

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Prognostic factors in metastatic breast cancer: a prospective single-center cohort study in a Finnish University Hospital
AUTHORS	Karihtala, Peeter; Jääskeläinen, Anniina; Roininen, Nelli; Jukkola, Arja

VERSION 1 – REVIEW

REVIEWER	Hailin Tang SYSUCC China
REVIEW RETURNED	29-Mar-2020

GENERAL COMMENTS	<p>The authors have investigated the predictive value of ER status and initial lymph node status for clinical prognosis in breast cancer. This topic is of potential interest and the predictors might be very useful in clinical practice. However, there are several points to be addressed.</p> <p>Major concerns:</p> <ol style="list-style-type: none">1. The study cohort was relatively small as breast cancer patients are usually divided into four different subtypes and larger population is needed for stratification. Here, the SEER database from the USA might help to further validate the current results in this study.2. As a relatively cohort might result in heterogeneity and bias for analysis, the authors might discuss this in the discussion part or more patients should be included in this study.3. The lymph node status and hormone receptor status have been reported as reliable predictors in previous studies. The authors might need to further discuss the innovative points in this study. <p>Minor concerns:</p> <ol style="list-style-type: none">1. A flow chart including inclusive criteria, exclusive criteria and statistical analysis method might better help to explain the study designs.2. Statistical proper nouns, such as HR, P, 95%CI should be in italic form.
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REVIEWER	Chris Pyke University of Queensland, Australia
REVIEW RETURNED	11-Apr-2020

GENERAL COMMENTS	<p>This interesting study addresses a troubling clinical problem: what is the prognosis of a patient now that the breast cancer has recurred.</p> <p>I would offer the following:</p>
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	<ul style="list-style-type: none"> - how complete was the follow up? (were any of the 594 lost to follow up, or do these 594 represent a subset of patients who have complete follow up?) - were Neo Adjuvant Chemotherapy patients excluded? - did lymph node identification/surgery/treatment alter during the decade from 2003? - a statement in the Methods should address this eg: all surgery to the primary tumour was carried out according to guideline x - a potential limitation of the study is that the investigators have not (yet?) compared these prognostic variables to theststed (in the Discussion) established prognostic factors (DFI, Bone only mets, ER pos) - perhaps a second paper? <p>Otherwise, well constructed, well discussed</p>
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REVIEWER	Tzu-Pin Lu Department of Public Health, National Taiwan University, Taiwan
REVIEW RETURNED	04-May-2020

GENERAL COMMENTS	<p>The authors presented a prospective breast cancer study to report important factors associated with the outcome of metastases. The authors need to address the following issues before its publication.</p> <ol style="list-style-type: none"> 1. The authors need to put more efforts to explain the differences of outcome in different subtypes. It is well-known that different subtypes in breast cancer have severely different outcomes and thus it should be taken into consideration. 2. The authors must compare their results with other datasets, such as SEERs, the Cancer Registry in other countries. They should not just describe them in Discussion and must present them in Results. 3. In the single variate analysis, the authors shall consider multiple test correction issue. 4. The authors shall describe more clearly about the descriptive statistics of the metastasis traits, such as the size and the comparisons between the primary and second tumor tissues, 5. I doubt the usage of the Cox regression. Did the authors check the hazard as a constant through the study period?
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VERSION 1 – AUTHOR RESPONSE

Reviewers' Comments to Author:

Reviewer: 1

Reviewer Name: Hailin Tang

Institution and Country: SYSUCC, China

Please state any competing interests or state 'None declared': None declared.

The authors have investigated the predictive value of ER status and initial lymph node status for clincial prognosis in breast cancer. This topic is of potential interest and the predictors might be very useful in clincial practice. However, there are several points to be addressed.

Major concerns:

1. The study cohort was relatively small as breast cancer patients are usually divided into four different subtypes and larger population is needed for stratification. Here, the SEER database from the USA might help to further validate the current results in this study.

Reply: We thank the Reviewer for these comments regarding subtyping, sample size and stratification. We divided the patients into five groups according to biological subtypes per ESMO 2015 guidelines. As shown in the Table 1, the number of patients with each subtype consisted of 3 to 29 patients. We agree with the Reviewer that subgroup or multivariate analysis could not be reliably performed with a such low number of patients. Consequently, we have now discussed this topic as a limitation of the study in both in the Strengths and limitations of the study and in the Discussion sections.

The idea of including SEER or other registry data would be interesting and can be used in the future to validate the current results. Indeed, there are already some retrospective data with outdated treatment modalities supporting our finding of the initial lymph node metastasis as a prognostic factor in metastatic breast cancer. This along with the compelling evidence of ER negativity of primary tumor as an adverse prognostic factor in metastatic breast cancer has been discussed in pages 10-11. We have now more underlined the strengths of the current study with a prospective setting and modern treatment modalities in the Discussion as the Reviewer 1 suggests also below.

2.As a relatively cohort might result in heterogeneity and bias for analysis, the authors might discuss this in the discussion part or more patients should be included in this study.

Reply: We understand Reviewer's point here. We have now more emphasized the relatively low number of patients with metastatic breast cancer in the cohort in both the Strengths and limitations of the study and in the Discussion sections.

3.The lymph node status and hormone receptor status have been reported as reliable predictors in previous studies. The authors might need to further discuss the innovative points in this study.

Reply: We agree with the Reviewer that the initial ER status as a prognostic factor in metastatic breast cancer has been established previously. Nevertheless, the role of initial nodal status has not been uniformly found as a such factor and studies assessing this topic with prospective setting have been lacking. To underscore this, the strengths of the current study have now been more carefully discussed. These points have been added both in the Strengths and limitations of the study and in the Discussion sections.

Minor concerns:

1.A flow chart including inclusive criteria, exclusive criteria and statistical analysis method might better help to explain the study designs.

Reply: We thank Reviewer for this idea and we have now included a flow chart as Figure 1.

2.Statistical proper nouns, such as HR, P, 95%CI should be in italic form.

Reply: We agree with the Reviewer that these nouns are usually in italic form, but in BMJ Open, they seem to be in non-italic form.

Reviewer: 2

Reviewer Name: Chris Pyke

Institution and Country: University of Queensland, Australia

Please state any competing interests or state 'None declared': none declared

This interesting study addresses a troubling clinical problem: what is the prognosis of a patient now that the breast cancer has recurred.

I would offer the following:

- how complete was the follow up? (were any of the 594 lost to follow up, or do these 594 represent a subset of patients who have complete follow up?)

Reply: The survival data was updated last time in January 2019, when there was a median follow-up of 102.0 months. Importantly from the point of view of this particular study, all patients with aim to receive any oncological therapy to metastatic breast cancer within Oulu University Hospital District, are admitted to the Department of Oncology at Oulu University Hospital, where the data was collected. Thus, we expect that there are likely not many patients who would have been lost to follow-up. We obviously recognize that it is still possible that some patients may have moved to the area of other hospital district or abroad after their initial breast cancer diagnosis.

- were Neo Adjuvant Chemotherapy patients excluded?

Reply: Neoadjuvant chemotherapy was very rarely administered in Finland during the study period and almost solely to the patients with locally very advanced tumors. Unfortunately, the dataset did not information whether neoadjuvant chemotherapy was given, but these patients still were not excluded from the study. We have now mentioned this in the first paragraph of the Materials and Methods section.

- did lymph node identification/surgery/treatment alter during the decade from 2003? - a statement in the Methods should address this eg: all surgery to the primary tumour was carried out according to guideline x

Reply: We thank Reviewer for noting this. There may have been some changes in the use of surgical techniques during the study period 2003-2013. Since the dataset was centered on oncological treatments, we did not have exact data on the specific surgical techniques. However, breast surgeons in Oulu University Hospital follow the guidelines of the Finnish Breast Cancer Group, and this has been clarified in the first paragraph of the Materials and Methods, as the Reviewer suggests.

- a potential limitation of the study is that the investigators have not (yet?) compared these prognostic variables to theststed (in the Discussion) established prognostic factors (DFI, Bone only mets, ER pos) - perhaps a second paper?

Otherwise, well constructed, well discussed

Reply: We actually tested the if ER positivity, along with some other traditional prognostic factors would be associated with survival in metastatic breast cancer. These results are presented in the fourth paragraph of the Results section. ER status was also included to the multivariate analysis as described in the last paragraph of the Results section.

On the other hand, we did not previously compare in these analyses bone metastases versus other sites of metastases and analysis was neither done according to the disease-free interval. We have now performed these analyses as the Reviewer suggests. The first site of metastasis only in bone (versus elsewhere) or disease-free interval of 24 months or less were not statistically significant prognostic factors in this dataset. We have mentioned these new results in the Results section. We have now also mentioned in the beginning of the Results section that the median disease-free interval was 39.0 months.

Reviewer: 3

Reviewer Name: Tzu-Pin Lu

Institution and Country: Department of Public Health, National Taiwan University, Taiwan

Please state any competing interests or state 'None declared': None

The authors presented a prospective breast cancer study to report important factors associated with the outcome of metastases. The authors need to address the following issues before its publication.

1. The authors need to put more efforts to explain the differences of outcome in different subtypes. It is well-known that different subtypes in breast cancer have severely different outcomes and thus it should be taken into consideration.

Reply: We absolutely agree that there are significant differences in the biology and outcomes of breast cancer subtypes. This was shown also in the current study, where metastatic breast cancer patients with luminal A -like disease had significantly prolonged survival, while e.g. those with triple-negative breast cancer had dismal outcomes. This has been now discussed in more detail in the page 12 as the Reviewer suggests. We have now also reported the median metastatic breast cancer survival rates of each five subtypes in the second paragraph of the Results section. We have now also added the survival comparison between luminal A-like compared to other subtypes

2. The authors must compare their results with other datasets, such as SEERs, the Cancer Registry in other countries. They should not just describe them in Discussion and must present them in Results.

Reply: We understand the Reviewer's point here. The idea of including registry data would be interesting and actually there are already some quite large retrospective datasets published from this topic. The strength in the current study was its prospective setting and up-to-date treatment modalities, which could not be achieved using e.g. SEER database. We have now more underlined the unique nature and the strengths of the current study with a prospective setting and modern treatment modalities in the Discussion.

3. In the single variate analysis, the authors shall consider multiple test correction issue.

Reply: We agree with the Reviewer that multiple testing corrections were not used in this study. This has been now mentioned in the Statistical analyses paragraph in the amended manuscript. After discussing with statisticians, we consider that multiple comparison corrections are too conservative to be used in the current study, since there are not “arbitrary” variables in this study (Rothman KJ Epidemiology 1990 1(1):43-46).

4. The authors shall describe more clearly about the descriptive statistics of the metastasis traits, such as the size and the comparisons between the primary and second tumor tissues,

Reply: We thank Reviewer for this comment. Unfortunately, this dataset did not include data on metastatic tissue, with the exception of the first site of metastasis, which has been reported in the Table 1. Indeed, metastasis biopsies were quite rarely taken at the time of the collection of the study material and guidelines have more strongly recommended metastasis biopsies during the last years.

5. I doubt the usage of the Cox regression. Did the authors check the hazard as a constant through the study period?

Reply: We thank Reviewer for pointing out multivariate analysis methods. We discussed the use of Cox regression method in this particular study also with statisticians. We still consider Cox regression as an appropriate method here, since we needed to take time variable into account, as the hazard was not constantly the same.

VERSION 2 – REVIEW

REVIEWER	Hailin Tang SYSUCC
REVIEW RETURNED	25-May-2020

GENERAL COMMENTS	This manuscript has been corrected. I think that it is appropriate for publication.
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REVIEWER	Chris Pyke University of Queensland, Australia
REVIEW RETURNED	20-May-2020

GENERAL COMMENTS	I am satisfied with this revision.
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REVIEWER	Tzu-Pin Lu Institute of Epidemiology and Preventive Medicine, Department of Public Health, National Taiwan University, Taiwan
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REVIEW RETURNED	21-May-2020
GENERAL COMMENTS	I appreciate the efforts of authors to address my previous comments and I am satisfied with most of them. However, I still have a concern about the last comment of using cox model. I suggest the authors to perform a statistical test to check whether their data follow the proportional hazard assumption before directly using cox model.

VERSION 2 – AUTHOR RESPONSE

We thank you for your interest in our manuscript “The presence of axillary lymph node metastases at the time of definitive breast cancer surgery predicts shorter survival in metastatic disease” (ID bmjopen-2020-038798.R1).

We would also like to thank Reviewer 3 for his/her constructive and useful comment regarding the Cox model. To be exact, the comment from the Reviewer was:

“I appreciate the efforts of authors to address my previous comments and I am satisfied with most of them. However, I still have a concern about the last comment of using cox model. I suggest the authors to perform a statistical test to check whether their data follow the proportional hazard assumption before directly using cox model.”

As the Reviewer suggests, we have now checked with the log minus log plot that all covariates in the Cox model of the manuscript follow the proportional hazard assumption. Therefore we suggest that the criteria for using Cox regression are met in the current model. We have added the following sentence to the last paragraph of the Results section: “The proportional hazards assumption was met in the analysis.”

Hopefully the manuscript now fulfils your requirements and is ready to be published in BMJ Open. We would be pleased to answer any questions related to this manuscript.