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Reviewer A

Dear authors,

1. In the abstract, you should write the full name Controlling nutritional status before use abbreviations CONUT; likewise, in the text as a rule you should write full name before abbreviation (SYSUCC page 5, line 7).

Reply1: We have modified as advised.

Changes in the text: see page2, line8; see page 5, line 9.

2. “We conducted a retrospective analysis of 1367 breast cancer patients who underwent surgery between December 2010 and October 2012”.

I think patients underwent overall treatment (surgery, radiotherapy, hormonotherapy, etc) you should modify this sentence. The same in the title. Prognostic significance of the CONUT score in surgically treated breast cancer patients.

Reply2: We thanks for the reviewer’s comments. We recruited 1367 breast cancer patients who underwent surgery between December 2010 and October 2012, you advised that these patients underwent postoperative therapy, while these therapies were beyond the period (December 2010 and October 2012). Therefore, we did not make any change in the substance “We conducted a retrospective analysis of 1367 breast cancer patients who underwent surgery between December 2010 and October 2012”. You mentioned that in the title, the “surgically” is impertinent and we have modified. In order to avoid misunderstanding, we did not take postoperative therapy into univariate and multivariate analyses, and we made new tables.

Changes in the text: see Table2, Table3 and Table4.

3. Is your mortality rate similar to mortality rate in western countries? If it is were not similar you would discuss it in the discussion and limitations of the study.

Reply3: We agree with the reviewer’s comment that our mortality rate was different from mortality rate in western countries. However, the 5-years OS of our study was 86.7%, within the range of other publications of China from 50.2% (PMID: 27478317) to 90.8% (PMID: 28976077) and was comparable with the large sample (n=5809) study of our center at 89.3% (PMID: 22625227). The poor prognosis may

cause by special national conditions of China (poor awareness of breast cancer, late onset of diagnosis and treatment, and lack of medications such as Herceptin) and a relatively short life span of Chinese. We modified our article as advised and have added discussion about this question.

Changes in the text: see page9, line21---page10, line10, and page11, line4-6

4. Introduction should be clarified, organized and shortened, it is a enumerations of repetitive facts.

Reply4: We thank for the reviewer's comments. we have modified our article as advised and we integrated the opinions of both editors. We reduced remarks about precision medicine and we added description of breast cancer therapy.

Changes in the text: see page 4, line 4-18

5. DMFS could be omitted

Reply5: we accepted your suggestion and we deleted DMFS. We also deleted the figure of DMFS.

Changes in the text: see Figure2.

6. How many patients were lost in the follow-up? They should be mentioned in the limitations or you should mentioned the limitations of the method used.

Reply6: we formed a figure about the patient's entry and exclusion.

Changes in the text: see Figure1.

7. The text has some mistakes example the use of capital letters.

Reply7: we have corrected these mistakes. There were some transcription mistakes and we have corrected them.

Changes in the text: "patients" was changed into "patient's ", see page4, line 13. "were" was changed into "was", see page5, line10. See page2, line20-22 and page7, line10-12.

8. Results. Description of data demonstrated in Table 2 can be omitted.

Reply8: we adopted your proposal and we removed this part.

9. Table 2. TNM and clinical stage (is it clinical or pathologic?) are the same, you can showed using intrinsic subtypes instead of ER, PR, HER2, Ki-67. I do not understand N=301; what does it mean?

Reply9: In Table 2, TNM and clinical stage are same. It is pathologic. In order to avoid misunderstanding, we used "pTNM stage" rather than "clinical stage". We had intended to use intrinsic subtypes instead of ER, PR, HER2, Ki-67 in multivariate

analyses. Subtype and ER, PR, HER2, Ki-67 were all significant in OS, however, in DMFS, the P value of subtype was 0.086, in order to unify factors in both survival time, we adopted ER, PR, HER2, Ki-67 rather than subtype. We added data about subtype and made a new Table2,3 and 4. N=301 is a transcription mistake, I have corrected it.

Changes in the text: see page5,line21-page6,line1, see Table2, 3 and 4.

10. In yours series there are 69% ER+, N1 48% and HER2 28% and 51% hormone therapy and 82% adjuvant chemotherapy. You should discuss these findings.

Reply10: we discussed these findings in Discussion. We excluded postoperative therapy, therefore, we did not describe about “51% hormone therapy and 82% adjuvant chemotherapy”.

Changes in the text: see page9, line5-12.

11. I would like you to do and correlation between CONUT scores and OS and RFS before you use a cut off point.

Reply10: before conducting this research, we have studied a lot about the prognosis of CONUT in different tumor species and we found that the best cutoff was aet at 3, therefore, we directly used this cutoff point, see page5, line15-16.

12. In my opinion , your work shows that preoperative CONUT as a mark of general risk is related to OS and DFS, but there are some flaws and limitations to say more things, you could shortened your work and focus on your results.

Reply12: we accepted your suggestion. No matter in introduction or discussion, we focused more on breast cancer and CONUT. We also diminished other description.

Changes in the text: see section of Introduction and Discussion.

Reviewer B

The authors conducted a retrospective study to assess the prognostic significance of the Controlling Nutritional Status (CONUT) score in 1,367 breast cancer patients. It was found that the CONUT score was an independent predictor of overall survival (OS) and recurrence-free survival (RFS).

However, it is necessary that some aspects are reviewed:

- TITLE: must appear in the title Controlling Nutritional Status (CONUT) score in full.

Reply1: we modified as advised.

Changes in the text: see page1, line2-3.

- ABSTRACT

The authors need to clarify which parameters were used to calculate the CONUT score and that the higher the score, the nutritional status is worse. This is not clear in the article.

Reply2: We thank for the reviewer's comments. We added sentences about parameters that were used to calculate CONUT and the relationship between the score and individual nutritional status.

Changes in the text: see page 2, line 11-14.

- INTRODUCTION

- Page 3, lines 9-19: the authors discuss precision medicine excessively. This stretch can be reduced by focusing on the approach to breast cancer patients.

Reply3: we reduced description about precision medicine and we added some about the approach to breast cancer patients.

Changes in the text: see page3, line5-18.

- Page 3, line 22; page 4, lines 1, 2: "Further, there have been studies demonstrating that activation of the host immune system is detrimental for improving the patients overall survival [10, 11]." Is this statement correct?

Reply4: It is a writing error, we have corrected it, "detrimental" turned into "beneficial".

Changes in the text: see page 4, line1.

- Authors could comment more on the studies that applied the CONUT score.

Reply5: In this part, we had listed several tumor species and we mentioned this in text (see page4, line8-10). We think your suggestion is reasonable and we add comment on the studies that applied the CONUT score in Discussion.

Changes in the text: see page8, line14-22.

- Page 4, lines 16-18: include distant metastasis-free survival in the objectives, which was also investigated.

Reply6: we have deleted the part according to the former editor.

- PATIENTS AND METHODS:

1,367 patients were included in the study.

Between December 2010 and October 2012, how many women with breast cancer

were treated at the institution? How many were excluded? Why? How many met the inclusion criteria? Please clarify.

Reply7: we made a figure about patients' entry and exclusion.

Changes in the text: see figure1.

Page 5, lines 1, 2: It is known that breast cancer patients stage IV have a worse prognosis. Usually, these patients are not included in studies that investigate prognosis. I recommend authors to exclude patients with stage IV.

Reply8: We thank for the reviewer's comments. Patients in advanced stage who could conduct a surgery may benefit from reducing tumor burden (PMID: 25384943, PMID: 30005779). The prognosis of these patients differs from those who cannot be operated on. The CONUT is an immune-inflammatory-nutritional indicators. After consulting references, we observed that worse nutrition and chronic inflammation are related with invasion and metastasis. And we noticed that that TNM stage was related to CONUT ($P=0.027$). Therefore, our results provided more robust inflammatory responses in response to more aggressive tumors and higher tumor burdens and have verified the prognostic significance of CONUT. We added discussion about this part.

Changes in the text: see page9, line11-19.

Page 5, lines 16, 17. The authors report that they used the St Gallen criteria to classify the expression of ER, PR, HER2 and Ki67. It is not usual to categorize Ki67 as positive and negative. In this sense, I ask authors to make explicit in the manuscript how the expression of ER, PR, HER2 and Ki67 was classified.

Reply9: we identified ER and PR positive if there were at least 1% positive heterologous tumor cell nuclei in the sample evaluated by immunohistochemistry (IHC). HER-2 status was assessed using a semiquantitative score (0–3+). Patients with 2+ IHC staining for HER2 underwent fluorescencein-situ hybridization (Fish) to confirm HER2 positivity or negativity. We re-wrote Ki67 definition, in the text and tables. Ki67 was stratified into two group, the cutoff was 14%.

Changes in the text: see Table2 and text (see page5, line21-page6, line1).

Page 5, line 24. In the definition of overall survival, was death from breast cancer? Please clarify.

Reply10: The death was not only from breast cancer; therefore, we added “from various causes” after death.

Changes in the text: see page6, line6.

Page 6, line 14: include values for severe.

Reply11: we have added the score.

Changes in the text: see page6, line19.

Page 6, line 20: please include the minimum and maximum follow-up time.

Reply12: we added the minimum and maximum follow-up time.

Changes in the text: see page7, line1.

Page 7, lines 5, 6: please clarify how Ki67 was rated positive and negative.

Reply13: about this question, we have answered in Reply9, and we have used $\geq 14\%$ and $<14\%$ instead of positive and negative. According to former editor, we deleted some description about Table2, including some about Ki67.

Changes in the text: see page5, line25 and table2.

- DISCUSSION

The CONUT score has been validated as a prognostication tool?

Reply14: The CONUT score had been confirmed in various cancers about its prognostic significance. We aimed to verify its significance in breast cancer.

Authors should focus on discussing the findings of the present study. Data from other studies with different types of cancers must be provided. Data such as sample size, study design, staging should be part of the discussion. This allows the reader to be informed of the performance of the CONUT score in assessing the prognosis (OS, RFS, DMFS) of other types of cancer such as renal, gastric, prostate, colorectal.

Reply15: We thank for the reviewer’s comments. We added some details as advised.

Changes in the text: see page8, line14-22.