

Dear editors and reviewers,

I feel very honorable that you could give comments on our manuscript and we have opportunity to further improve our manuscript. We have tried our best to revise our manuscript point-by-point in yellow. My co-authors and I will feel very appreciated if we could get the chance to further revise once our manuscript is not eligible. Thank you very much.

Your sincerely,

Hai-Tao Zhao

Email: zhaoh@pumch.cn

Reviewer #1:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: This is an excellent study of the epigenetic heterogeneity of gastric cancer. The study is well designed and the results are interesting. I have no specific comments.

Answers to reviewer 1: We sincerely appreciate your valuable remarks and thank you for your affirmation of our article.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: Thank you very much for asking me to review this manuscript by Bian et al. This is the observational study to identify the specific DNA methylation sites that influence the prognosis of GC patients and explore the prognostic value of a model based on subtypes of DNA methylation. The result of the study is of interest and may help improve outcome prediction, and facilitate precision therapy for

patients with GC. Overall, this study was well conducted with good methodology and intelligible English. The number of participants in the study is large enough. Furthermore, minor comment that I would like to propose: 1. Title: Proper and cover all the core result from the study. 2. Abstract: Address all of the important component from the study. However, please provide a brief introduction to the background section. 3. Key words: could cover this study. 4. Introduction: Describe the overall basic knowledge for this study. Moreover, the aim of the study is clear. 5. Method: The present study is methodologically well conducted. 6. Results: The result of this study is of interest. 7. Discussion: The manuscript clearly interprets the finding adequately and appropriately. In addition, the manuscript could highlight the key points clearly. The previous significant paper involved were included in the discussion, I suggest discussing more in this aspect in the discussion part. 8. Illustrations and tables: I congratulate the authors for the captions to the figures very explicative and complete.

Answers to reviewer 2: We deeply thank you for taking the time to review our manuscript and gave us the chance to revise our manuscript. As you mentioned in 2nd comment, we have added a brief background section in the abstract. As you mentioned in the 7th comment, we have followed your advice and carefully modified the text again to better describe our results in the discussion section. These changes were highlighted in yellow in the revised manuscript. We sincerely hope to hear from you in case of any further improvement of our manuscript.

Reviewer #3:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: I have read with great interest the manuscript entitled "A signature based on molecular subtypes of DNA methylation predicts overall survival in gastric cancer". The article is well written, and the findings are well detailed. Research is well conducted, and statistics is appropriate. The message of the manuscript supported

by the results – The high-risk group showed a markedly poor prognosis compared to the low-risk group in both the training and test datasets – is of great impact for the readers. This work may improve Clinicians' understanding of the epigenetic landscape of gastric cancer and facilitate precision medicine for these patients. Specific comments: Please shorten the introduction. Please be consistent with the second paragraph of the introduction. Please contextualize recently study results with those already available, in the discussion. Please check some of the references.

Answers to reviewer 3: Thank you very much for your valuable comments and suggestions. We have shortened our introduction in the revised manuscript according to your suggestion. We also rewritten the second paragraph of the introduction; we modified the discussion according to your advice to contextualize recently study results with those already available. These changes were highlighted in yellow in the revised manuscript. Finally, we carefully edited the references with the help of Auto-Analyser in the submitting system to meet the journal's standards.

Reviewer #4:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: GC ranks as the third leading cause of cancer-related death worldwide. Epigenetic alterations contribute to tumor heterogeneity in early stages. In this study, to address the epigenetic heterogeneity of gastric cancer, three subgroups based on DNA methylation were identified and each subtype was associated with distinct survival and clinical features. A signature based on molecular subtypes of DNA methylation was built to predict the survival of gastric cancer patients and showed good performance. The manuscript is well researched and well written, and may improve our understanding of the epigenetic landscape of gastric cancer and facilitate precision medicine for these patients. I have only a minor point to discuss. I would suggest authors add a flow chart to show the process of case inclusion and exclusion more clearly.

Moreover, please check the paragraph 2 in Page 5, the word in the fourth line " imputed" should be corrected with "impute". I recommend that the manuscript can be published after a minor editing. Sincerely

Answers to reviewer 4: Your advice is very important for the integrity of our study and we really thank you for your instructive opinion. A flow chart has been added in the revised manuscript to illustrate the process of the study. In the revised manuscript, we have corrected the word "imputed" with "impute".