Author's response to reviews

**Title:** The expression and clinical significance of extracellular matrix protein 1 and vascular endothelial growth factor-C in the lymphatic metastasis of human breast cancer

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**Author's response to reviews:** see over
Dear Editors and Reviewers:

Thank you for your comments concerning our manuscript entitled “The expression and clinical significance of extracellular matrix protein 1 in the lymphatic metastasis of human breast cancer” (ID: 1899149268567887). The comments are valuable and very helpful for revising and improving our paper, with important guiding significance to our researches. We have read the comments carefully and made some corrections. The revised contents are marked with “tracked changes” in the manuscript. The responds to the reviewer’s comments are enclosed.

We appreciate for Editors/Reviewer’s warm work earnestly, and hope that the correction will increase the priority of our manuscript for publishment.

Thank you very much for your consideration.

Yours sincerely,

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Responds to the reviewer’s comments:

Reviewer's report:

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The ms investigates the protein and molecular expression pattern of ECM1 in human breast cancer, and its correlations with the clinicopathological characteristics and lymphangiogenesis. The authors analyzed 41 patients and found that both protein and mRNA of ECM1 were higher in BC tissues respect to epithelial tissues and lymph nodes. Moreover, they found that ECM1 positively correlated with the status of ER and LMVD, but did not find correlation to the status of lymph node metastasis. The authors concluded that ECM1 may facilitate lymphangiogenic progression and be a considerable marker that forecast lymphatic infiltration of breast cancer in clinical use.

Major Compulsory Revisions:

The paper deals with an interesting topic and related to debated results of the actual literature.

Response: Thank you for your kind consideration.

I believe that are some limitations for this study, which may weaken the results obtained. ECM1 alone is not sufficient to facilitate lymphangiogenesis, which may require multiple lymphangiogenic factors. The authors only demonstrated that a correlation exists, and these findings supported a role for ECM1 in the lymphatic progression of breast cancer, an area that will require further study to assess the broader applicability of their preliminary data. So, the authors may increase the number of subjects before to conclude that ECM1 "is a marker that forecast lymphatic infiltration of breast cancer in clinical use".
**Response:** Thank you for the comments. As the limitations in our study, the prediction of ECM1 in lymphatic infiltration of breast cancer would not be extensively clinical use at present. Considering the conscientiousness, we would like to improve the conclusion (refer to the CONCLUSION section).

In the present study, both mRNA and protein expression of *ECM1* were significantly elevated in breast cancer tissues, compared with the adjacent normal epithelium. The protein expression was positively correlated with LMVD. Although the number of our patients was 41, the association between ECM1 expression and LMVD was statistically significance.

Specimen collection is time-consuming. Meanwhile, gaining specimens included breast cancer tissues, the matched noncancerous breast epithelial tissues and one of the suspicious metastatic axillary lymph nodes from the same patient who have never received preoperative treatment and metastasis tumors needs more time. If it is also required to increase the cases, for example to add the cases to 60, the whole process would need more than 3 months. So, if the number of patients is not required rigorously, should we retain the number of cases and modify certain presentations in the conclusion?

Moreover, according to the debated and contrasting results of literature (due also to the different Abs and specimens used in the different studies), the authors should increase the BC patients correlating their results with more specific lymphoangiogenic factors, actually totally neglected (like VEGF-A/VEGFR-2, PDGF-AA/PDGFR-alfa, VEGF-C/VEGFR-3, FGF-2, etc).

**Response:** In the revised manuscript, we consulted new literatures and presented the debate
between lymph node metastasis and the expression of ECM1 more fully (refer to BACKGROUND section).

Although additional factors implicated in lymphangiogenesis include FGF, PDGF, IGF, VEGF-A/VEGFR-2, etc. It is common to assess the role of these growth factors by determining whether their effects in lymphatic metastasis are mediated directly or indirectly via the VEGF-C signaling. As suggested, we added VEGF-C as another lymphangiogenic factor to compare the expression of ECM1 and VEGF-C with LMVD in clinical breast cancer specimens. We analyzed the expression pattern of VEGF-C in the according specimens and combined the results into the text (refer to corresponding sections).

Actually they should also soften their conclusions, avoiding the actual phrase stating "ECM1 as a marker which facilitate lymphangiogenic progression and plays a significant role in the lymphatic metastasis of human breast cancer".

**Response:** The conclusion has been soften according to the comments (refer to CONCLUSION section).

**Level of interest:** An article whose findings are important to those with closely related research interests.

**Quality of written English:** Needs some language corrections before being published.

**Response:** We have made some necessary language polish.

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:** 'I declare that I have no competing interests'.