WJCO Manuscript NO 53841: Response to the Reviewers' Comments

We thank the editor and reviewers for taking time from their busy schedules to provide a constructive critique that has helped lift our revised manuscript in both content and clarity.

We have highlighted the changes in the revised manuscript.

In detailed response to the **REVIEWER COMMENTS:**

REVIEWER #1:

We thank the reviewer for his/her comments that our paper was "well designed and discussed", with our conclusions "appropriate and rationale". Our detailed responses are as follows:

Specific Comments:

1. Please check the few spelling and grammatical error and typos in the text.

RESPONSE:
We apologise for grammatical errors and typos. We have done a thorough check to correct grammatical errors and typos.

REVIEWER #2:

We thank the review for his/her comments. We are grateful for the opportunity to address his/her concerns and the suggestions have helped elevate our study.

Our detailed responses are as follows:

Specific Comments:

1. The patients analyzed in the study were diagnosed as breast cancer and treated from 1985 to 2018. It needs to be confirmed that all histologies and immunostainings were reviewed. That is because ASCO-CAP guideline was changed a couple of times. The data needs to be carefully reviewed.

RESPONSE:

We have managed to review the pathological reports of all 864 of our patients included in the study. These included description of histological subtype and immunostainings. We acknowledge that the ASCO-CAP guideline has been revised over the years. As such, we have defined HER2+ Invasive Lobular Carcinoma (ILC) as "an immunohistochemistry (IHC) score of 3+ or an IHC score of 2+ with a HER2 to Chromosome 17 (HER2/CEP17) ratio $\geqslant$2.0 for samples after 1 January 2014 and HER2/CEP17 ratio $\geqslant$2.2 for samples before 1 January 2014 on fluorescence in situ hybridization (FISH) testing."

2. In addition, anti-HER2 therapy began around 2000. The authors described 54% patient received HER2-directed therapy. As the authors stated, this is reasonable since the number of patients from 1985 to 2000 and that from 2000 to 2018 may be approximately equal. However, the data on prognosis may be biased. The prognostic factor needs to be carefully reviewed. It is also plausible that the analysis separated into before 2000 and after 2000.

RESPONSE:
We thank the reviewer for highlighting this point. We have analysed the overall survival for patients diagnosed before and after 2000. There were 39 and 825 patients in the < 2000 and ≥ 2000 categories respectively. As only a small number of patients were diagnosed before the advent of anti-HER2 therapy and only one death occurred at 10th year in ⩽ 2000 category. Thus, segregating the data into these two subsets may not does not significantly affect the survival outcome in our overall cohort.

REVIEWER #3:

We thank the review for his/her comments. We are appreciative of the suggestions he/she made to improve the analytical value of our study.

Our detailed responses are as follows:

1. The authors should address more detailed clinical pathological parameters especially follow-up for all patients in “Materials and Methods”.

RESPONSE:
We thank the reviewer for making this suggestion. Under “Materials and Methods”, we have added in clinicopathological parameters as “Clinical variables included patient demographic factors such as age at diagnosis, gender, ethnicity, disease factors such as tumour side, size, grade, stage, nodal status, lymphovascular invasion, ER, PR and HER2 status, sites of recurrence, as well as treatment given such as chemotherapy, radiotherapy, surgery and anti-HER2 therapy.” (Page 5, Para 2, Lines 6-9)

2. The authors should reanalyze multivariate analysis after including the all clinicopathological parameter such as lymph-vascular invasion, lymph node metastasis etc.

RESPONSE:
While we had collected data on additional variables such as tumour side, nodal status, lymphovascular invasion and sites of recurrence, we were selective in the variables included in our multivariate analysis. Only variables with p-value < 0.03 in the univariate cox regression model were included in the multivariable model. Final multivariable model was selected after stepwise, forward and backward variable selection method. We have incorporated this part in the statistical analysis section of manuscript for better clarity. (Page 7, Para 2, Lines 6-11)

3. There are many small errors in this manuscript, for example, the title of journal in references is inconsistent.

RESPONSE:
Thank you very much for pointing this out. We have corrected these inconsistences in our revised manuscript and in the reference list below.

REVIEWER #4:

We thank the review for his/her comments that our manuscript is “very informative and well written”. We would be happy to revise the manuscript as per other comments to refine our study further.

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