Peer Review File

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Reviewer A

Comment 1: The authors described in abstract, "ER-/PR+ metastatic breast cancer has similar clinicopathological characteristics, metastatic models, and prognostic characteristics with triple negative breast cancer (TNBC)". But the authors did not show the adequate findings in result in abstract. Please describe them in abstract adequately.

Reply 1: Thank you very much for your kind comments. We have added descriptions of clinicopathological characteristics, metastatic models, and prognostic characteristics about ER-/PR+ metastatic breast cancer in abstract based on your suggestions:

we have modified our text as advised (see Page 3, line 14-19): The ER-/PR+ subtype had the highest proportion of de novo metastatic breast cancer, and similar clinicopathological characteristics, prognosis with TNBC. Single PR positivity was an independent risk factor for CSS in multi- visceral metastasis subgroup comparing to TNBC. Meanwhile, no significant difference in OS or BCSS between ER-/PR+ and ER-/PR- patients in all breast cancer patients or in stage IV breast cancer patients.

Comment 2: In methods, results, tables, and figures, I was sometimes complicated whether the finding was about all the cases or stage 4 cases only. Please make them understandable more.

Reply 2: We appreciate so much for your sincere suggestion! In our results, we firstly shown the differences clinical and pathological characteristics between four subtype breast cancer (including all the case) in Table 1. The purpose is to find potential risk or benefit factors based on ER and PR status. The Table 2 shown the metastasis model in stage 4 cases, which also can be regarded as a subgroup analysis (including stage IV case) of Table 1. In the table 3, based on all case (M0 patients was a reference group), we explored the independent risk factors for bone metastasis and visceral metastasis by multivariate logistic regression. All included factors were from significant clinical factors in Table1.Table1-Table3 mainly prove the significant and indispensable role of ER and PR status for metastasis risk and sties (bone or visceral sites) in all cases, and explored other potential independent risk factors.

In Table 4, ER-PR+ and ER+/PR- status were explored a significant and independent role for cancer specific survival (CSS) in all patients, early-stage patients and IV stage patients respectively by multivariable logistic regression. Multivariable logistic regression model eliminated the confound factors to further ensured significant survival differences in KM curves.

In the Table 5, we focus on all single hormone receptor breast cancer cases (ER+/PR- and ER-/PR+) to explore potential beneficial clinical methods. And the survival could be promoted by chemotherapy in ER-/PR+ subtype.

Our mainly logic lines and purpose to explore the different clinical-pathological characteristics including metastasis mode between ER-/PR+ subtype and other subtype. And The prognosis value of ER-/PR+ was performed both in all case and stage IV subgroup.

We have added descriptions in methods and results about our analysis and findings as advised (see Page 10, line 7-8 and Page 13, line 6-7,18-22) to make them understandable more.

Comment 3: In table 3, please show number of patients in each factor in the first line. Although the authors showed number of patients in table 1, table 1 showed all the patient in stage 1 to 4 and table 3 showed stage 4 only.
Reply 3: We are very appreciative of your comments!
we have modified our text as advised (see Table3: page23 line 1): We have added the show number of patients in each factor in the first line based on your suggestion.

Reviewer B
Comment 1: Of the two subgroups of single hormone receptor positivity (ER+/PR- and ER-/PR+), the prognosis of ER+/PR- have been studied in multiple studies, so not innovative. It is more interesting on ER-/PR+ subgroup. It has a debate as to if ER-/PR+ biologically exists or just IHC staining artifact. With several papers, in particular Li et al. JAMA Network 2020, which analyzed SEER dataset, what are the new findings from the current paper?
Reply 1: We are very appreciative of your comments!
In our analysis, we only included the her-2 negative patients to exclude the influence of anti-her2 therapy.
Our new findings included that ER-/PR+ patients had the highest proportion of novo stage IV patients in all patients and had a similar metastasis pattern with TNBC patients. That is to say, the two groups of advanced patients tended to develop visceral metastasis, but not bone metastasis. Meanwhile, chemotherapy was found an independent protective factor for all ER-/PR+ patients.

Comment 2: As the clinical features, de novo metastatic patterns, and survival outcomes of ER-/PR+ and ER-/PR- are quite similar, could the small group of ER-/PR+ just be due to technical error in PR measurement and it is actually the triple negative breast cancer? The study actually did not show any different between ER-/PR+/HER2- and ER-/PR-/HER2-. It is unclear if ER-/PR+ patients could receive benefit from hormonal therapy as hormonal therapy data are not available from SEER
Reply 2: we are very appreciative of your comments! In our study, there was no significant difference in OS and CSS between ER-/PR+/HER2- and ER-/PR-/HER2-. In previous study, ER-/PR+ patients got better survival compared to TNBC may be beneficial from anti-her2 therapy. However, a study from Chinese Academy of Medical Sciences and Peking Union Medical College shown this group still benefit from adjuvant endocrine therapy of patients. In ER-/PR+/HER2-group, cases with adjuvant endocrine therapy had significantly better RFS. Although it is a small group, single PR status should be regarded an independent predictive factor for hormonal therapy.
(Refenence: Ying Fan, MD, Xiaoyan Ding, MD, Binghe Xu et.al Prognostic Significance of Single Progesterone Receptor Positivity: A Comparison Study of Estrogen Receptor Negative/Progesterone Receptor Positive/Her2 Negative Primary

Breast Cancer with Triple Negative Breast Cancer. Medicine, 2015)

Comment 3: Table 4 should also present the contrast between ER-/PR+ and ER-/PR- because that is the main results of this paper. The other contrasts (comparing with ER+/PR+) present known results in the literature.
Reply 3: We are very appreciative of your kind and professional suggestions!
We have modified our text as advised (see Table4: page24): We have added the contrast between ER-/PR+ and TNBC.

Comment 4: As both bone and visceral metastases are included in the logistic regression models of Table 3, it is unclear what is the reference group. If the focus on ER's or PR's influence on bone metastasis, single bone metastasis and bone + other metastasis should be combined into one group in the analysis.
Reply 4: We are very appreciative of your sincere comments and suggestions! The logistic regression models included all cases. The reference group is M0 patients. We also modified the including criterion and combined single bone metastasis and bone + another metastasis into one group. So, the bone metastasis risk means de novo single bone metastasis and bone + other metastasis comparing with stage I-III patients and Visceral Metastasis risk means de novo single and multi-visceral Metastasis comparing with stage I-III patients.
We also added descriptions in results as advised (seeTable3 and Page10: line14-19).

Minor comments:
Comment 5: Figure 2. the figure and its legend is not consistent.
Reply 5: We modified the figure legend.

Reviewer C
Comment 1: The introduction can include if there are any previous studies done with regarding to similar studies and what different can this study add to current knowledge? novelty to be highlighted in the article.
Reply 1: We are very appreciative of your sincere comments and suggestions! Previous similar studies had been shown in Page5 line10-13. Meanwhile, we added some description about the differences about our study. We have modified our text as advised (see Page6 line9-10).

Comment 2: Does it challenge existing paradigms?
Reply 2: We are very appreciative of your comments! The current guidelines don't include the ER-PR+ subtype and it was considered by some researchers a technical error in PR measurement, for a rather low ratio of such subtype and PR mechanism. In clinical work, it is difficult to ensure the predictive and prognosis value of single PR positive and therapy methods including the hormone therapy. So, we explored the metastasis model of ER-/PR+ patients and risk factors for cancer specific survival in such rare subtype. Although our results shown no significant differences in survival between ER-/PR+ and TNBC for a lack of adjuvant endocrine therapy in seer database.

A study from the Department of Medical Oncology, Cancer Hospital& Institute, Chinese Academy of Medical Sciences and Peking Union Medical College adjuvant endocrine therapy shown still benefit this group of patients. (In ER-/PR+/HER2-group, cases with adjuvant endocrine therapy had significantly better RFS.) The single PR status should be accepted and chemotherapy and adjuvant endocrine therapy considered. We have modified our text as advised (see Page18: line13-22)

Comment 3: What is the strength of the study?
Reply 3: We are very appreciative of your comments!
There were some strengths of the study.
Clinical-pathological characteristics of ER/PR+: ER-/PR+ patients had the highest proportion of novo stage IV patients in all patients.
Metastasis mode of ER+/PR- and ER-/PR+ subtype and influence on metastasis site from single PR status: ER-/PR+ patients prefer to visceral metastasis.
Influence on survival from single PR+ and PR-: ER-/PR+ patients had similar even worse survival compared to TNBC.
Risk and protective factors for all ER-/PR+ patients: Chemotherapy should be considered in ER-PR+ patients.
We have modified our text as advised (see Page 18) including adding descriptions strengths of the study.

Comment 4: The conclusion can be stronger if summarized what the findings mean in the "grand scheme of things"?
Reply 4: We are very appreciative of your comments! we have modified our text as advised (see Page18 line15-21 and Page19 line1-4) including adding descriptions strengths of the study.