We also compared the impact of different gastrectomy methods on the survival of patients according to the reviewers' suggestions. We found that there was no significant difference between 5-year CSS (64.9%) of patients receiving total gastrectomy and 5-year CSS of patients (63.3%) receiving partial gastrectomy (Supplement Figure. 1c).

The types of chemotherapy, details of radiation therapy, and types of surgical procedures are not given. The authors acknowledge that data in SEER database is incomplete. Presumably most who received chemotherapy were treated with CHOP, but how many received rituxan? Did it improve outcome? Did some receive non-anthracycline containing chemotherapy regimens? How did they do compared to others? Is dosage of radiation available? Did patients who underwent surgery undergo partial or complete gastrectomy? Is this information available for any patients in SEER? If so, there should be an effort to incorporate that information into the predictive model.

Response: We agreed with reviewers' comments and we try to incorporate factors which may have an impact on survival. However, due to limited information of SEER database and detail information of adjuvant therapy, we are unable to further analyze the impact of rituxan, non-anthracycline chemotherapy and specific dosage of radiation on the survival of patients. This is
one of the limitations of this study, which can be confirmed by more prospective follow-up studies. There was no significant difference between 5-year CSS (64.9%) of patients receiving total gastrectomy and 5-year CSS of patients (63.3%) receiving partial gastrectomy (Supplement Figure. 1c). 275 patients received surgery while 140 patients received total gastrectomy and 135 patients received partial gastrectomy.

No pathologic information is recorded except that patients had DLBCL. Much information is available in the literature about differing outcomes depending on the details of the DLBCL, such as cell of origin, and (in the stomach) whether DLBCL arose de novo or in association with a MALT lymphoma. Co-expression of MYC and BCL2, and presence or absence of MYC, BCL2 and/or BCL6 rearrangements may also impact survival. If any of this information is available, it should be incorporated into the authors’ model.

Response: As mentioned before, we tried to incorporate factors which may have an impact on survival. In our study, we included patients with pathological diagnosis of [ICD-O-3] 9680/3, primary diffuse large B-cell lymphoma of the stomach in the SEER database. However, because the database cancer not provide more detailed pathological types and gene expression. It is impossible to analyze the impact of different pathological types or gene types on survival, which is one of the limitations of this study. According to the results of multivariate analysis, we developed a prognostic model based on a large sample. The conclusions of this study can be used as the basis for further research. And the influence of different pathological types or gene types on survival can be confirmed by more prospective multi-center clinical research data. We have added the information in the limitation with red front.

Under "long term patient survival" there is a line that says "cancer-specific death of primary gastric diffuse large B cells is not constant" but it should probably say "cancer-specific death rate of primary gastric diffuse large B cell lymphoma is not constant"

Response: We replaced "cancer-specific death of primary gastric diffuse large B cells is not constant" with" cancer-specific death rate of primary gastric diffuse large B cell lymphoma is not constant".

Luigi Rigacci (Reviewer 2): The paper is interesting but in my opinion the conclusions are not sufficiently supported by the methods. First of all, and the authors confirm too, this is a retrospective analysis with a lot of bias:

why do exclude deaths non tumor related?
Response: In this study, we compared overall survival and cancer specific survival of patients. 5-year CSS (59.3%) was significantly higher than 5-year OS (52.4%) (Supplement Figure. 1a). In order to explore the impact of the disease on long-term survival of patients and make the purpose of this study clear, we included CSS as the end point of the study. We have added the information in the discussion part with red front.

why do exclude those who died within 30 days?

Response: The majority within 30 days is most caused by surgery or complications. Cancer-specific survival can be better studied by excluding patients who died within 30 days. We have added the information in the discussion part with red front.

It is not possible to produce a normogram with these data, I think that it could be useful to distinct patients according to treatment and realise a nomogram according to treatment. Probably it is important to know if patients submitted to surgery has a better outcome than other (as supposed by authors) or the outcome of those treated with chemotherapy alone and so on.

Response: In this study, we try to incorporate factors which may have an impact on survival. Finally, we developed a prognostic model according to the results of multivariate analysis. The C index is 0.714. In order to make the model easy to use, we further develop a web-based survival rate calculator to help scholars accessing the survival of patients. We found that cancer specific survival of patients receiving surgical is better than that of non-surgical patients in a specific population, and cancer specific survival of patients receiving chemotherapy is better than patients did not receiving chemotherapy patients.

It is clear that mortality is superior in the first two years but it is not clear that in the following years what is due. Usually not for lymphoma but for complications.

Response: We agreed with reviewers' comments. However, because the database cancer not provide the information of complications. It is impossible to analyze the impact of complications on survival, which is one of the limitations of this study. We have added the information in the discussion part with red front.

The authors can not use the term 'metastases' in a lymphoproliferative disease it is conceptually wrong.

Response: We replaced “metastases” with “dissemination” with red front.
Line 21-22 page 5 'active treatment.....’ after two years I think that an active follow-up is more important than a therapy.

Response: We replaced ”active treatment” with “active follow-up” with red font.

Supplement figure1a 5-year cancer specific survival rate of patients is 59.3% and 5-year overall survival rate of patients 52.4%

Supplement figure1b 5-year cancer specific survival rate of patients who receive chemotherapy is 65.1% while no chemotherapy is 38.1%

Supplement figure1c 5-year cancer specific survival rate of patients who receive partial gastrectomy is 63.3% total gastrectomy is 64.9%