Peer Review File

-More backgrounds and interpretations are required in the introduction and discussion, especially the main and novel findings from this study.

Reply: Thank you for your insightful comments and suggestions. We appreciate the opportunity to enhance our manuscript and agree that providing more background and interpretation would significantly improve the paper. We have added relevant content.

Changes in text: "By clarifying HOX-immunological links, ... EC cases" (see Page 4 lines 105-107)

-Detailed description of all method sections is required.

Reply: Thank you for your constructive feedback regarding the methods section of our manuscript. We have added relevant content.

Changes in text:"In our analysis, ... HOX gene expression profiles."(see Page 5 lines 135-139) and "Kaplan-Meier survival ...HOX genes."(see Page 5 lines 142-144)

-what are the novelty, limitations, and perspectives of this work? the discussion should include these.

Reply: Thank you for your insightful comments and suggestions. We have added relevant content.

Changes in text: "Key novelty is the multi-omics profiling of HOX dysregulation in EC. ... immunotherapy opportunities."(see Page 11 lines 330-335)

-please merely don't heap up the data, more comparison and interpretation.

Reply: Thank you for your insightful comments and suggestions. We have added relevant content.

Changes in text:"Integrating HOX dysregulation ... heterogeneity and help improve subclass-directed management."(see Page 10 lines 300-302)

-could the authors provide more solid data to strengthen the conclusion of this work?

Reply: Thank you for your suggestion to provide more solid data. We understand the importance of robust data in supporting our conclusions. In our study, we utilized extensive data from comprehensive databases, ensuring a broad and representative sample size. Our findings are based on these large-scale datasets, which we believe lend substantial weight and generalizability to our conclusions.

Changes in text: None.

-Some previous studies have used similar methods, I think it will benefit the reader if the authors could include the following references, which would provide readers with a more complete understanding of the whole study like PMID: 35887651.

Reply: Thank you for suggesting the inclusion of additional references to enrich our study. In accordance with your recommendation, we have incorporated the cited literature, including the

study with PMID: 35887651, into our manuscript. This addition provides a more comprehensive context and supports the relevance of our methodology in relation to previous research.

Changes in text: "Ni L, Tang C, Wang Y, et al. Construction of a miRNA-Based Nomogram Model to Predict the Prognosis of Endometrial Cancer. ..."(see Page 13 lines 393-394)

The paper titled "Comprehensive analysis of HOX family genes in endometrial cancer" is interesting. The study used bioinformatics techniques to clarify the potential role of HOXs from a multiomics perspective, and our findings provide a foundation for future investigations into the molecular mechanisms of HOXs in EC. However, there are several minor issues that if addressed would significantly improve the manuscript.

1) What is the patterns and prognostic roles of TMB and immune infiltration in endometrial cancer? It is recommended to add relevant content.

Reply: Thank you for your valuable suggestion to explore the patterns and prognostic roles of Tumor Mutational Burden (TMB) in endometrial cancer. In this study, we have focused extensively on immune infiltration, providing detailed insights into its implications. However, due to constraints in our dataset and the scope of our research, we were unable to include a comprehensive analysis of TMB. We recognize the importance of TMB in cancer research and hope to incorporate this aspect in future studies.

Changes in text: "Recent studies ... cancers (28,29), warranting investigations into similar links in EC."(see Page 11 lines 320-323)

2) What is the relationship of HOX family genes and immune microenvironment in endometrial cancer? It is recommended to add relevant content.

Reply: Thank you for your valuable suggestion to include information on the relationship between HOX family genes and the immune microenvironment in endometrial cancer. Following your recommendation, we have revised the manuscript to incorporate this aspect. This new section discusses the potential influence of HOX gene expression on immune cell infiltration and activity within the tumor microenvironment of endometrial cancer. We believe this addition provides a more comprehensive view of the subject and enhances the manuscript's contribution to our understanding of endometrial cancer.

Changes in text:"Our study demonstrated ... prognostic predictions and immunological research in EC"(see Page 10 lines 303-312)

3) How to use bioinformatics to mine the core genes of endometrial cancer and analyze the survival prognosis and the immune infiltration pattern of patients? It is recommended to add the content of the discussion.

Reply: Thank you for your valuable suggestion to discuss the use of bioinformatics in identifying core genes of endometrial cancer and analyzing survival prognosis and immune infiltration patterns. We have now included this discussion in our manuscript. This section elaborates on the methodologies and implications of our bioinformatics analysis, emphasizing its potential in advancing the understanding and treatment of endometrial cancer.

Changes in text: "Our study demonstrated ... prognostic predictions and immunological research in EC"(see Page 10 lines 303-312)

4) Figures 1,4,8,10 and S1 are not clear enough. It is recommended to provide clearer figures again.

Reply: Thank you for your valuable feedback regarding the clarity of Figures 1, 4, 8, and 10 in our manuscript. We appreciate your attention to detail and agree that enhancing the quality of these figures is essential for effectively conveying our research findings.

We have thoroughly reviewed your suggestions and are currently working on revising Figures 1, 4, 8, and 10 to ensure they meet the necessary standards of clarity and precision. Our aim is to provide clearer and more informative visuals that will better support the text and overall understanding of the manuscript.

Regarding Figure S1, we have carefully considered your recommendation and the content of the figure in relation to the overall manuscript. After a thorough evaluation, we have concluded that removing Figure S1 would be the most appropriate course of action, as it does not significantly impact the comprehension or integrity of the article. This decision is made to maintain the cohesiveness and quality of our work.

We are committed to ensuring that our manuscript meets the highest standards of academic excellence, and your insights have been instrumental in this process. We will submit the revised figures as soon as they are ready and look forward to your further guidance.

Changes in text: (see Page 15,18,21,23)

5) How can the results of this study help to develop therapeutic strategies against endometrial cancer? It is recommended to add relevant content.

Reply: Thank you for your suggestion to clarify how our study's results could inform therapeutic strategies against endometrial cancer. We have added a section that elaborates on this aspect.

Changes in text: "Critical future steps include validating HOXB9 ... open immunotherapy opportunities."(see Page 11 lines 333-335)
"Exploring the underpinning mechanisms can open new avenues to improve EC immunotherapy."(see Page 11 lines 339-340)

6) 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: Thank you for your suggestion to incorporate in vivo and in vitro experimental studies. Our current study is focused on a comprehensive bioinformatics analysis, which lays the groundwork for future experimental research. While we acknowledge the value of experimental validation, our present resources and study design were dedicated to leveraging extensive bioinformatic datasets. We hope to extend our findings through experimental studies in future work to further validate and complement our bioinformatics insights.

Changes in text: None.

7) The introduction part of this paper is not comprehensive enough, and the similar papers have not been cited, such as "Management of endometrial cancer: current insights and future directions, PMID: 35117370 ". It is recommended to quote this article.

Reply: Thank you for suggesting the inclusion of additional references to enrich our study. In accordance with your recommendation, we have incorporated the cited literature, including the study with PMID: 35117370, into our manuscript. This addition provides a more comprehensive context and supports the relevance of our methodology in relation to previous research.

Changes in text: "Laganà, Antonio Simone. "Management of endometrial cancer: current insights and future directions." ..."(see Page 13 lines 391-392)

8) It is recommended to add molecular typing of endometrial cancer and related research progress in the discussion.

Reply: We appreciate your suggestion to incorporate molecular typing of endometrial cancer and its research progress into our discussion. In line with your recommendation, we have added relevant content.

Changes in text: "Importantly, ... subclass-directed management."(see Page 9 lines 279-284)

"Integrating HOX ... subclass-directed management."(see Page 10 lines 300-302)

Reviewer C

1. Please check to see if more than references (>1) should be cited in the following sentences, as 'studies' are used.

   Previous **studies** *have shown that HOXA5 is critically involved in the proliferation, differentiation, and apoptosis of cancer cells (12).*

Reply 6: Thank you for your valuable suggestions regarding our manuscript. In accordance with your recommendations, we have added the pertinent reference to Ding, Fengqin et al.'s study, "HOXA5 Is Recognized as a Prognostic-Related Biomarker and Promotes Glioma Progression Through Affecting Cell Cycle," published in Frontiers in Oncology in 2021. This addition enriches our discussion on the role of HOXA5 in cancer cell proliferation, differentiation, and apoptosis, and aligns with the latest research in the field.

Changes in the text: We have modified our text as advised.(see Page 13, Lines 397-399).

   Recent **studies** *also indicate potential associations between specific HOX genes with microsatellite status and immunotherapy responses across cancers [26], warranting investigations into similar links in EC.*

Reply: Thank you for your insightful suggestions concerning our manuscript. In response to your recommendation, we have incorporated the relevant study by Qi, Lina et al., titled "The Effects of Differentially-Expressed Homeobox Family Genes on the Prognosis and HOXC6 on Immune Microenvironment Orchestration in Colorectal Cancer," published in Frontiers in Immunology in 2021. This addition addresses the potential associations between specific HOX genes, microsatellite status, and immunotherapy responses in cancers, further emphasizing the importance of exploring these links in endometrial cancer (EC).

Changes in the text: We have modified our text as advised. (see Page 14, Lines 432-434).

2. Please confirm if 'NA' in Table 1 means not available. If yes, it is suggested to clarify the reasons at the end of the table.

Reply: Thank you for your attention to the details in our manuscript. Regarding the notation 'NA, not applicable,' used in certain sections, it actually indicates instances where information is missing or was not collected.

Changes in the text: We have modified our text as advised.(see Page 15, Line 443).

3. Please check to see if any description should be added to Figure 1A. Please also check Figure 7A and 9C
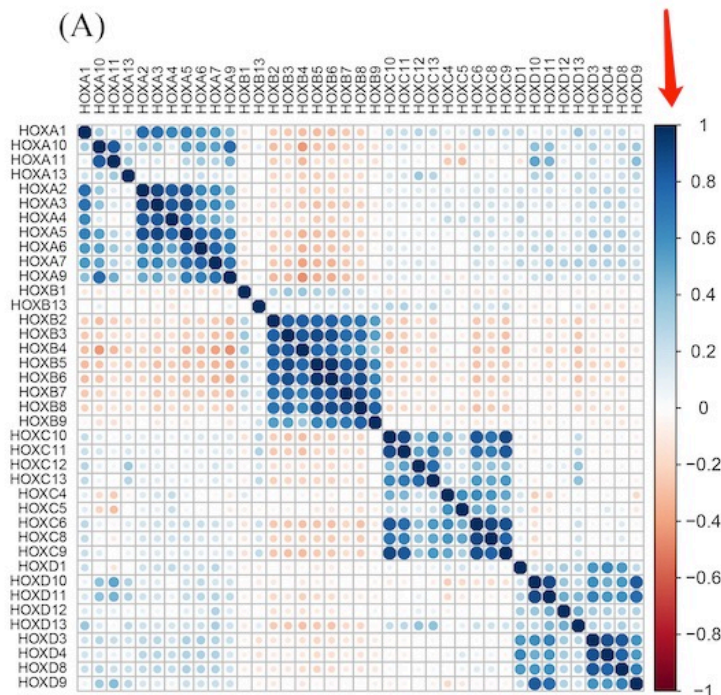
Reply: Thank you for pointing out the need for clearer descriptions in Figures 1A, 7A, and 9C/D of our manuscript. We have reviewed these figures and would like to provide the following clarifications:
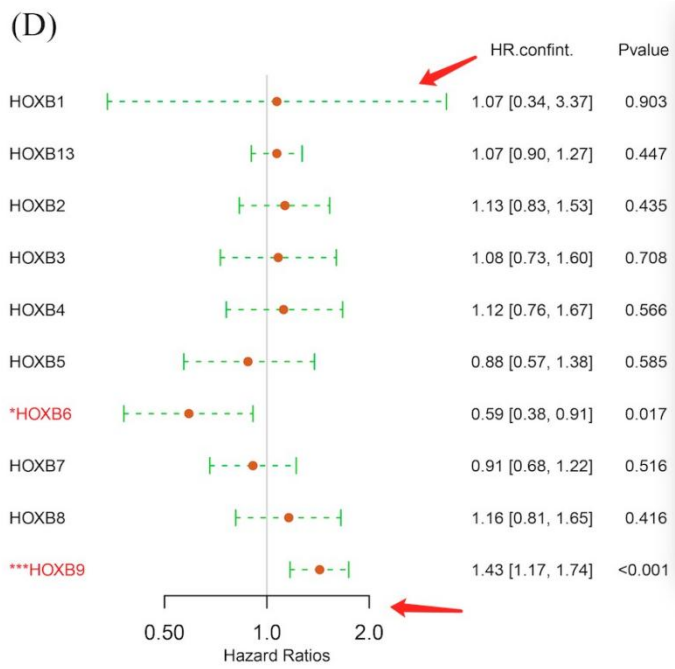
In Figure 1A, the color blue indicates a positive correlation, while red indicates a negative correlation. The intensity of the color represents the strength of the correlation, with deeper shades indicating stronger correlations.

Changes in the text: We have modified our text as advised. (see Page 15, Lines 446-447).

In Figures 7A and 9C. Here, blue signifies a negative correlation, and red represents a positive correlation. Again, the depth of the color correlates with the strength of the association, where deeper colors denote stronger correlations.

Changes in the text: We have modified our text as advised.(see Page 20, Line 480 and see Page 22, Lines 496-497).

4. Please extend the x-axis in Figure 4D. Please also check Figure 4E and 4F.

(D)

	HR.confint.	Pvalue
HOXB1	1.07 [0.34, 3.37]	0.903
HOXB13	1.07 [0.90, 1.27]	0.447
HOXB2	1.13 [0.83, 1.53]	0.435
HOXB3	1.08 [0.73, 1.60]	0.708
HOXB4	1.12 [0.76, 1.67]	0.566
HOXB5	0.88 [0.57, 1.38]	0.585
*HOXB6	0.59 [0.38, 0.91]	0.017
HOXB7	0.91 [0.68, 1.22]	0.516
HOXB8	1.16 [0.81, 1.65]	0.416
***HOXB9	1.43 [1.17, 1.74]	<0.001

Hazard Ratios: 0.50 1.0 2.0

Reply: Thank you for your suggestion to adjust the x-axis in Figure 4D of our manuscript. We have carefully reviewed Figures 4D, 4E, and 4F and have made the necessary modifications as per your recommendation.

Changes in the text: We have modified our figures as advised.(see Page 18, Line 463).