We would like to thank the Editor and Reviewers for their positive and constructive comments, which were valuable and helpful for improving this paper. Our team has gone carefully through all the comments, addressed all the questions, and provided point-by-point responses below.

Science editor:

This study designed a strategy to integrate multimodal data and investigated whether iCEMIGE improves risk stratification of breast cancer patients. The topic of this study is novel and innovative which may provide some new information. The paper is well organized, however, there are some concerns. Please compare the new strategy with other methods, which more accurate? Make a discussion about it. Please add more references since the asked reference number of basic research is 30 at least.

Language Quality: Grade A (Priority publishing)
Scientific Quality: Grade B (Very good)
Respond: We thank the science editor for the positive comments. iCEMIGE is the first framework integrating cell-morphometrics, microbiome, and gene biomarker signatures for risk stratification in breast cancer. Comparisons of iCEMIGE with a single modal biomarker (i.e., MAPS, CMPS, and GEPS) demonstrated significantly improved accuracy of prognosis prediction (Figure 3 and Supplementary Figure 2). In addition, we have also demonstrated that iCEMIGE is significantly superior in predicting overall and progression-free survival compared to the PAM50-based molecular subtype (Figure 6A and Supplementary Figure 4A), which is one of FDA approved biomarkers and is currently used in clinical practice. All these comparative results indicate that multimodal integration (iCEMIGE) can more accurately predict the prognostic risk of breast cancer patients, consistent with the previous perspective [1]. We extended the discussions and added more references (now total 32 references in the revised version).

1. Boehm KM, Khosravi P, Vanguri R, Gao J, Shah SP: **Harnessing multimodal data integration to advance precision oncology**. *Nat Rev Cancer* 2022, **22**(2):114-126.

Reviewer #1:

Scientific Quality: Grade B (Very good)
Language Quality: Grade A (Priority publishing)
Conclusion: Minor revision

Respond: We thank the reviewer for the positive comments regarding our manuscript.

Specific Comments to Authors:

1. The topic selection is novel and innovative.
   Respond: We thank the reviewer for the positive comments about our manuscript.

2. The content is substantial, the pictures are rich, and the results are more reliable.
   Respond: We thank the reviewer for the positive comments concerning our manuscript.

3. Can the three indicators observed in the article (CEll-morphometrics, MIcrobiome, and GEne biomarker signatures) be explained.
   Respond: We thank the reviewer for this comment. Representative examples of CMBs have been provided in Supplementary Figure 1 in our original submission, which characterizes the cellular level's heterogeneity and their surrounding microenvironments. The gene and microbiome signatures are involved in the pathways that play a critical role in cancer development.

4. Whether it can be combined with the molecular typing of breast cancer for further hierarchical analysis. The introduction of molecular typing of breast cancer is the basis for its diagnosis and treatment in breast cancer.
   Respond: We thank the reviewer for this comment. Our algorithm is generically designed to incorporate reorientations from different modalities, and as a result, it is straightforward to include molecular subtypes. However, since molecular subtypes did not show any significant association with prognosis when we included cell-morphometrics biomarkers (Figure 2C), so we included molecular subtyping as part of iCEMIGE. In addition, we also demonstrated that molecular subtypes did not show any significant association with OS and PFS when we included iCEMIGE in the model (Figure 6A and Supplementary Figure 4A).

Reviewer #2:
Scientific Quality: Grade A (Excellent)
Language Quality: Grade A (Priority publishing)
Conclusion: Accept (High priority)

Respond: We thank the reviewer for the positive comments regarding our manuscript.

Specific Comments to Authors:
1. "We designed a strategy to integrate multimodal data and investigated whether iCEMIGE improves risk stratification of breast cancer (BC) patients". maybe your team had compared with other methods, accuracy of the new strategy?
   Respond: We thank the reviewer for this comment. As we addressed the comments from Editor, all results from different comparisons indicate that multimodal integration (iCEMIGE) can more accurately predict the prognostic risk of breast cancer patients (details refer above).

2. Why said "MRI is more likely (without guarantee) to mine model-specific representation with independent clinical value via a step-wise mechanism", evidence?
   Respond: We thank the reviewer for this comment. Different from modal-specific raw data integration (MDI), the modal-specific representation integration (MRI) first optimizes the model-specific representation per outcome to ensure the clinical relevance of each derived representation (e.g., imaging biomarkers or gene biomarkers); then unifies their possibly independent clinical values to realize an integrated translational impact (e.g., diagnosis, and/or prognosis). As a result, MRI is more likely (without guarantee) to mine model-specific representation with independent clinical value via a stepwise mechanism. In contrast, MDI approaches function in a black-box fashion, where no modal-specific representation learning is involved.

3. If used in breast cancer patient, how long need each assessment?
   Respond: We thank the reviewer for this comment. The proposed algorithm works in speed and accuracy, which takes less than a minute per patient assessment once the data is ready. Furthermore, the major time-consuming component is data acquisition (e.g., sequencing and histology).

4. How much need each time? if you could use this method in patients, how many years your team would detect for each patent, maybe 5y, 10y?
   Respond: We thank the reviewer for this comment. We showed the nomogram model to predict 5-year and 10-year OS and PFS of breast cancer patients. The established nomogram model can be easily extended to any time (e.g., to a 20-year prediction) if we have enough patients with sufficient follow-up time in the training cohort.