Author’s response to reviews

Title: Pathological profiles and clinical management challenges of breast cancer emerging in young women in Indonesia: a hospital-based study

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Author’s response to reviews:

Dear Editor,

Thank you very much for considering our manuscript BMWH-S-00501 “Pathological profiles and clinical management challenges of breast cancer emerging in young women in Indonesia: a hospital based study” for publication. We are very pleased about the overall positive evaluation of our manuscript (“fill a gap”, “subject of interest”, “shed a light”). We appreciate all comments raised by the reviewers which provide us an opportunity to improve our manuscript. We thank for the offer to resubmit our revised version addressing all reviewer comments and suggestions. A point by point-reply describing all changes made in detail is included. The changes in the revised text are highlighted in blue.
Corrections to Technical comments:

1. Include the email addresses for all authors on the title page.
   Done as requested, please see Page1

2. Please rename 'Introduction' heading to 'Background'.
   Done as requested, please see Page 4.

3. Please rename 'Material and Methods' heading to 'Methods'.
   Done as requested, please see Page 5.

4. Abbreviations.
   Done as requested, list of all abbreviations used in this manuscript has been included, please see page 13.

5. Please reformat your Declarations.
   Done as requested accordingly, please see page 14.

6. Please state clearly the role the funder(s) had in your study in the "funding" section of the declarations.
   Done as requested, please see page 14.

7. Co-author Darwito Darwito's initials and contributions are missing from the "authors' contributions"

   Initial of Darwito Darwito is ‘D’ that has been included in the Author’s contribution. Originally, he has only one name ‘Darwito’ and we use both as first and family names.

8. Please remove duplicate tables in your manuscript file.
   Done as requested.
Editor Comments:

REVIEWER 1:

# Major Revision: The analysis should compare patients <40 to the rest of the cohort. Tables should present HR and 95% CI.

Apologies for the confusion. Although we collected data for all breast cancer, this particular manuscript focuses on young breast cancer which has been associated with aggressive behavior and faces complex challenges in the clinical management including issues related to late presentation, adherence to treatment plan, and worse survival. Therefore we only analyzed women with breast cancer who were younger than 40 years. We have clarified this in the Methods as follows, ‘Of this population, 114 (11.4%) were 40 year-old or younger, thereby meeting the definition of young breast cancer and were included in the analysis.’

We have presented HR and 95% CI in the revised manuscript.

# Minor Revision:

1. Fertility concern, genetic risk and psychological need in the abstract but no data

2. Delete "is" from second sentence of paragraph 2 of the introduction "….annual mortality is over 500,000".

Done as suggested, please see Page 4 line 4.

3. Denominator to clarify "500,000" and "55,000" and "20,000" are mortality rates.

From the Reference no.1 in which data was collected in 2011, total incidence of breast cancer worldwide 1,383,000 and estimated deaths 458,400. From the reference no.2, data was collected in 201 when total Indonesia population 247,000,000; total breast cancer incidence 48,998 and total death 21.4%*92,200=19,730. YBCs comprise around 10% of total breast cancer patients.

4. The use of abbreviation is inconsistent, need to introduce the first time the word is used.

Done as suggested. We introduce the abbreviation in the body of the manuscript text as well as explained in the list of abbreviation.

5. Add "median age at diagnosis is 48 years old" after "while in Indonesia, ….." in place of "it is younger (48 years-old)" to improve the grammar of the sentence (last sentence of the first paragraph).

Done as suggested. Please see page 4 line 7.
6. Correction: delete have (Paragraph 2, fifth sentence)
   Done as suggested. Please see page 4 line 16.

7. Insert “a” in the first sentence of last paragraph of introduction.
   Done as suggested. Please see Page 5 line 3.

8. Add timing for smoking and correct the grammatical error “smoke” and “in their lifetime”
   Done as suggested. Please see Page 6 line 14-15.

9. Add “a” in the subtype Luminal A and Her2
   Done as suggested. Please see Page 6 line 8-9.

10. Spell out Her2 and FISH and IHC before abbreviating
     Done as suggested. Please see Page 6 line 3 and 6.

11. The sentence describing the physical activity assessment is very unclear and has poor grammar, please rewrite.
    Done as suggested. Please see Page 6 line 15-20.

12. Provide some information on the validity of measure of physical activity for this cohort.
    Done as suggested. Please see Page 7 line 1-2 with additional reference #12.

13. "Parity was determined by…" add "number of" before full term pregnancy.
    Done as suggested. Please see Page 7 line 6.

14. First sentence of the statistical analysis section, add "the" after "carrying out". Also replace "carrying out" with "conducting".
    Done as suggested. Please Page 7 line16.

15. PFS is mentioned without describing what this stands for.
    Done as suggested. Please see Page 7 line 13.

16. First sentence of second paragraph, "Around 7%." add "of" before "patients".
    Done as suggested. Please see Page 8 line 8.

17. In the treatment choice section, replace "attended" with "received" when referencing chemotherapy.
18. The Discussion has lots of grammatical errors and is poorly written. Needs to be revised to improve writing and reduce errors.

Done as suggested. Please see the whole discussion.

19. How was urban and rural defined?

Definition of urban and rural varies among different countries causing direct international comparison is relatively difficult. We used administrative definition officially given by Indonesian government to the local administration as urban (kota) or rural (desa).

Please see Page 7 line 2-4.

20. Each table needs a clear title that describes the population and setting and sample size

Done as suggested. Please see Table 1-3.

21. What is "mSBR grading", please add footnote to describe

Done as suggested. Please see footnote at Page 6.

22. Where are the hazard ratios and confidence intervals described in the text? There is space to include in the tables. These provide important information.

Hazard ratio and confidence intervals have been added to the Table. Please see Table 1-3.

REVIEWER 2:

Assaad Kesrouani (Reviewer 2): The subject is of interest and could shed light over breast cancer epidemiology.

1. There is however some flaws in the methodology. Selection bias is not appropriately addressed by the authors.

Thank you for the Reviewer’s comments. We agree with the Reviewer that findings from this research need to be interpreted carefully while considering potential sources of bias. For this study we included all breast cancer patients treated at the Department of Surgery in 2012-2017 (N=1259) and analyzed all patients younger than 40 years-old (N=144). Because this research was hospital-based we have further mentioned potential selection bias as a limitation in the Discussion as follows, ‘A limitation in this study was that we only included breast cancer patients who were treated in the Department of Surgery, thereby our data may have not included
terminally ill patients for whom any surgery was not indicated. This may have resulted in underestimation of disease progression in our study. A population-based study is therefore necessary to replicate our findings in a wider population’.

Please see Page 13 line 3-6.

2. A tertiary center usually gets the 'bad' and younger patients; could this be the case in Indonesia? Is there any correlation with the country' statistics regarding this question? How many patients were referred and how much were followed by the center.

After implementation of national health insurance in Indonesia (Badan Penyelenggara Jaminan Sosial, BPJS) in 2013, vertical referral system has been introduced. Patients will be first treated at the primary health care center and will be referred to the secondary and tertiary health center if could not be managed in the previous health care center. Sub-specialist doctors for cancer treatment will mostly available in the tertiary health center. Therefore, cancer patients who cannot be treated in secondary health center due to relapse/advance stage/with other complication are usually referred to the tertiary health center. In 2016, a total of 171.9 million people who were covered by the universal health insurance, 120.9 million people visited primary health care, 49.3 million patients visited secondary and tertiary health care centers, and 7.6 million were hospitalized in secondary and tertiary health care centers (BPJS report). Actual number of cancer patients (breast cancer patients) who were referred to secondary and tertiary health care centers were not yet reported.

Please see Page 13 line 7-8

REF#32