

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 made modifications and corrections which we hope meet your approval. We revised the manuscript according to your kind advice and detailed suggestions. Here below is our description on revision.

### **Reviewer #1**

#### *Comments to the Author*

Interesting article looking at prognostication based on a novel scoring system using blood parameters (5 in total) compared and used in combination with TNM staging. I find the statistics somewhat dense and confusing. There is no clear outline of what is a high BPM is and what constitutes a low BPM. The cut offs for what is high or low is not explained. Similarly the calculation of BPM includes calculations using numbers where it is not fully explained in the text how they have been derived (there is comment regarding supplementary methods but this is not included in my download data). The comment of low LNR and high Ca19:9 is totally obtuse. Are these the 01 and 1 calculations referred to. I have not clear outline how I could attempt to use this formula on my patients. This is a fatal flaw which must be addressed The authors note that not all patients received adjuvant chemotherapy. Were these patients included in the calculations of survival. If they did not receive chemotherapy as a result of slow or poor recovery after surgery, they should be removed from the study or calculated as a separate group to validate whether they may also be used in the calculations as complications are in themselves a cause of poorer outcomes.

#### *Responses to the comments of Reviewer #1*

1. I find the statistics somewhat dense and confusing.

Response: The least absolute shrinkage and selection operator (LASSO) is a

popular method for regression with high-dimensional predictors [1-3]. LASSO has been extensively used for optimal selection of variables in high-dimensional data with a robust prognostic value and low correlation among each other to prevent over-fitting [4,5]. In the present study, we applied the LASSO Cox regression model in the developing data to select the significant variables that can accurately predict the prognosis of gastric cancer (GC). A novel scoring system based on 5 blood parameters, namely Blood Parameters (BPM) score, was then constructed and validated. Details of the statistics are described in the Supplementary Methods section of Supplementary Materials, and we have uploaded the files.

2. There is no clear outline of what is a high BPM is and what constitutes a low BPM. The cut offs for what is high or low is not explained.

Response: In the current study, the optimum cutoff value for BPM score was selected on the basis of the association with the patients' OS by using X-tile plots (-0.93). We then assigned patients to a high- (BPM score  $\geq$  -0.93) or low-BPM (BPM score  $<$  -0.93) group with this value. The corresponding contents have been modified in the RESULTS section with red color.

3. Similarly the calculation of BPM includes calculations using numbers where it is not fully explained in the text how they have been derived (there is comment regarding supplementary methods but this is not included in my download data).

Response: The LASSO Cox model uses an L1 penalty to shrink some regression coefficients to exactly zero. The penalty parameter  $\lambda$ , called the tuning parameter, controls the amount of shrinkage. With larger  $\lambda$ , the estimates of weaker factors shrink towards zero, so that only the strongest predictors remain in the model. The optimal values of the penalty parameter  $\lambda$  were determined by tenfold cross-validations. We selected  $\lambda$  via 1-SE (standard error) criteria, i.e., the optimal  $\lambda$  is the largest value for which the

partial likelihood deviance is within one SE of the smallest value of partial likelihood deviance. A prognostic model was then constructed based on the selected variables using Cox regression coefficients in the developing cohort. In the present study, we established BPM score, based on 5 out of 9 candidate blood parameters: albumin, lymphocyte-to-monocyte ratio (LMR), neutrophil-to-lymphocyte ratio (NLR), carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9 via the LASSO model. Details of the statistics are described in the Supplementary Methods section of Supplementary Materials, and we have uploaded the files.

4. The comment of low LNR and high Ca19:9 is totally obtuse. Are these the 01 and 1 calculations referred to.

Response: According to reviewer's suggestion, we have modified the corresponding contents in the RESULTS section: In this formula, LMR, NLR, and CA 19-9 were valued as 0 or 1;  $LMR \leq 3.2$ ,  $NLR \geq 3.9$ , and  $CA\ 19-9 \geq 37$  U/mL were assigned a score of 1, and a value of 0 otherwise.

5. I have not clear outline how I could attempt to use this formula on my patients. This is a fatal flaw which must be addressed.

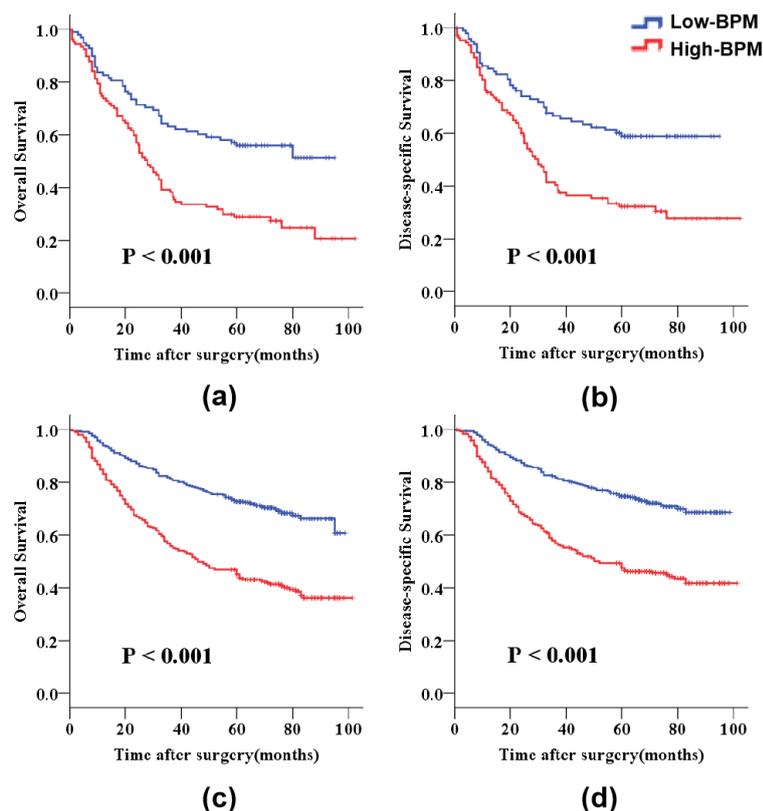
Response: Our findings may have important uses in prognostic stratification, therapeutic intervention, and postoperative surveillance strategies. For example, patients with a high BPM score will be recommended to receive postoperative multimodality treatment, such as chemotherapy, immunotherapy, targeted therapy, etc. And more regular follow-up schedule will be offered to early detect recurrence, which may provide survival benefit [6]. A patient example of how the model can be used in clinical practice was provided in the Supplementary Materials. We have added the corresponding contents to the DISCUSSION section with red color.

6. The authors note that not all patients received adjuvant chemotherapy.

Were these patients included in the calculations of survival. If they did not receive chemotherapy as a result of slow or poor recovery after surgery, they should be removed from the study or calculated as a separate group to validate whether they may also be used in the calculations as complications are in themselves a cause of poorer outcomes.

Response: In accordance with reviewer's suggestion, we assigned patients to an Adjuvant-Chemotherapy (AC) or non-AC group based on the receipt of postoperative adjuvant chemotherapy and then performed the Kaplan-Meier survival analysis. The results revealed that high-BPM patients had a poorer prognosis compared with low-BPM patients in both AC and non-AC groups (all log-rank  $P < 0.001$ , Supplementary figure 3). Thus, the BPM score was effective for risk stratification even in patients who did not receive adjuvant chemotherapy. We have added the corresponding contents to the RESULTS section with red color.

**Supplementary figure 3.** Kaplan-Meier survival analysis of overall survival and disease-specific survival in Adjuvant-Chemotherapy (AC) and non-AC groups. (a+b: AC group; c+d: non-AC group)



**Reference:**

- [1] Tibshirani R. The lasso method for variable selection in the Cox model. *Stat Med* 1997; 16(4):385-95.
- [2] Tibshirani R. Regression shrinkage and selection via the lasso: a retrospective. *Journal of the Royal Statistical Society Series B-Statistical Methodology* 2011; 73:273-282.
- [3] Goeman JJ. L1 penalized estimation in the Cox proportional hazards model. *Biom J* 2010; 52: 70-84.
- [4] Jiang Y,Zhang Q,Hu Y,et al.ImmunoScore Signature: A Prognostic and Predictive Tool in Gastric Cancer.*Ann Surg* 2018;267:504-513.
- [5] de Vries EM,Wang J,Williamson KD,et al.A novel prognostic model for transplant-free survival in primary sclerosing cholangitis.*Gut* 2017;67:1864-1869.
- [6] Fujiya K, Tokunaga M, Makuuchi R, Nishiwaki N, Omori H, Takagi W, Hirata F, Hikage M, Tanizawa Y, Bando E, Kawamura T, Terashima M. Early detection of nonperitoneal recurrence may contribute to survival benefit after curative gastrectomy for gastric cancer. *Gastric Cancer* 2017; 20: 141-149

## **Reviewer#2**

### Comments to the Author

This study is well written and presented. A combination of 5 blood parameters are used to correlate the OS and DSS of 850 gastric cancer patients. The question remains as to the utility of the correlations and the usefulness of them in future research and clinical studies. Are the authors going to change their clinical practice on the basis of these results? and if so how? These implications could be made more clear.

### Responses to the comments of Reviewer #2

1. Are the authors going to change their clinical practice on the basis of these results? and if so how? These implications could be made more clear.

Response: In our study, we found the BPM score, a novel scoring system based on 5 blood parameters, is predictive of long-term outcomes in stage II-III GC patients. This tool may have important uses in prognostic stratification, therapeutic intervention, and postoperative surveillance strategies, especially after incorporating TNM stage. For example, patients with a high BPM score will be recommended to receive postoperative multimodality treatment, such as chemotherapy, immunotherapy, targeted therapy, etc. And more regular follow-up schedule will be offered to early detect recurrence, which may provide survival benefit <sup>[1]</sup>. A patient example of how the model can be used in clinical practice was provided in the Supplementary Materials. We have added the corresponding contents to the DISCUSSION section with red color.

### **Reference:**

[1] Fujiya K, Tokunaga M, Makuuchi R, Nishiwaki N, Omori H, Takagi W, Hirata F, Hikage M, Tanizawa Y, Bando E, Kawamura T, Terashima M. Early detection of nonperitoneal recurrence may contribute to survival benefit after curative gastrectomy for gastric cancer. *Gastric Cancer* 2017; 20: 141-149

### **Reviewer#3**

#### Comments to the Author

The manuscript no. 50185 entitled "Blood Parameters Score: a novel scoring system predicts the long-term outcomes in stage II-III gastric cancer patients" has demonstrated the new prognostic indicator for prediction the outcomes of gastric cancer patients. The authors have proposed to use BPM-score, which generated from the combination of 5 markers, as a poor prognostic indicator for gastric cancer. The article is scientific relevance with high quality. The analysis is good, using training set and validate set. However, a small point needs to be clarified:

Since some the markers used in this study, such as NLR and CA19-9, have been documented to be poor prognostic markers. To prove that measuring of multi-marker (as BPM score) has more benefits than using only one marker, the authors should compare the power of BPM-score in prognostic prediction of gastric cancer with each individual marker.

#### **Responses to the comments of Reviewer #3**

1. To prove that measuring of multi-marker (as BPM score) has more benefits than using only one marker, the authors should compare the power of BMP-score in prognostic prediction of gastric cancer with each individual marker.

Response: According to reviewer's suggestion, we compare the areas under-the-curve (AUC) values using ROC analysis in the entire cohort. The BPM score exhibited a higher prognostic accuracy (0.680) than each individual marker, including albumin (0.640,  $P < 0.001$ ), LMR (0.580,  $P < 0.001$ ), NLR (0.546,  $P < 0.001$ ), CEA (0.578,  $P < 0.001$ ), and CA 19-9 (0.565,  $P < 0.001$ ). We have added the corresponding contents to the RESULTS section.

In conclusion, we have checked the manuscript and revised it according to all the comments. Revisions in the text are shown using red color for additions, and strikethrough font for deletions. We submit here the revised manuscript as well as a list of changes. If you have any question about this manuscript, please don't hesitate to let me know.

Sincerely yours,

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