Peer Review File

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In this manuscript, the authors conducted retrospective analyses of existing data to examine the prognostic and diagnostic values of CIAPIN1 expression in invasive breast cancers. Several different data analyses were performed on the publically available data sets from the sources such as TCGA. The study was done comprehensively, which resulted in a large amount of information to characterize the expression of this gene in breast cancer in relation to the disease types and patient survival. Such information may be useful for the audience, especially for the breast cancer research field. However, the authors' claim for the potential value of CIAPIN1 as a biomarker for identifying certain types of breast cancer is not convincing.

Comment 1: For instance, the authors state that CIAPIN1 is significantly overexpressed in basal-like carcinomas. However, the fold difference in the expression levels is not remarkably large compared with the other breast cancer types, albeit the statistical significance (Fig. 3J). It is unlikely that this level of difference is enough for practical use in diagnostic or prognostic evaluations.

Reply 1: We thank you for reminding us this important point. We analyzed the difference of expression of CIAPIN1 in different types of invasive breast cancer through network database. Although the results obtained had statistical differences, the folding differences in expression levels were not significant and the results were not convincing. After in-depth discussion, our team unanimously agrees with your suggestions. We have decided to remove the corresponding result descriptions and figures, and revise and adjust this part of the content again to improve the overall quality of the manuscript. We have revised the text to address your concerns and hope that it is now clearer.

Changes in the text: we have modified our text as advised (see Page 10, line 173-180).

Comment 2: Page 10, line 170 - 177 Likewise, many of the data sets shown in Fig. 3A-I demonstrate statistically significant differences between the groups. However, there is little fold change between them, and it is unclear if such small changes represent any meaningful difference in the disease characteristics. The study largely lacks thorough evaluations of this aspect.

Reply 2: We thank you for your careful reading of our paper and providing us some keen scientific insight. We analyzed the difference of the expression of CIAPIN1 in different subgroups of invasive breast cancer through the network database. Although the results obtained had statistical differences, the folding differences in expression levels were not significant and the results were not convincing. After in-depth discussion, our team unanimously agrees with your suggestions. We have decided to remove the corresponding result descriptions and figures, and revise and adjust this part of the content again to improve the overall quality of the manuscript. We feel sorry for causing you unnecessary troubles in reviewing, we hope that the revised version may

meet your requirements.
Changes in the text: we have modified our text as advised (see Page 10, line 173-180).

Comment 3: This study provides a large amount of information about CIAPIN1 in breast cancer; however, it is unclear how any of this information is beneficial or how it will be used for clinical purposes.
Reply 3: We thank you for your careful reading of our paper and providing us some keen scientific insight. CIAPIN1 was discovered by Shibayama H et al. in 2004. Currently, only 86 articles can be retrieved through the keyword" CIAPIN1; cyclokine-induced apoptosis inhibitor 1 "(as of March 25, 2023). There are few studies on CIAPIN1 in tumors. At present, the research on CIAPIN1 in breast cancer is only in the aspect of multidrug resistance. Through TCGA and other online databases, we found that the expression of CIAPIN1 mRNA and protein was up-regulated in invasive breast cancer. Furthermore, survival analysis showed that invasive breast cancer patients with high expression of CIAPIN1 had poor prognosis. ROC curve shows that CIAPIN1 has certain accuracy in the diagnosis of invasive breast cancer. The nomograph model showed moderate accuracy in predicting OS in IBC patients for 1, 3, and 5 years. The expression level of CIAPIN1 is positively correlated with the expression of multiple key tumor immune escape related target molecules such as TP53, CTLA-4, PD-1, and TIGIT, suggesting that CIAPIN1 may play a negative regulatory role in tumor immunity. At the same time, the expression of CIAPIN1 was positively correlated with the level of Th2 cells, Th1 cells, regulatory T cells, macrophages and other immune cells in invasive breast cancer. CIAPIN1 may play a role in the tumor immune response of invasive breast cancer. By analyzing the data of invasive breast cancer in the public database of the network, our research preliminarily analyzed and discussed the expression, prognosis and diagnostic value of CIAPIN1 in invasive breast cancer. There has been no relevant literature on this aspect before, and our research has certain novelty. Next, we will validate the conclusions through tissue samples, cells, and animal models, and continue to deepen our exploration of this research direction. Thank you again for your valuable suggestion.
Changes in the text: we have modified our text as advised (see revision manuscript).

Comment 4: Fonts are too small in many figures. Especially those figures directly copied/pasted from TCGA or other public data sources.
Reply 4: We thank you for your careful reading of our paper and providing us some keen scientific insight. According to your suggestion, we have appropriately adjusted the font size in some figures without changing the authenticity of the results, making the figures content easier to read and understand. We feel sorry for causing you unnecessary troubles in reviewing, we hope that the revised version may meet your requirements.
Changes in the text: we have modified our figures as advised (see Figure 1-10).

Comment 5: Figure 1A needs definitions of the abbreviations for cancer types.
Reply 5: We thank you for reminding us this important point. We have added the

acronyms and full names of cancer types shown in Figure 1A for the convenience of readers.
Changes in the text: we added cancer acronyms as advised. (see Page 20, line 385-397).

Comment 6: Figure 2 needs to clearly indicate which ones are cancer tissues and which ones are normal tissues.
Reply 6: We added labels in Figure 2 to distinguish invasive breast cancer tissue from normal tissue. We feel sorry for causing you unnecessary troubles in reviewing, we hope that the revised version may meet your requirements.
Changes in the text: see Figure 2.

Comment 7: In the text, the authors should explain the immune subtypes indicated in Figure 3.
Reply 7: We thank you for reminding us this important point. We have deleted this section of content and figure 3.
Changes in the text: none.

Comment 8: Page 15, line 274 – 283 This paragraph is an introduction to CIAPIN1, and it should be moved to the Introduction.
Reply 8: Thank you very much for this valuable suggestion. After careful discussion, we agree that your suggestions are very beneficial to improving the quality of our manuscripts. We have appropriately combined this paragraph with the introduction to CIAPIN1 in the Introduction to increase the readability of the manuscript.
Changes in the text: we have modified our text as advised (see Page 5, line 59-73).

Comment 9: The authors should avoid the use of many undefined abbreviations throughout the manuscript (e.g. STAD, CHOL, OC, IBC, LIHC, etc.).
Reply 9: Your suggestions are very helpful in improving the quality of our manuscripts. We replaced undefined abbreviations in the manuscript with the full name of cancer. At the same time, we have also added the acronyms and full names of cancer shown in Figure 1A for the convenience of readers.
Changes in the text: we have modified our text as advised (see Page 9, line 163; Page 14-16, line 272-298).

Comment 10: The manuscript needs to be edited by a professional English writer.
Reply 10: Thank you very much for this valuable suggestion. Our manuscript has been edited and polished by a professional language polishing company, and English professionals have been consulted and revised for grammar and language issues in the manuscript, with a view to meeting the standards of publication. Thank you again for your valuable suggestion.
Changes in the text: we have modified our text as advised (see revision manuscript).