

Review report

Final title: Association of *p53* codon 72 polymorphism with expression status of hormone receptors like ER, PR, and HER-2 in invasive ductal breast carcinoma in Bangladeshi women

Title at submission: Association of *p53* Codon 72 polymorphism with ER, PR, and HER-2 status in invasive ductal breast cancer: A retrospective study



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D: Anonymous
G: Anonymous

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Ethical approval

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Trial registration number

Not applicable

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Reviewer A: Sharmin Akter Sumi, ORCID: 0000-0002-7599-1510

Overview

The concept of the article was good. I think this research will be useful in the next treatment plan of breast cancer patients in Bangladesh.

However, it would have been better if the introduction had mentioned estrogen receptor, progesteron receptor, human epidermal growth factor receptor positive and negative meaning. When should I say positive and when should I say negative? Moreover, it is better not to mention the retrospective study in the title, it is better to say it in the method.

It would have been better if the name of the country was given in the Title slide, indicating which country the work is being done in. It would be better if the introduction had explained what it mean to be a estrogen receptor positive and negative , progesteron receptor positive and negative and same as HER2 positive and negative. The method does not say whether the sample was taken from males or females. Because men also get breast cancer. The results in the back say a little bit that it will be taken from women, but this should be mentioned in the method.

It is not stated whether the patients from whom the histology blocks were taken had received chemotherapy or radiotherapy. It is not stated whether they had any cancer other than breast cancer or whether it was given in the exclusion criteria.

1. Comment Appropriateness of the Title.

In the title before saying ER and PR it will be better to say hormone receptor like ER, PR. It Should Be Mentioned Whether It Is being done on male or female. If it is being done on women it should be given female breast cancer.

It would be better to include the retrospective study in the method section rather than in the title. And if possible, it would be better to include the country in which it is being conducted.

Response The title has been revised as per reviewer's suggestion (Lines 2-6).

2. Comment Completeness and accuracy of the Abstract.

The abstract mentions Bangladeshi women. This means that work is being done on Bangladeshi women, which is not mentioned in the method or even in the title slide. Rationale is absent in abstract.

Response The sex of the sample population has been included in the Method section (Line 162), also the tile is revised (Lines 2-6).

Abstract is revised as per recommendation of the reviewer (Lines 59-63).

3. Comment The Methods are described in sufficient details so that the study can be reproduced. Whether ethical concerns have been well described.

In method study type should be given in retrospective study and omit the molecular investigation word. Here not mentioned these paraffin block either taken from male or female and there age ranges. Here also not mentioned that whether these patient received chemotherapy or radiotherapy. Here not mentioned whether these patient had any other cancer. There is also absent of sampling technique.

Response The method section is revised in as per reviewer's suggestion (Lines 161-191).

4. Comment Straightforward, clear, and logical Storytelling.

It would be better if the introduction had explained what it mean to be a estrogen receptor positive and negative , progesteron receptor positive and negative and same as HER2 positive and negative.

Response The reviewer's comment is addressed in the revised Methods section for clarification (Lines 186-188).

Reviewer D: Anonymous

Overview

This retrospective study included 203 cases of histologically confirmed invasive ductal breast carcinoma. Histopathological status as well as immunohistochemical status for ER, PR, and HER2 expression were collected. *p53* codon 72 polymorphism detection was done by PCR-RFLP. This study suggested that the GC genotype at codon 72 of the *p53* gene is associated with increased susceptibility to axillary lymph node metastasis, more lymph node involvement, and reduced PR expression in IBC patients. I think this study is okay except for a few minor mistakes. But the discrepancies of the results of this current study with recent other studies should be addressed before considering *p53* codon 72 polymorphism as a potential auxiliary prognostic biomarker.

5. Comment Appropriateness of the Title.

Authors had shown the association of *p53* Codon 72 polymorphism with ER, PR, and HER-2 status as well as tumor stage in invasive ductal breast cancer in the result section, but "tumor stage" is missing in the title. So, "tumor stage" can be included in the title.

Response By "lymph node involvement" the authors actually meant the number of lymph node involved in the metastatic IDC of the study samples. The confusion is clarified in revised manuscript (Table 1, Lines 597-598).

6. Comment Completeness and accuracy of the Abstract.

On page no. 3, line no. 57 (result section) and 61 (conclusion), "axillary lymph node metastasis" and "lymph node involvement" seem similar. These should be distinguished clearly.

Response The Result section and Conclusion section has been revised accordingly.

7. Comment The Methods are described in sufficient details so that the study can be reproduced. Whether ethical concerns have been well described.

Please mention the steps taken to prevent bias in the method section.

Is there any confounding variable? If any, it should be mentioned in the method section.

Response The reviewer's suggestions have been addressed in the methods section.

Steps taken to prevent or reduce bias in the study is mentioned in "Study design, place and sampling" section (Line 161-191).

The study was designed with some exclusion criteria so that there are no confounding variables that may create bias in results (e.g. recurrent IDC patients, IDC patients who received extensive treatment, bilateral IDC patients, patients who had other cancers than IDC).

8. Comment Quality, clarity and appropriateness of the Table(s).

1. In table no. 1, under the heading of tumor staging, T3, number of patient will be 28 (14%)

2. In table no. 2, under the heading of axillary lymph node metastasis, the total number of patients is mismatched: (Pro/Pro: total number of patients is 28 instead of 42) and (Arg/Pro: total number of patients is 91 instead of 119).

3. Axillary lymph node metastasis and lymph node involvement express similar meanings. These two headings should be appropriately distinguished.

Response The Tables of the manuscript are revised in the manuscript by addressing the reviewer's comments (Lines 597-598 and 601-604).

9. Comment Major redundancy between text and tables/figures in the Results section.

In the tables, PR expression was categorized as negative or positive. But in the results section, the authors showed an association with lowered PR expression. Similar terminology would be better.

Response The authors appreciate the reviewer for pointing out the mistake. In the revised manuscript, the mistake is corrected.

10. Comment Pertinence of the Discussion section whether it justify the main message of the manuscript without repeating the results.

1. The authors have mentioned the discrepancies of the results of this study with recent other studies; the reason behind this should be discussed in the discussion section.

2. Metastasis to axillary lymph nodes and lymph node involvement express the same meaning; these should be clarified.

3. On page no. 14, line no. 315, it will be PR instead of PgR.

4. In this study, heterozygous GC genotype & homozygous GG genotype both were found to be associated with metastatic ductal carcinoma, lymph node involvement, and lowered PR expression. But on page no. 15, line no. 327-328, the authors have mentioned only the heterozygous genotype having susceptibility towards breast cancer along with metastasis.

Response The discussion section is revised, mistakes are corrected and clarifications have been given as per reviewer's suggestion (Lines 319-378).

11. Comment Appropriateness of the overall length of the article.

The length of the article should be decreased.

Response The authors tried to reduce the length of some sections of the manuscript. Although to address some reviewer's comments and editorial review some detailed explanations were included.

12. Comment Standard of English for publication.

Some sentences are too long and complex. These sentences can be changed into simple sentences.

Response The authors revised the manuscript to accommodate more simplified sentences as per reviewer's recommendation.

Reviewer G: Anonymous

Overview

The title "Association of p53 Codon 72 polymorphism with ER, PR, and HER-2 status in invasive ductal breast cancer: A retrospective study", is a good title which is done in Bangladesh perspective. So, it was preferable to discuss in relation to Bangladesh as well as our sub continent. Genomic studies in medical fields is not common in our country. So, this study will show a path for the future researchers.

13. Comment Appropriateness of the Title.

Line-3, 'cancer' replaced by ' carcinoma'

Response The authors highly appreciate the reviewer's time and inputs into this article.

Title of the manuscript has been revised (Lines 2-6).

14. Comment Completeness and accuracy of the Abstract.

Line-48, 'invasive breast carcinoma' replaced by ' invasive ductal breast carcinoma'.

Response Abstract is revised (Lines 62-63).

15. Comment Clarity of the rationale for conducting the study is given in the Introduction section.

Line-79, better to be add "etc. " after ' parity'

Response The corrections have been made (Lines 115).

16. Comment The Methods are described in sufficient details so that the study can be reproduced. Whether ethical concerns have been well described.

Line-128-141: As a study place, please add " Bangladesh".

Response The authors revised the methods section as per reviewer's recommendation (Lines 165-167).

17. Comment Quality, clarity and appropriateness of the Table(s).

Line-534, Table1. Sub heading: Patients (n=203) replaced by 'Patients n(%) '.

Make a common alignments of digits eg. 21(10.3%), 77(38.0%), 02(01.0%).

Table1, 'Cancer grade' will be ' Tumour grade'. Axillary lymph node 'metastasis' replaced by ' status'.

In table2 & 3, digit alignment also needed.

Line-542, table3, '(number of patients, n=42)' will be '(n=42)'. 'Axillary lymph node ' will be ' Axillary lymph node metastasis'.

Response The Tables are revised as per reviewer's comments. Table 1 Lines 597-598. Table 2 Lines 601-604 and Table 3 Lines 606-611.

18. Comment Major redundancy between text and tables/figures in the Results section.

Line- 219&220: ' cancer grade II(79.32%) and Tumour stage II(82%) ' will be ' Tumour grade II(n= ?, 79.32%) and Tumour stage II(n= ?,82.0%).

Line -220: ' 48%' will be ' Forty eight percent'.

Line-231: 'breast cancer' will be replaced by ' invasive ductal breast carcinoma'.

Response The authors appreciate the reviewer's comment. Also, the recommended corrections have been made (Lines 276-279).

- 19. Comment** Pertinence of the Discussion section whether it justify the main message of the manuscript without repeating the results.

Lines-283: 'Maturation' may be replace by 'menstruation'.

Response The authors appreciate the reviewer's comment. Also, the recommended corrections have been made (Lines 332-333).

- 20. Comment** Whether the Conclusion of the manuscript is supported by the data.

Association with the prognosis of the invasive duct cell breast carcinoma may be done.

Response The authors appreciate the reviewer's comment. Also, the recommended corrections have been made (Lines 394-395).

- 21. Comment** Whether the manuscript is supported by appropriate and up-to-date References.

Some of the journals name mentioned in 'italic' font and some are not. It should be in uniform font according to BSMMUJ rules.

Response Updated references have been included wherever possible (Lines 449-592).

Responsible editor: M Mostafa Zaman, ORCID: 0000-0002-1736-1342

- 22. Comment** The current version has 13% plagiarised text; the final version should have less than 10%.

Response The authors are thankful to the editor for kind attention to this article and highly appreciate the important editorial comments. Authors made some corrections in the text to address the editorial requirement.

- 23. Comment** Study type: This is a cross-sectional study of biological samples conducted at two health facilities during the specified period. The authors' description of the retrospective study is incorrect.

Response In the revised manuscript, the Methods section is rewritten to clarify the study design and sampling (Lines 161-191).

- 24. Comment** The main problem of the study is the non-representativeness of the sample. Authors should clarify this in the limitations with special emphasis on the possible bias introduced by this. It is not known how representative the 374 samples collected from the two centres are. Additionally, 45% of the sample could not be used, which is extremely high.

Response The issue mentioned by the editor has been addressed and clarified in the "Study design, place and sampling" section of Methods in the revised manuscript (Lines 161-191).

- 25. Comment**
- Analysis: There are numerous age groups with a small number of individuals. Why is this necessary given that the age groups have not been used in any subsequent analysis? Similarly, the cancer grades and tumour stage were not employed in any follow-up analysis.
 - The authors mentioned using the chi-square test for analysis. However, the tables provide odds ratios with their 95% confidence intervals, which derive from a logistic regression analysis. Conceptually, these two tests should yield similar results (which has been the case here). Therefore, the authors should select only one chi-square test.
 - Then, another analysis should be conducted using multiple logistic regression to adjust the results for age, cancer grade, and tumour stages. This table could be provided in exchange for a histopathology slide. Presentation of histopathology is not the objective of the study, but rather the *p53* codon polymorphism.

Response

- The number of age groups are reduced as per editorial recommendation. The cases were distributed to age groups to find the more susceptible group of females to invasive ductal breast carcinoma (Lines 265-271).
- Tumor grade and tumor stage are included in Table 3 as an additional analysis recommended by the editor (Lines 606-611).
- As per the editor's recommendation the Table 3 of previous submission has been omitted. Chi-squared tests were done by using SPSS Statistics v25 software. There is an option in this software to calculate OR and 95% CI while doing Chi-squared test.
- As per editor's recommendation, the histopathology slide images are removed and a new Table 3 representing multiple logistic regression analysis between (a) the genotypes and (b) axillary lymph node metastasis, hormonal receptor expression status (present/positive and absent/negative) of ER, PR and HER-2 was done by adjusting results for age, tumor grade and tumor stages (Lines 606-611).