Author’s response to reviews

Title: Clinicopathological characteristics and health care for Tibetan women with breast cancer: a cross-sectional survey

Authors:

Yu Zhao (zhaoyulan002@163.com)
Han Luo (luohanhuan@126.com)
Xin Zhang (568484778@qq.com)
Za Bianba (tashidelek2009@126.com)
Lin Li (s2007124@163.com)
Qian Wang (409663772@qq.com)
Lei Guo (guolei0520@163.com)
Dian Wang (xzzqrmyyyb@163.com)
Yong Ze (zyg13989999353@sina.com)
Shan Zheng (zhengshan@cicams.ac.cn)

Version: 3  Date: 16 Mar 2019

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Yong-ge Ze

Vice Prof.,  Department of Oncology, Tibet Autonomous Region People's Hospital, 18 Lin-kuo North Road, Lhasa, Tibet Autonomous region 850000, China

Tel: +86-891-637-1750
Fax: +86-891-637-1462
E-mail: zyg13989999353@sina.com

Shan Zheng

Prof.,  Department of Pathology
Dear Prof. Linda Gummlich:

Thank you for your letter of “Your submission to BMC Cancer - BCAN-D-18-00625R2” and for the reviewers’ comments concerning our manuscript titled “Clinicopathologic characteristics and health care for Tibetan women with breast cancer: a cross-sectional survey”. We have studied their comments carefully and the paper has been appropriately altered according to the reviewers' comments. In the revision, there are two colored highlights. The yellow ones represent the words we’ve adjusted this time. The grey ones with double strikethrough represent the words which we’ve deleted.

We answered the questions to the referees’ comments as follows:

Eva Kantelhardt (Reviewer 2):

Thank you for the chance to again see the manuscript mentioned above. The authors have now again made changes to the text and the conclusion.

I still feel that the conclusions are beyond the findings especially since the numbers from which the conclusions are drawn are very low.

This is an exploratory analysis conducted in Tibet, where characterized by sparse population and limited health care resources. We involved in 273 patients in our study, and the conclusions are drawn from the statistically significant results. We thank the reviewer for raising the concern on uncertainty of the findings. As such, we have modified our conclusions to make sure readership taking into consideration of the study limitations and uncertainty of our findings (Page 4, Line 4-6; Page 11, Line 1-2; Page 17, Line 1-3).

This manuscript should be seen by a statistician.
We have referred the suggestions from two medical statisticians for the issues of statistical analysis in this study. Results are generated by rerunning the models under the supports from statisticians (Page 3, Line 19- Page 4, Line 2; Page 10, Line 8-15; Page 35, Line 1- Page 36, Line 7, Table III) and we thanked them in the Acknowledgments (Prof. Zhao and Ph. D. Xia, Page 20, Line 5-8).

Additionally I have to say that the authors incorporated changes to address my concerns but there are new inconsistencies in the manuscript due to passages which are no longer correct.

E.g. in the abstract the passage about advanced stage BC was removed in the result section (since incorrect) but still the authors conclude: "Except for advanced stage BC, the clinicopathological characteristics ... improved during different HCSs."

We have revised this part in the conclusion (Page 4, Line 4-6).

And again, comparing 3 different health care systems and seeing the largest difference comparing large groups (183 and 76) with a group of 14 out of 273 cases seems problematic to me.

We treat HCS as a categorical variable with 3 levels in the multivariate logistic regression. Level 1 (the group of 14 patients) was assigned as the reference. The results suggested that the difference between level 3 (76 patients) and level 1 is statistically significant (p value were 0.013 for AJCC stage and 0.030 for T stage). The conclusion draws carefully from this finding in the update version of our study.

Feng Gao (Reviewer 3):

This is a well written manuscript. The authors conducted a study, for the first time, to assess the clinicopathological characteristics of Tibetan females with breast cancer at presentation. The statistical methods are properly used. The authors are well aware of the strength and limitation for this study. However, there are a few issues in the data presentation and interpretation, especially in the paragraph for "Relationship between clinicopathological characteristics of 273 Tibetan females with BC from different HCSs".
1. Page 8 line 4: The statement "Only invasive BC was included in analysis" is rather confusing. Are these 3 cases with DCIS included in Tables 1 and 2?

All these 3 cases with DCIS were included in Tables 1 and 2. However, we only analyze invasive BC in the relationship between clinicopathological characteristics of Tibetan females with invasive BC from different HCSs.

2. Page 8 line 28: it is unclear which assumption was used for "multinomial logistic regression". Is it using the generalized logit function (in which each non-reference category is contrasted with the reference category), or adjacent-category logit function (in which each category is contrasted with the following category), or the cumulative logit model (which assumes a natural order among all categories). The reviewer expects it is the cumulative logit (which is the default choice for major statistical packages such as SAS and SPSS), but it is better to spell out because it seems the authors also mentioned the other choices at the end of paragraph (page 10 lines 40-45).

In the latest version of our analysis, we employ multivariate logistic regression rather than multinomial logistic regression because stages are treated as binary variables. Updates were made in this version of our manuscript (Page 8, Line 11).

3. Page 8 line 31: it is unclear why other baseline characteristics such as "Social economic status" were not included as covariates

The SES was not an independent variable in multivariate logistic regression. As an alternative, HCS and census register are used as proxy to the SES in our study. We add this statement in this version (Page 8, Line 15-16; Page 12, Line 20-21). So, we did not include the SES to avoid collineation.

4. Page 9 line 53: the statement "we included only invasive BC that were only 3 cases of DCIS" is rather confusing.

We revised this statement to make it more concise (Page 10, Line 1-3).
5. Page 10 line 23: the statement "based on the local advanced (III) stage" is rather confusing. Does the author mean "using stage III as reference"?

We compared stage I+II with stage III. We revised this statement to make it more concise (Page 10, Line 11-14).

6. Page 10 lines 15-20 and Table 3: for the logistic model of T4 stage, it is unclear why the variable HCS ends with only a single OR. Because HCS is a categorical variables with 3 levels, it is better to be presented by two indicators (similar to that of presented in the model for AJCC stage).

We have modified our results, in which HCS was treated as a categorical variable with 3 levels and 2 ORs (Page 10, Line 8-14; Page 35, Line 1-Page 36, Line 7, Table III).

7. Table 3: is is unclear why multinomial logistic regression was used for AJCC stage if the comparison is only between I+II vs III.

In the latest version of our analysis, we employ multivariate logistic regression rather than multinomial logistic regression because stages are treated as binary variables. Updates were made in this version of our manuscript (Page 35, Line 1-Page 36, Line 7, Table III).

We thank the reviewers and are confident that this adequately addresses the issues raised. We look forward to hearing from you again in due course.

Yours sincerely,

Yong-ge Ze and Shan Zheng