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)	Nomogram predicting overall prognosis for invasive micropapillary carcinoma of the breast: a SEER-based population study.
AUTHORS	Liu, Jianpeng; Xi, Wei; Zhou, Jiahao; Gao, Wei; Wu , Qiaolin

VERSION 1 – REVIEW

REVIEWER	Ian Fentiman Guy's Hospital, Research Oncology
REVIEW RETURNED	22-Mar-2023

GENERAL COMMENTS	This nomogram joins an over-crowded collection of publications on survival of patients with invasive micropapillary carcinoma, none of which have been cited by the authors of this manuscript. Li D, et al. A competing nomogram to predict survival outcomes in invasive micropapillary breast cancer. J Cancer (2019) 10: 6801-6812. Ye F-G, et al. Nomogram for predicting preoperative lymph node involvement in patients with invasive micropapillary carcinoma of breast: a SEER population-based study. BMC Cancer (2018) 18:1085-1093. Meng X, et al. Nomogram predicting the risk of locoregional recurrence after mastectomy for invasive micropapillary carcinoma of the breast. Clin Breast Cancer (2020) 21; 368-76. Zhao Y, e al, Nomogram for predicting overall survival in patients with invasive micropapillary carcinoma after breast-conserving surgery: a population-based analysis. Frontiers in Surgery (2022) doi 10.3389 Wang X, et al. Analysis of prognostic factors and construction of prognostic models for invasive micropapillary carcinoma of the breast. Comput Mathematical Methods in Medicine (2022) Article ID 1072218, 9. Chen Y, et al. A prognostic nomogram based on risk assessment for invasive micropapillary carcinoma of the breast after surgery. Cancer Medicine (2023) 00:1–13. Cheng Y, et al. Development and validation of nomograms to predict survival in patients with invasive micropapillary carcinoma of the breast. BMJ Open (2023) ;13:e065312. The latter 2 publications are very recent but the authors should have been aware of the others.

REVIEWER	Francesk Mulita University General Hospital of Patras, Department of Surgery, Breast Unit
REVIEW RETURNED	30-Mar-2023

GENERAL COMMENTS	I was glad to review the work of the authors regarding this very interesting article on nomograms predicting overall survival for invasive micropapillary carcinoma of the breast. The manuscript is well-written and the incorporated tables and figures make the study easy to follow. I strongly recommend acceptance for publication of the paper after minor changes. Despite the major advances in breast cancer surgery, there are still numerous unanswered questions regarding the histological subtype of Invasive micropapillary carcinoma. 1)" Hormonal and HER-2 positivity in invasive micropapillary carcinoma (IMPC) of the breast is also commoner when compared to other Non-Specific Type (NST) carcinomas. IMPC occurs either as a pure form or more often as a component of mixed NST carcinoma." Add this information to the introduction section and consider citing the recently published articles: https://pubmed.ncbi.nlm.nih.gov/35310681/ https://pubmed.ncbi.nlm.nih.gov/36352293/ https://pubmed.ncbi.nlm.nih.gov/35388282/ 2) "According to the literature, evidence from observational studies has linked the pathogenesis of diseases like breast cancer with adipose tissue and mainly with the adipokines that are secreted in its microenvironment, with the catalog continuously expanding" I would like a brief discussion on the role of adipokines in Invasive micropapillary carcinoma of the breast. Please consider citing the recently published article: https://pubmed.ncbi.nlm.nih.gov/36900364/

REVIEWER	Luca Cima Pathology Unit, Santa Chiara Hospital, Department of Laboratory Medicine
REVIEW RETURNED	16-Apr-2023

GENERAL COMMENTS	Liu et al. report an interesting original research about the identification of independent prognostic factors in patients with invasive micropapillary carcinoma of the breast and the development of a nomogram to predict the overall survival of that patients. I think that the work is suitable for publication in BMJ Open journal but it requires some minor changes: - Page 5, line 6: replace the statement "confirmed by positive histology" with the statement "confirmed by histopathological report" - Page 5, line 16: replace the words "regional nodes" with the words "regional lymph-nodes" and do the same throughout all the article - Page 5, line 23: replace the words "White and other" with "white and others" - Page 5, live 27: the grade undifferentiated/anaplastic doesn't exist in Breast Pathology, please remove this concept and refer to the Nottingham grading system (van Dooijeweert C, van Diest PJ, Ellis IO. Grading of invasive breast carcinoma: the way forward. Virchows Arch. 2022 Jan;480(1):33-43. doi: 10.1007/s00428-021-03141-2. Epub 2021 Jul 1. PMID: 34196797; PMCID: PMC8983621.) - Page 7, line 6: please refer to the grades 1, 2 and 3 of the

	Nottingham grading system - Page 10, line 19: please replace the acronym "IDC" for invasive breast carcinoma with the acronym "IBC" and do the same throughout all the article. - Page 10, line 19: please replace the term "subtype" with "special type" and do the same throughout all the article.

REVIEWER	Eiji Nakatani Shizuoka Graduate University of Public Health, Graduate School of Public Health
REVIEW RETURNED	29-Apr-2023

GENERAL COMMENTS	This study aimed to identify prognostic factors for invasive micropapillary carcinoma (IMPC) of the breast and develop a reliable nomogram to predict overall survival (OS) in patients with IMPC. Using data from the SEER database, independent prognostic factors such as age at diagnosis, hormone receptors, the number of positive lymph nodes, and clinical stage were identified. The nomogram demonstrated excellent consistency and predictive ability, offering valuable insights into the risk of each prognostic factor and aiding physicians in predicting 1-, 3-, and 5-year OS for IMPC patients. The content of the study is highly important. Still, the authors are advised to address the following concerns regarding ethics and reproducibility by revising the methodology section and providing appropriate information: 1. Ethical approval for using the SEER database: It is crucial to explicitly state information regarding the ethical approval required for using the SEER database in the description of research methods. It would be desirable to confirm that proper approval has been obtained and provide the details. 2. Anonymity of the SEER database: In the research methods, it is necessary to clearly state that the data obtained from the SEER database is sufficiently anonymized and patient privacy is protected. Specifically, explain that personal information within the dataset has been appropriately removed or masked, and researchers cannot access individual patients. 3. ROC-AUC calculation method: A detailed explanation of the ROC-AUC calculation method in survival time analysis is needed, including the selection of thresholds, computation of prediction probabilities, and calculation of AUC (area under the curve). Additionally, it may be helpful to provide information on software or packages used for ROC-AUC calculation, if necessary. 4. Calculation of annual survival rates using the nomogram: In the nomogram diagram, it is essential to explain the details of how annual survival rates are calculated. This includes clarifying how the scores of each element in the nomogram are summed and converted into the final prediction probabilities. Furthermore, using the nomogram, it would be desirable to provide formulas and conversion methods for calculating 1-year, 3-year, and 5-year survival rates.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

1.This nomogram joins an over-crowded collection of publications on survival of patients with invasive micropapillary carcinoma, none of which have been cited by the authors of this manuscript.
Response: Thanks for your kind reminder. We have added these information in the revised manuscript.

Reviewer 2

1." Hormonal and HER-2 positivity in invasive micropapillary carcinoma (IMPC) of the breast is also commoner when compared to other Non-Specific Type (NST) carcinomas. IMPC occurs either as a pure form or more often as a component of mixed NST carcinoma."
Add this information to the introduction section and consider citing the recently published articles:
https://pubmed.ncbi.nlm.nih.gov/35310681/
https://pubmed.ncbi.nlm.nih.gov/36352293/
https://pubmed.ncbi.nlm.nih.gov/35388282/
Response: We greatly appreciate the helpful suggestions. We have added these information in the revised manuscript (Page 3).

2. "According to the literature, evidence from observational studies has linked the pathogenesis of diseases like breast cancer with adipose tissue and mainly with the adipokines that are secreted in its microenvironment, with the catalog continuously expanding"
I would like a brief discussion on the role of adipokines in Invasive micropapillary carcinoma of the breast. Please consider citing the recently published article:
https://pubmed.ncbi.nlm.nih.gov/36900364/
Response: We appreciate your great comments. The purpose of our study is to analyse the correlation between clinicopathological factors and prognosis. Data of adipokines could not be collected directly from the SEER database, so we could not discuss the relationship between adipokines and prognosis.

Reviewer 3

- Page 5, line 6: replace the statement "confirmed by positive histology" with the statement "confirmed by histopathological report"
Response: Thanks for your kind reminder. We have replaced the statement in the revised manuscript.

- Page 5, line 16: replace the words "regional nodes" with the words "regional lymph-nodes" and do the same throughout all the article
Response: Thanks for your kind reminder. We have replaced the words in the revised manuscript.

- Page 5, line 23: replace the words "White and other" with "white and others"
Response: Thanks for your kind reminder. We have replace the words in the revised manuscript.

- Page 5, live 27: the grade undifferentiated/anaplastic doesn't exist in Breast Pathology, please remove this concept and refer to the Nottingham grading system (van Dooijeweert C, van Diest PJ, Ellis IO. Grading of invasive breast carcinoma: the way forward. Virchows Arch. 2022 Jan;480(1):33-43. doi: 10.1007/s00428-021-03141-2. Epub 2021 Jul 1. PMID: 34196797; PMCID: PMC8983621.)
Response: Thanks for your kind reminder. As the date of the grade was downloaded directly from the SEER database, and histological information for each case was not available, so we could not re-grade the cases from the SEER database based on the Nottingham score. Although reviewer's suggestions are very interesting, we would like to take your suggestion in future work.

- Page 7, line 6: please refer to the grades 1, 2 and 3 of the Nottingham grading system
Response: Thanks for great comments. We were not able to re-grade the cases in the SEER database based on the Nottingham score. We would like to use the Nottingham grading system in future.

- Page 10, line 19: please replace the acronym "IDC" for invasive breast carcinoma with the acronym "IBC" and do the same throughout all the article.
Response: Thank you very much for your suggestion. We are sorry for our negligence and we have replace the acronyms in the revised manuscript.

- Page 10, line 19: please replace the term "subtype" with "special type" and do the same throughout all the article.
Response: Thanks for your kind reminder. We have replace the term in the revised manuscript.

Reviewer 4
1.Ethical approval for using the SEER database: It is crucial to explicitly state information regarding the ethical approval required for using the SEER database in the description of research methods. It would be desirable to confirm that proper approval has been obtained and provide the details.
Response: Thanks for your kind reminder. Patient data were collected from the SEER database. This database holds data related to the incidence of cancer from 18 population-based cancer registries that represent about 30% of the population of the USA.

2. Anonymity of the SEER database: In the research methods, it is necessary to clearly state that the data obtained from the SEER database is sufficiently anonymized and patient privacy is protected. Specifically, explain that personal information within the dataset has been appropriately removed or masked, and researchers cannot access individual patients.
Response: Thanks for your kind reminder. The data released from the SEER database did not require informed patient consent because cancer is a reportable disease in every state in the US.

3.ROC-AUC calculation method: A detailed explanation of the ROC-AUC calculation method in survival time analysis is needed, including the selection of thresholds, computation of prediction probabilities, and calculation of AUC (area under the curve). Additionally, it may be helpful to provide information on software or packages used for ROC-AUC calculation, if necessary.
Response: Thanks for your kind reminder. We have mentioned the methodology calculation in the methods section of the article. The SEER data were extracted using SEERStat 8.4.0, and statistical analyses were performed using SPSS version 26.0 (IBM-SPSS Inc., Armonk, NY).

4.Calculation of annual survival rates using the nomogram: In the nomogram diagram, it is essential to explain the details of how annual survival rates are calculated. This includes clarifying how the scores of each element in the nomogram are summed and converted into the final prediction probabilities. Furthermore, using the nomogram, it would be desirable to provide formulas and conversion methods for calculating 1-year, 3-year, and 5-year survival rates.
Response: Thanks for your kind reminder. The detailed annual survival rates are calculated by pagage comes with the R language. Firstly, the relevant prognostic factors were determined and assigned by univariate and multivariate cox regression analysis in the early stage, and 1-year, 3-year, and 5-year survival rates of patients were evaluated by the sum of assigned values.

VERSION 2 – REVIEW

REVIEWER	Luca Cima Pathology Unit, Santa Chiara Hospital, Department of Laboratory Medicine

REVIEW RETURNED	30-May-2023

GENERAL COMMENTS	The requests were satisfied, from my side the manuscript can be considered 'accepted' for publication in BMJ Open

REVIEWER	Eiji Nakatani Shizuoka Graduate University of Public Health, Graduate School of Public Health
REVIEW RETURNED	25-May-2023

GENERAL COMMENTS	Thank you for the opportunity to review your manuscript. After carefully considering your responses to my comments, I regret to inform you that I cannot recommend the manuscript for publication in its current form due to the following reasons: Ethical approval for using the SEER database: While you've stated that the SEER database is publicly available and de-identified, there is no specific confirmation or proof based on ethical guidelines provided. Anonymity of the SEER database: The assertion that no personal information is included in the SEER database is noted. However, a detailed explanation of how this anonymity is maintained or how personal data is handled during the data processing stages is lacking. ROC-AUC calculation method: I noticed you mentioned the software and packages used for the ROC-AUC calculation, but the specific computation process is not explained sufficiently. Calculation of annual survival rates using the nomogram: The description of the use of an R package and a statistical method for calculating survival rates is understood, but the specific application and calculation details are unclear. Given these significant issues, I recommend that the manuscript be revised to address these concerns before resubmission. I hope my comments are helpful for the improvement of your manuscript.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 4

Dr. Eiji Nakatani, Shizuoka Graduate University of Public Health

Comments to the Author:

Thank you for the opportunity to review your manuscript. After carefully considering your responses to my comments, I regret to inform you that I cannot recommend the manuscript for publication in its current form due to the following reasons:

Ethical approval for using the SEER database: While you've stated that the SEER database is publicly available and de-identified, there is no specific confirmation or proof based on ethical guidelines provided.

Response: Thanks for your comments. We have submitted an expedited ethical review to the Ethics Committee in Clinical Research of the First Affiliated Hospital of Wenzhou Medical University. It has now been approved.

Anonymity of the SEER database: The assertion that no personal information is included in the SEER database is noted. However, a detailed explanation of how this anonymity is maintained or how personal data is handled during the data processing stages is lacking.

Response: Thanks for your comments. We have edited the manuscript according to your instructions (Page 5).

ROC-AUC calculation method: I noticed you mentioned the software and packages used for the ROC-AUC calculation, but the specific computation process is not explained sufficiently.

Response: Thanks for your comments. We have revised the manuscript according to your instructions (Page 6).

Calculation of annual survival rates using the nomogram: The description of the use of an R package and a statistical method for calculating survival rates is understood, but the specific application and calculation details are unclear.

Response: Thanks for your comments. We have revised the manuscript according to your instructions (Page 5).

Given these significant issues, I recommend that the manuscript be revised to address these concerns before resubmission. I hope my comments are helpful for the improvement of your manuscript.

Reviewer: 3

Dr. Luca Cima, Pathology Unit, Santa Chiara Hospital

Comments to the Author:

The requests were satisfied, from my side the manuscript can be considered 'accepted' for publication in BMJ Open