Author’s response to reviews

Title: Association Between Delayed Initiation of Adjuvant CMF or Anthracycline-based Chemotherapy and Survival in Breast Cancer: A Systematic Review and Meta-analysis

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Author’s response to reviews: see over
Dear Senior Editor,

Please re-consider our manuscript "Association Between Delayed Initiation of Adjuvant CMF or Anthracycline-based Chemotherapy and Survival in Breast Cancer: A Systematic Review and Meta-analysis" (MS:6902514198943725) for publication in BMC Med. Thank you very much for reviewing our previous manuscript. We would also like to thank the reviewers for their thoughtful and constructive comments. According to the editor’s suggestions and the reviewers’ concerns, we have revised our manuscript and added new information where appropriate. We are pleased to resubmit our revised manuscript to you for further consideration.

Below, we include a point by point response to the reviewers’ concerns.

Reviewer’s comments:
Referee 1:
The authors state that only “high validity” studies are included in the meta-analysis, however, they include the study by Samur et al. (reference 4). It seems that this study has no adjustment and does not fulfil the inclusion criteria stated. Accordingly, I suggest that the study is excluded.

Our response:
We tried our best to increase the reliability of positive results and did not exclude the studies with negative outcome even though the results were not adjusted for other prognostic factors. As we have stated in the footnote of Table 1, although the study by Samur et al had an unadjusted HR, we did not exclude this study to increase the reliability of positive results of meta-analysis. Of note, the study by Samur et al is included in DFS analysis but not in OS analysis and does not change the main results of our meta-analysis. We have acknowledged the reason why we included the Samur’s study in the Results part.

Reviewer’s comments:
Totally 34,193 patients are included in the analysis. Because of heterogeneity the authors exclude the study by Cold et al. leaving 28,128 patients back in the final analysis. However, at least 19,383 of the patients are >65 years (57% of all patients; 69% of patients included in the final analysis) (inclusion criteria in Hershman (reference 6) and Nurgaliev (reference 20)). The median age for breast cancer diagnosis is 61 years. The authors need to comment/discuss the age distribution of the patient population, including potential impacts on the conclusion.

Our response
We appreciate the reviewer’s professional comments on the age distribution and its potential impacts on the on the conclusion. We have added the corresponding contents in the Discussion part.
Reviewers comments:
Minor comments:
Reference 14 is not mentioned in the manuscript?
Our response:
We have inserted the Reference 14 at the right place.

Reviewer’s comments:
Estrogen receptor status should be included in Table 1.
Our response:
Yes, we have revised it accordingly.

Reviewer’s comments:
Several typographical errors should be corrected.
Our response:
We have revised them accordingly.

Reviewer’s comments:
Referee 2:
1) It should be stressed that the meta-analysis examines a mixed patient population, in terms of nodal, hormone receptor and menopausal status. Though most of the included studies had performed adjustments for those factors, is the effect of AC delay on survival the same for patients with infiltrated lymph-nodes and those without, or for pre- and postmenopausal women?
Our response:
We agree with the reviewer that the meta-analysis examines a mixed patient population and the effect of AC delay on survival might be different for patients with different clinicopathological features. However, because of a lack of individual information of patients, it is currently difficult to perform sub-meta-analysis according to lymph node status or menopausal status, and our results reflect an overall effect. We have acknowledged this limitation in the Discussion part.

Reviewer’s comments:
2) In the Eligibility and validity of literature-based data section it is stated that “first, the relevant prognostic factors were adequately described between comparator groups; second, either the comparison groups were balanced for the relevant prognostic factors, or the reported results were adjusted for other prognostic factors”. However (Table 1), in the study by Samur et al. no adjustment for covariates had been made, and in the study by Kerbrat et al. the adjusted factors had not been reported. In the footnote of Table 1, the
authors state that "although this study (Samur et al) had an unadjusted HR, we did not exclude this study with negative outcome to increase the reliability of positive results of meta-analysis". It should be mentioned in the Results section.

Our response:
Yes, we agree with reviewer and have mentioned corresponding contents in the Results section. We did not exclude the study by Samur et al with an unadjusted HR since this study has a negative outcome and inclusion of it might increase the reliability of positive results of meta-analysis. Regarding the study by Kerbrat et al, the HRs had been adjusted although the factors for adjustment were not specified.

Reviewer’s comments:
3) In the studies by Hershman et al. and Nurgalieva et al. (Table 1), which were the AC regimens administered? Did any patients (and if yes, at which percentage) receive taxanes?

Our response:
Neither of these two studies has declared which AC regimens have been administered.

Reviewer’s comments:
4) It should be more clear which percentage of the whole patient population received CMF or anthracycline-based AC. Was there a different impact of AC delay on survival, in patients administered CMF vs. those treated with anthracycline-based AC?

Our response:
We admitted that understanding the percentage of the whole patient population received CMF or anthracycline-based AC would make sense. However, due to the limitation of original data of studies (most of them did not provide this information) our meta-analysis could not further analyze this issue. We have acknowledged this limitation in our Discussion. As well, we have modified the title of our paper and constricted the chemotherapy regimens in “CMF and anthracycline-based chemotherapy”.

Reviewer’s comments:
5) The studies cited in the Discussion (Buzdar et al, Shannon et al, Sanchez et al, Alkis et al, Altundag et al) were not included in the meta-analysis due to low validity. The specific reasons for the exclusion of those studies could be mentioned. For example, in the study by Shannon et al the analysis was adjusted for prognostic factors. Why was this study not considered of high validity and not included in the meta-analysis? The authors could make more clear the definition of high and low validity.

Our response:
Yes, we agree with reviewer that the specific reasons for the exclusion of those studies should have been included in the manuscript. We did not include the five studies since none
of them have reported sufficient data to calculate an adjusted and quantitative HR for meta-analysis. In the study by Shannon et al, although the Cox proportional hazards regression model was used and the analysis was adjusted for prognostic factors, the authors did not provide the HR estimates.

Reviewer’s comments:
Referee 3:
1. The authors should define their search period more clearly, instead of writing “The literature search was conducted before January-29 2013” they should state exactly which period from...to...was covered.
Our response:
Yes, we have revised it accordingly.

Reviewer’s comments:
2. The authors state that “When necessary, the corresponding author of the paper was contacted to retrieve additional information.” Please briefly state for which study additional information has been given by the original study authors and what kind of information.
Our response:
We have contacted Shannon (J Clin Oncol 2003;21:3792-3797), Sanchez (Breast Cancer Res Treat 2007;101:215-223) and Alkis (Med Oncol 2011;28:1255-1259) for more information about the HR and 95% CI of their outcomes. However, there was no reply (Alkis) or the original data were too old to retrieve (Shannon and Sanchez). We have deleted that sentence in the revised version.

Reviewer’s comments:
3. Please assess the quality of each study, even if you don’t use this information for the analysis which I agree has significant limitations but it is important information for the reader.
Our response:
According to the suggestion of reviewer, the study quality was assessed using the 9-star Newcastle-Ottawa Scale (The Newcastle-Ottawa Scale for assessing the quality of nonrandomized studies in meta-analyses. Ottawa, Canada: Dept of Epidemiology and Community Medicine, University of Ottawa. http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm. Accessible on March-1, 2013).

Comments from the editor:
As highlighted by referee 2, it is currently unclear whether your results can be extrapolated to the adjuvant chemotherapy regimens that are more in use in the clinic
today. Further consideration of your manuscript is based on whether your results are broadly clinically applicable; we would be grateful if you could emphasize the clinical relevance to other regimens in the Discussion section.

Our response:
Yes, we have discussed the limitation of our result and emphasize the clinical relevance to other regimens in the Discussion section.

Comments from the editor:
There are a small number of editorial changes that should be made to your manuscript, which I have listed below:

1. Please modify the title to modify the specific type of adjuvant chemotherapy that is being investigated

   Our response:
   Yes, we have revised our title according to your suggestion.

Comments from the editor:
2. As discussed above, please emphasize the broad clinical relevance in the Discussion section by explaining how the results can be extrapolated to other adjuvant chemotherapy regimens.

   Our response:
   Yes, we have revised it according to your suggestion. New information is added in the Discussion part.

Comments from the editor:
3. Authors' contributions: please include this section at the end of your manuscript. More information can be found at http://www.biomedcentral.com/bmcmed/authors/instructions/researcharticle#formatting-contributions

   Our response:
   Yes, we have revised our manuscript accordingly.

We hope that the editors as well as reviewers can satisfy our answers.
Thank you for your consideration.
Sincerely yours,

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