Peer Review File

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Reviewer A

-All figure captions need to be elaborated more. For example, Fig. DEG between what group VS what group. Please clearly elaborate the data included in each figure in the caption.

Reply 1: Thanks for your valuable suggestions. According to the suggestions, we have made corresponding adjustments by red color in the caption of figures. In this study, the study group had bone metastasis in breast cancer (BRCA), while the control group had no bone metastasis in BRCA. Fig 1-2 showed the expression and results of functional enrichment analysis of differentially expressed genes (DEGs) in the bone metastasis group. Fig 3A-C showed the process of 28 key DEGs in the bone metastasis group identified and construction of score model.

Changes in the text: We have made corresponding adjustments by red color in the caption of Fig 1-3.

-Overall, it is still not clear how to use this model. Please explain more in the introduction and conclusion.

Reply 2: We appreciate the reviewer's feedback and academic rigor. In this study, we constructed a prognostic model based on 28 key DEGs in BRCA with bone metastasis. If the prognostic model is applied in clinical practice, your own queue will be used firstly for external validation (calculate risk points for each patient based on the formula) to determine the median risk score. Then, the subsequent enrolled patients are grouped based on this median risk score. According to the suggestions, we have made some modifications in the results and conclusion. We look forward the modifications to meeting your expectations.

Changes in the text: In the result, the calculation formula for risk score was listed (see Page 7, line 213-224). In the conclusion, we made some modification (see Page 13, line 441-444).

Reviewer B

The objective of the study is very interesting. However, the manuscript has many flaws. The main, and most important, flaw concerns the data included. The authors propose to develop predictive models for bone metastasis. However, there are no patients with metastasis in other sites in their analyses to test whether the model has good accuracy for bone metastasis compared to others.

Reply 3: We appreciate the reviewer's feedback and academic rigor. And, we totally agree with the opinions of reviewers. Due to limited data on patients with

metastases in other sites, relevant explorations were not conducted in this study. In our future research, we can further collect data and improve it.

In the Introduction, the first paragraph is extensive and combines many topics that should be covered in separate paragraphs, such as incidence, prognosis and models. Lines 44, from "Based on [...] to line 49, ending in "[...] the past decade" do not add useful information to the study. How important is the age of diagnosis for the objective of the study? Regarding the first part of survival, in the rest of line 49 to line 52 there is already enough and necessary for the objective.
Reply 4: Thank you for your careful review and academic rigor. According to your suggestion, we have made significant modifications to introduction. It highlights the threat of breast cancer to women's health, and why to build a prediction model based on bone metastasis in BRCA patients.
Changes in the text: We have made corresponding modifications by red color in the introduction (see Page 2, line 47- 52, 54-68, and Page 3, line 69- 82, 89-91).

Other articles, not only by Chen et al, show that the most common site of metastasis is the bones. Citing just one article on something so studied is very reductionist. Examples: DOI: 10.1186/s12885-019-6311-z; DOI: 10.1186/s13058-019-1201-5; PMID: 3420442.
Reply 5: Thank for your careful review and academic rigor again. According to your suggestion, we have modified our text as advised.
Changes in the text: We added some references according to the suggestions (see Page 2, line 62~65).

What is the relationship between the therapies of bone metastasis and the objective of the study, which is the development of predictive models for bone metastasis?
Reply 6: Thank for your careful review and your questions. The common sites of metastasis in BRCA patients include bone, lung, liver, and brain. Among the above metastatic sites, bone metastasis is most common, accounting for approximately 65%~75% of metastasis cases, with the 5-year overall survival rate being about 20%. Therefore, we want to construct a prognostic prediction model based on differentially expressing genes in bone metastases, which can provide a promising method for clinical decision-making and prognosis prediction for BRCA patients. Meanwhile, screening for prognostic biomarker genes and pathways in BRCA may provide potential therapeutic targets for future treatment.
Changes in the text: We have made corresponding modifications by red color in the conclusion (see Page 3, line 101- 104; Page 12, line 395- 397; Page 13, line 431–433, 440-444).

Regarding the methodology, what type of ROC analysis was performed? Time-dependent? It is not clear in the manuscript. Regarding AUC, the authors did not present confidence intervals.
Reply 7: Thank you for your good question. It is a time dependent ROC curve. The time dependent ROC curve produced by the SurvivalROC software package does not

have a confidence interval, only the ROC curve used to determine whether the patient is ill has a confidence interval. There is also no confidence interval in following references.

① A Robust Hypoxia Risk Score Predicts the Clinical Outcomes and Tumor Microenvironment Immune Characters in Bladder Cancer. doi: 10.3389/fimmu.2021.725223. eCollection 2021.

② Angiogenesis-related lncRNAs predict the prognosis signature of stomach adenocarcinomadoi: 10.1186/s12885-021-08987-y.

Still on methodology, in the corresponding section (subtopic Statistical Analysis), the authors do not mention several methodologies that appear throughout the manuscript. In addition to ROC analysis, logistic regression and nomograms. They do not mention how they tested proportionality in the models where this is necessary (except Kaplan-Meier for Cox regression). However, they do not mention how they tested proportionality for the continuous variable age, incorporated in the nomograms. Furthermore, in the nomograms the authors included T, N and M, which are the criteria for the stage, a variable that was also included, generating redundancy.

Reply 8: Thank you for your good question again. When constructing the prognostic model, we divided the training set and validation set based on a 4:1 ratio, which was not included in the nomogram and single factor analysis. Because nomograms are graphical prediction models and typically used to predict the probability of specific outcomes or events. Unlike traditional models, Nomogram is a prediction tool based on statistical analysis, without the need for training and validation set partitioning like other models. The Nomogram model is based on empirical formulas and statistical analysis of large sample data, and can provide personalized prediction results by inputting different prediction indicators. Because the risk score included in the Nomogram model has been validated in previous models, similar to the following literature, our Nomogram model did not divide the training and validation sets.

① A Robust Hypoxia Risk Score Predicts the Clinical Outcomes and Tumor Microenvironment Immune Characters in Bladder Cancer. doi: 10.3389/fimmu.2021.725223. eCollection 2021.

② Angiogenesis-related lncRNAs predict the prognosis signature of stomach adenocarcinomadoi: 10.1186/s12885-021-08987-y.

The genes should be presented in a table, and not in full, in the Results section. The current arrangement makes it difficult to read the article.

Reply 8: Thanks for your valuable suggestions. According to the suggestions, we have made corresponding modification in the revised version.

Changes in the text: We have made corresponding modification in the revised version (see Page 6, line 195-202).

The subtopic "Multi-omics analysis of clinical predictive value of the prognostic model for BRCA" contains information that should be in the Introduction section.
Reply 9: Thanks for your valuable suggestions again. According to the suggestions, we have made corresponding modification in the revised version.
Changes in the text: We have made corresponding modification in the revised version (see Page 3, line 101-104)

In the Discussion there is a recap of the methodology used. This is not appropriate.
Reply 10: Thank you for pointing this out. According to your suggestion, we have made significant modifications to discussion in the revised version.
Changes in the text: We have made corresponding modification in the revised version (see Page 10, line 331-344; Page 11, line 354-371; Page 12, 378-382, 398-413; Page 13, line 414-433.)