Peer Review File

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Reviewer A

Comment 1: Did the authors consider patient treatment data (chemotherapy/radiotherapy) as a factor in the modelling? i.e., treatment naïve vs post treatment recurring breast tumour samples. Was there a difference in the identified HOTAIR-miR-130a-3p-HMGB3 axis in pre- vs post treatment patient samples? How can the proposed ceRNA play a role in treatment naïve vs post-treatment tumours?
Reply 1: Thank you for your question. There could be several reasons why we did not observe any significant differences in the identified HOTAIR-miR-130a-3p-HMGB3 axis between treatment-naive and post-treatment recurring breast tumor samples in our study. One possibility is that the sample size of our study was not large enough to detect subtle differences between the two groups. In this study, 80 samples were collected after radiation therapy, 108 samples were collected before radiation therapy, and the remaining samples did not have any information available. Another possibility is that the HOTAIR-miR-130a-3p-HMGB3 axis is not significantly affected by chemotherapy or radiotherapy in breast cancer patients, and that other factors may play a more important role in treatment response and recurrence. It is also possible that the timing of the post-treatment samples in our study was not optimal for detecting differences in the HOTAIR-miR-130a-3p-HMGB3 axis. The expression levels of these molecules may have already returned to baseline levels by the time the post-treatment samples were collected. Further studies with larger sample sizes and more detailed treatment histories may be needed to fully understand the role of the HOTAIR-miR-130a-3p-HMGB3 axis in breast cancer treatment response and recurrence.

Comment 2: Some datasets on TCGA have additional Reverse Phase Protein Array (RPPA) data providing a protein signature. Was RPPA data available for any of the patient datasets used in this study? How do you propose protein array data be incorporated in the identification of a prognostic biomarker?
Reply 2: We searched the TCGA RPPA Data (https://api.gdc.cancer.gov/v0/data/c3802b58-a2bf-41dc-8a67-99e8610a1e82), but found no information regarding the protein-coding gene HMGB3. As a result, we were unable to use the RPPA data for identification purposes.

Minor points

Comment 1: Please fix - 'hemotherapy' to 'chemotherapy' in Line 59 of the Introduction.
Reply 1: We have modified our text as advised. (see Page 2, line 59)

Comment 2: Please elaborate and add references to point made in Line 86-87 of Introduction. The sentence is vague.
Reply2: We have made more appropriate edits and citations for the vague content in this section. (see Page 3,line 86-90)

Comment 3: How do the authors propose to functionally test the findings of this study? What in vitro/in vivo models do the authors propose to use to study the ceRNA network? Authors

should elaborate in the Discussion section.
Reply3: We appreciate the reviewer's important question regarding the functional validation of our findings. As the role of long non-coding RNA (lncRNA) in cancer development is complex, functional validation is essential to demonstrate the biological significance of our results. We have added relevant content in the Discussion section. (see Page 14,line 444-457)

Comment 4: The blue spots representing lncRNAs in Fig 4 can be made brighter. It is quite hard to see, as there are very few of them the network modelling.
Reply4: We have increased the brightness of the blue spots in Fig 4. (See figure4-ceRNA - revised)

Reviewer B

Comment 1: This study is based on bioinformatics analysis. It is recommended to increase in vivo and in vitro experimental studies, which may be more meaningful.

Reply 1: We are conducting in vivo and in vitro experimental studies, and the experimental data are still being sorted out.

Comment 2:What is the correlation between DNA methylation and gene transcription in the pathogenesis of breast cancer? It is recommended to add relevant contents.

Reply2：DNA methylation modification is a hot research topic in epigenetics. Its involved in regulating gene expression, gene silencing, DNA damage repair, and cancer, and other important biological processes, gene methylation is mainly in the areas rich in GC base sequence of the CpG, gene under the action of the corresponding methylation transferase regulate the expression of cancer gene, oncogene and DNA damage repair, etc.

Changes in the text: we have modified our text as advised (see Page 12, line 378-383)

Comment 3:What is the biological significance of the HOTAIR-miR-130a-3p-HMGB3 axis in the proliferation of breast cancer cells and the synthesis of genetic material? It is suggested to add relevant contents.

Reply3：According to the PubMed database, records about the interaction of HMGB3 and miR-130a-3p in cancer are not available.We hypothesize that hypomethylation may upregulate the expression of HOTAIR and HMGB3.We speculate that LncRNA HOTAIR promotes the proliferation and invasion/metastasis of breast cancer (BC) cells by targeting the miR-130a-3p-HMGB3 axis.

Changes in the text: we have modified our text as advised (see Page 13, line 429-432)

Comment 4:The introduction part of this paper is not comprehensive enough, and the similar papers have not been cited, such as “Competing endogenous RNA network analysis reveals pivotal ceRNAs in bladder urothelial carcinoma, PMID: 33718081”, “Integrative analysis of mRNA, miRNA and lncRNA profiles reveals the commonness between bladder cancer and breast cancer, PMID: 35117452”. It is recommended to quote this article.

Reply 4：We have modified our text as advised(see Page 3， line 92-97).

Comment 5:What is the greatest advantage of the prognostic risk model in this study? What is the biggest problem we are facing? It is suggested to add relevant content to the discussion.
Reply 5: The greatest advantage of the prognostic risk model in this study is that this is the first study to identify, via public databases and modeling, the HOTAIR-miR-130a-3p-HMGB3 axis as a prognosis-related biomarker. This axis may be a potential prognostic biomarker, providing a new research direction for the prognosis research of breast cancer. At the same time, the model in this study can also be used as a reference for screening other tumor prognostic biomarkers.The biggest problem is the lack of experimental verification in vivo and in vitro.. Furthermore, the molecular mechanism underlying the upregulated expression of HOTAIR and HMGB3 was not fully accessed, we need additional experiments to further verify these mechanisms.
Changes in the text: we have modified our text as advised (see Page 13, line 432-450)

Comment 6:It may be more meaningful to add functional research on key ceRNAs.
Reply 6:We need to conduct in vivo and in vitro experiments to study the effect of HOTAIR miR-130a-3p-HMGB3 axis on the proliferation, apoptosis and migration of breast cancer cells.

Comment 7:How to provide candidate targets for the treatment of breast cancer based on the results of this study? It is recommended to include relevant descriptions in the discussion.
Reply 7: In the subsequent experiment, we should further explore and verify the expression of selected prognostic markers in cancer and its predictive role on survival and prognosis of patients by combining with immunohistochemistry, Western blot, cell function and other tests. This may provide candidate targets for the treatment of breast cancer patients, thereby reducing the mortality rate and improving the prognosis of patients.
Changes in the text: we have modified our text as advised (see Page 14, line 452-457)

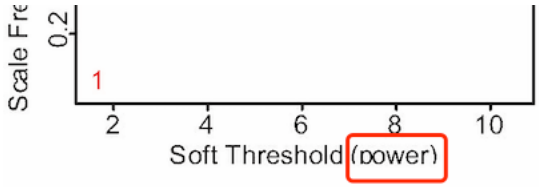
Reviewer C

Comment 1. Reporting Checklist
I didn't find the related information in the main text, please check. If it is not applicable, please fill with N/A.

Other information					
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	Page 11/Line 360-364	Data Availability Statement/Paragraph 1

Reply 2: We have filled with N/A here.

Comment 2. Figure 2
The word "power" is not complete, please revise.



Reply 3: We have revised the word“power”.See “figure2-WGCNA-revised”