

Novel Nomograms to Predict of Overall Survival and Cancer-specific Survival of Patients of Metaplastic Breast Cancer

Yongfeng Li

Zhejiang University School of Medicine Sir Run Run Shaw Hospital

Daobao Chen

Institute of cancer research and basic medical sciences of Chinese Academy of sciences

Haojun Xuan

Institute of cancer research and basic medical science of Chinese Academy of Sciences

Mihnea P. Dragomir

The University of Texas MD Anderson Cancer Center

George A. Calin

The University of Texas MD Anderson Cancer Center

Hongjian Yang

Institute of cancer research and basic medical sciences of Chinese academy of Sciences

Meng Chen

The University of Texas MD Anderson Cancer Center

hongchuan Jin (✉ hongchuanjin2020@126.com)

Department of Breast Surgery, Institute of Cancer Research and Basic Medical Sciences of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Hangzhou, Zhejiang 310022, P.R. China

Research

Keywords: metaplastic breast cancer, nomogram, overall survival, cancer-specific survival

Posted Date: October 27th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-96114/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background

Metaplastic breast cancer (MBC) is a rare type of breast cancer with an increasing incidence, we aim to develop clinical nomograms to predict the overall survival and cancer-specific survival for patients with MBC.

Methods

Patients data were collected from the SEER database between 1973 and 2015. All included patients were randomly assigned into the training and validation sets. Univariate and multivariate Cox analysis were performed to identify independent prognostic factors of MBC. These essential prognostic variables were combined to construct nomogram models to predict overall survival (OS) and cancer-specific survival (CSS) in patients with MBC. Model performance was evaluated by concordance index (C-index) and calibration plots.

Results

A total of 1835 patients were collected and divided into the training (1223) and validation (612) groups. The multivariate Cox model identified age, TNM stage, T stage, and N stage, chemotherapy and radiotherapy as independent covariates associated with OS, while these variables except for age and chemotherapy were independent prognostic factors of CSS. The nomogram constructed based on these covariates demonstrated excellent accuracy in estimating 3-, and 5-year OS and CSS, with a C-index of 0.759 (95% CI, 0.746-0.772) for OS and 0.766 (95% CI, 0.751-0.781) for CSS in the training cohort. In the validation cohort, the nomogram-predicted C-index was 0.754 for OS (95%CI, 0.734-0.774) and 0.752 (95%CI, 0.728-0.776) for CSS. All calibration curves exhibited good consistency between predicted and actual survival.

Conclusions

These nomogram models established in this study can help to enhance the accuracy of prognostic prediction, which may thereby improve individualized assessment of survival risks and facilitate to provide constructive therapeutic suggestions.

Background

Metaplastic breast carcinoma (MBC) is a relatively rare form of breast cancer with worse clinical outcomes and resistance to neoadjuvant systemic chemotherapies[1], accounting for 0.2-5% of all breast cancers [2]. The incidence of MBC is increasing since it was recognized as a distinct pathological diagnosis in 2000[3]. Histologically, MBC is classified into several subtypes, including spindle, squamous, chondroid, osseous and/or rhabdomyoid MBC[4]. MBC commonly shows a triple negative breast cancer (TNBC) phenotype, due to the lack of expression of the ER, PR and HER2 [5], and is

managed with surgical resection in combination with radiotherapy and chemotherapy [1]. However, only radiotherapy shows improvement on overall survival (OS) in MBC patients[6]. Compared with invasive ductal carcinoma, the 5-year survival rate for MBC remains poor owing to its rapid tumor growth rate and chemoresistance [7, 8]. The Surveillance, Epidemiology, and End Results database (SEER database) is an annually updated and population-based database, covering about 30% of the US population. It has become a distinctive resource to investigate special malignancies, such as MBC, by taking advantages of its wide range of data on cancer.

Nomograms have been proposed as a novel and dependable tool to incorporate demographic and clinicopathologic factors for accurate prognostic prediction of many cancers. They were generated from regression analysis and showed to compare favorably to the standard TNM staging systems. Currently, to our knowledge, there was no available nomograms for individual MBC patients derived from population-based data. Herein, we aim to establish a novel nomogram to forecast individualized survival of MBC depended on the personalized demographic, pathologic and therapeutic information from the SEER database.

Materials And Methods

Patient population

Date of patients with MBC diagnosed between 1973 and 2015 was obtained from the SEER program of the National Cancer Institute. Demographic variables of interest for each case included age at diagnosis, race, marital status, grade, status of ER and PR, American Joint Committee on Cancer (AJCC) tumor stage, T stage, N stage, and treatment information including (surgery for the primary site, record of chemotherapy and adjuvant radiotherapy). The following SEER ICD-0-3 codes, including 8052, 8070-8072, 8074, 8560, 8571, 8572, 8575, and 8980 were adopted to identify cases of MBC. Patients with unknown race and marital status, unavailable pathological or survival data were excluded. Figure 1 illustrates the detailed flow diagram for patients screening.

Nomogram construction and conformation

Patients were randomly divided into the training set and validation set with a ratio of 2:1. Univariate and multivariate analyses were carried out by employing the Cox proportional hazard regression models to determine the hazard ratio (HR) along with corresponding 95% confidence interval (CI) for all possible risk factors. All independent risk factors were identified by the forward stepwise selection method using the multivariate Cox proportional hazards models. The nomogram was established by combining all independent risk factors prognostic factors for the prediction of the 3-year and 5-year OS and CSS using the “rms” R package (cran.rproject.org/web/packages/rms). The Harrell’s concordance index (C-index) was used to access the discrimination, and . calibration curves were applied to estimate the consistency between the actual prognosis and the nomogram-predicted survival probability of the model.

Statistical analysis

IBM SPSS statistics 22 software (SPSS Inc., Chicago, IL, USA) was used to conduct statistical analysis. R software v 3.6.1 (<http://www.r-project.org>) was adopted to construct nomograms based on the multivariate results and the “RMS” package was used to develop survival models. The two-tailed *P*-value <0.05 was assumed statistically significant.

Results

Patients characteristics

We obtained a total 1835 patients with MBC in the study, and the demographic and clinical characteristics of included patients were presented in Table 1. All included patients were allocated randomly into two datasets, including 1223 patients randomly assigned to the training set and 612 patients to the validation set. Of these patients, 908 (50.5%) patients were diagnosed at the age more than 60 years, most patients (77.1%) were white, and 85.4% were married. For the degree of cancer differentiation, poorly differentiated (Grade III) was the most type 1425 (77.7%). 1504 (82.0%) and 1591 (86.7%) patients were observed to negatively express ER and PR, respectively. According to the AJCC7 system, stage III was the most type (61.1%), follow by stage I (23.3%) and stage III (15.5%). Most patients (58.0%) received mastectomy and were categorized as T2 stage (52.3%). Meanwhile, most patients (75.9%) were categorized as N0 stage. More than half of patients (67.6%) had undergone chemotherapy, while 48.8% patients had undergone radiotherapy.

Prognostic factors of OS and CSS

According to univariate analysis performed among the training cohort, eight variables including age, grade, TNM stage, T stage, N stage, surgery for the primary site, chemotherapy and radiotherapy were significantly associated with OS in patients with MBC. Meanwhile, those variables, except for age and chemotherapy, were also found to be significantly associated with CSS of MBC patients. Further multivariate analysis indicated that age, TNM stage, T stage, N stage, chemotherapy and radiotherapy were identified as independent prognostic factors of OS of patients with MBC. Moreover, TNM stage, T stage, N stage and radiotherapy were also identified as independent prognostic factors of CSS of MBC patients, as shown in Table 2 and Table 3.

Construction and validation of OS and CSS

According to the results of multivariate analysis, all independent prognostic factors in the training set were incorporated to create the nomograms for estimating 3- and 5- year OS and CSS of patients with MBC. Figure 2(a) and Figure 2(b) showed the prediction of the 3- and 5-year OS and CSS in the nomogram, respectively. Each factor was allocated a score on the points scale in the nomogram, and we can estimate the 3- and 5-year survival probability of patients with MBC by calculating the total score via adding up all points on the basis of personal patients features.

Nomograms were validated using C-index in the training set and validation set, respectively. The results showed sufficient accuracy in forecasting the prognosis of MBC in training set and validation set. The C-index of the nomogram for OS and CSS is 0.759 (95% CI, 0.746-0.772) and 0.766 (95% CI, 0.751-0.781) in the training set, respectively (Table 4). The C-index calculated from the validation set is 0.754 (95% CI, 0.734-0.774) in OS and 0.752 (95% CI, 0.728-0.776) in CSS, respectively. The calibration plots showed good coordination between prediction by nomogram models and observed outcomes in the probability of 3- and 5-year OS and CSS of patients with MBC in both training cohort and validation set (Figure 3).

Discussion

Metaplastic breast cancer is a kind of heterogenous breast cancer, which is relatively rare in clinical practice. Despite several studies have found risk factors related to the clinical outcomes of MBC patients[9-11], there is no recognized prognostic factors to predict the prognosis of MBC. Paul Wright et al.[12] found that for patients with positive or negative hormone receptors, there was no significant difference in the 5-year survival rate of MBC, which indicated that the status of hormone receptors could not be considered as a prognostic factor of MBC. Additionally, previous study demonstrated that the subtype of MBC could be an independent predictor of its prognosis[3]. Several studies revealed that the prognosis of MBC patients with larger tumor and lymph node metastasis are generally poor[9, 13]. In recent years, some studies have also focused on the relationship between gene signatures and prognosis of MBC patients, such as the high expression of RPL39[11] and the mutation of the colony stimulating factor 1 receptor (CSF1R)[14], all of which can indicate poor prognosis.

However, single prognostic factors play a limited role in predicting individual survival probability. Nomograms are graphical display of mathematical models for predicting cancer risk, prevention and therapeutic outcomes, which becomes increasingly popular clinical decision aids thanks to their ability to deal with complex problems in a systematic and unbiased manner[15-17]. It has been revealed that nomograms exhibited more excellent prediction precision and prognostic value in diverse malignancies than the existing tumor system[18, 19]. To construct a prognostic nomogram, we conducted univariate and multivariate analyses to find clinical characteristics that correlated with the OS and CSS of MBC patients on the basis of a large data set from the SEER database. We demonstrated that several clinicopathological characteristics were independent prognostic factors for OS, including age, grade, TNM stage, T stage, N stage, surg_prim_site, chemotherapy and radiotherapy. Furthermore, age, TNM stage, T stage, N stage, chemotherapy and radiotherapy were identified as independent prognostic factors for OS via multivariate analysis. In addition, grade, TNM stage, T stage, N stage, surg_prim_site and radiotherapy were found to be associated with CSS via univariate analysis, and further multivariate analysis confirmed that TNM stage, T stage, N stage and radiotherapy were independent prognostic factors for CSS of MBC patients. The nomograms established in this study showed favorable discrimination and calibration for 3-year and 5-year OS and CSS of MBC patients and offered a more accurate and personalized clinical tool for prognosis evaluation of MBC patients.

Prognostic studies have given conflicting results regarding factors associated with prognosis and survival [20-30]. In the present study, we critically evaluated the prognostic value of various factors based on a large cases of MBC recorded on the SEER. The clinical significance of age, TNM stage, T stage, N stage, chemotherapy, radiotherapy in MBC patients were highlighted in nomogram models. The result demonstrated that half of patients were older than 60 years, who suffered worst survival and poor OS. Of note, age showed no significant influence on CSS. Patients with older age generally accompanied a higher-risk histological phenotype[31], which has been considered as an independent risk factor and may eventually result in lower survival [31]. In these patients, surgical resection of the primary site is the mainstay of therapy with mastectomy more than lumpectomy, which was consistent with previous study[35]In addition, we found that chemotherapy is an independent prognostic factor for OS in MBC patients. Although it is correlated with CSS in univariate analysis, it is not an independent prognostic factor for CSS. It may result from the worse response to chemotherapy regimens in MBC[21, 25, 27, 36, 37]. Previous studies have concluded that radiotherapy was able to improve the survival of patients with MBC [8, 28, 38], and our data also demonstrated that radiation was independently prognostic factors associated with survival probability of patients with MBC. Moreover, radiotherapy was revealed to be able to reduce the risk of local recurrence[39]. T stage represents the tumor size and extrathyroidal extension, and our results demonstrated that T4 has an impact on OS and CSS in MBC patients, which was in line with previous population-based study of MBC [8]. LNM has been identified as a key prognostic indicator for a variety of malignancies, and the number of LNM has been included into the N-staging. Previous studies reported that lymph node status was significantly correlated with survival endpoints in patients with MBC [8]

There were several potential shortcomings in this study. First, retrospective data retrieved from the same database was used in the generation and validation of the nomogram models, which may lead to the risk of potential selection bias. Therefore, it would be more reliable to validate the nomograms in another dataset. Second, in this study, we only included two endpoints: 3- and 5-year survival. However, the assessment of recurrence risk is considered as a more meaningful endpoint than OS or CSS because of the rare specific mortality of MBC, which was not performed in this study owing to the lack of data with respect to recurrence in SEER database. Moreover, several other crucial prognostic factors, such as RET mutation status and calcitonin doubling times, were also unavailable in the SEER database

Conclusion

In the present study, the nomograms reliably predicted 3- and 5-year OS and CSS of MBC patients were successfully established and well-validated on the basis of large population from SEER. These nomograms could assist clinicians to estimate the risk of tumor surgery and other prognostic factors and make individualized decisions, although the models require more powerful evidence from prospective trials.

Abbreviations

MBC: Metaplastic breast cancer; CSS: cancer-specific survival; C-index: concordance index; SEER: the Surveillance, Epidemiology, and End Results ; CSF1R: colony stimulating factor 1 receptor

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

Funding

The study was supported by the Zhejiang Provincial Health Department Foundation (Grant No. 2018ky284), the Natural Science Foundation of Zhejiang Province (Grant No. LQ17H160013). The funding body was not involved in the design of the study, collection, analysis, and interpretation of data, nor the writing the manuscript. The content is solely the responsibility of the authors.

Authors' contributions

Conceptualization: YFL and DBC.

Data curation: YFL, HJX, MPD and GAC

Formal analysis: MPD and GAC.

Funding acquisition: YFL.

Project administration: HCJ, MC

Methodology:YFL, MPD, GAC and HJY.

Writing-original draft: YFL, MC .

Writing-review&editing: MC and HCJ.

All authors have read and approved the final manuscript.

Acknowledgements

We are grateful to all researchers of enrolled studies.

References

1. Rayson D, Adjei AA, Suman VJ, Wold LE, Ingle JN: **Metaplastic breast cancer: prognosis and response to systemic therapy.***Ann Oncol* 1999, **10**:413-419.
2. Moreno AC, Lin YH, Bedrosian I, Shen Y, Babiera GV, Shaitelman SF: **Outcomes after Treatment of Metaplastic Versus Other Breast Cancer Subtypes.***J Cancer* 2020, **11**:1341-1350.
3. Lee H, Jung SY, Ro JY, Kwon Y, Sohn JH, Park IH, Lee KS, Lee S, Kim SW, Kang HS, et al: **Metaplastic breast cancer: clinicopathological features and its prognosis.***J Clin Pathol* 2012, **65**:441-446.
4. Lakhani S, Ellis I, Schnitt S, Tan P, van de Vijver M: *WHO Classification of Tumours of the Breast*. 4 edn. Lyon: IARC; 2012.
5. Corso G, Frassoni S, Girardi A, De Camilli E, Montagna E, Intra M, Bottiglieri L, Margherita DSA, Fanianos DM, Magnoni F, et al: **Metaplastic breast cancer: Prognostic and therapeutic considerations.***J Surg Oncol* 2020.
6. He X, Ji J, Dong R, Liu H, Dai X, Wang C, Esteva FJ, Yeung SJ: **Prognosis in different subtypes of metaplastic breast cancer: a population-based analysis.***Breast Cancer Res Treat* 2019, **173**:329-341.
7. Tray N, Taff J, Adams S: **Therapeutic landscape of metaplastic breast cancer.***Cancer Treat Rev* 2019, **79**:101888.
8. Nelson RA, Guye ML, Luu T, Lai LL: **Survival outcomes of metaplastic breast cancer patients: results from a US population-based analysis.***Ann Surg Oncol* 2015, **22**:24-31.
9. Xiao M, Yang Z, Tang X, Mu L, Cao X, Wang X: **Clinicopathological characteristics and prognosis of metaplastic carcinoma of the breast.***Oncol Lett* 2017, **14**:1971-1978.
10. Lee H, Jung S, Ro JY, Kwon Y, Sohn JH, Park IH, Lee KS, Lee S, Kim SW, Kang HS: **Metaplastic breast cancer: clinicopathological features and its prognosis.***J Clin Pathol* 2012, **65**:441-446.
11. Dave B, Gonzalez DD, Liu Z, Li X, Wong H, Granados S, Ezzedine NE, Sieglaff DH, Ensor JE, Miller KD: **Role of RPL39 in metaplastic breast cancer.***JNCI: Journal of the National Cancer Institute* 2017, **109**:w292.
12. Wright GP, Davis AT, Koehler TJ, Melnik MK, Chung MH: **Hormone receptor status does not affect prognosis in metaplastic breast cancer: a population-based analysis with comparison to infiltrating ductal and lobular carcinomas.***Ann Surg Oncol* 2014, **21**:3497-3503.
13. Song Y, Liu X, Zhang G, Song H, Ren Y, He X, Wang Y, Zhang J, Zhang Y, Sun S: **Unique clinicopathological features of metaplastic breast carcinoma compared with invasive ductal carcinoma and poor prognostic indicators.***World J Surg Oncol* 2013, **11**:129.
14. Edenfield J, Schammel C, Collins J, Schammel D, Edenfield WJ: **Metaplastic breast cancer: molecular typing and identification of potential targeted therapies at a single institution.***Clin Breast Cancer*

2017, **17**:e1-e10.

15. Iasonos A, Schrag D, Raj GV, Panageas KS: **How to build and interpret a nomogram for cancer prognosis.***J Clin Oncol* 2008, **26**:1364-1370.
16. Balachandran VP, Gonen M, Smith JJ, DeMatteo RP: **Nomograms in oncology: more than meets the eye.***The lancet oncology* 2015, **16**:e173-e180.
17. Attiyeh MA, Fernández-Del CC, Al ME, Eaton AA, Gönen M, Batts R, Pergolini I, Rezaee N, Lillemoe KD, Ferrone CR: **Development and validation of a multi-institutional preoperative nomogram for predicting grade of dysplasia in intraductal papillary mucinous neoplasms (IPMNs) of the pancreas: a report from the pancreatic surgery consortium.***Ann Surg* 2018, **267**:157-163.
18. Wang Z, Qiu M, Jiang Y, Zhou Z, Li G, Xu R: **Comparison of prognostic nomograms based on different nodal staging systems in patients with resected gastric cancer.***J Cancer* 2017, **8**:950.
19. Zhang Z, Luo Q, Yin X, Dai Z, Basnet S, Ge H: **Nomograms to predict survival after colorectal cancer resection without preoperative therapy.***Bmc Cancer* 2016, **16**:658.
20. Foschini MP, Dina RE, Eusebi V: **Sarcomatoid neoplasms of the breast: proposed definitions for biphasic and monophasic sarcomatoid mammary carcinomas.** In; 1993-01-01.; 1993: 128-136.
21. Rayson D, Adjei AA, Suman VJ, Wold LE, Ingle JN: **Metaplastic breast cancer: prognosis and response to systemic therapy.***Ann Oncol* 1999, **10**:413-419.
22. Hennessy BT, Giordano S, Broglio K, Duan Z, Trent J, Buchholz TA, Babiera G, Hortobagyi GN, Valero V: **Biphasic metaplastic sarcomatoid carcinoma of the breast.***Ann Oncol* 2006, **17**:605-613.
23. Tse GM, Tan PH, Putti TC, Lui PC, Chaiwun B, Law BK: **Metaplastic carcinoma of the breast: a clinicopathological review.***J Clin Pathol* 2006, **59**:1079-1083.
24. Luini A, Aguilar M, Gatti G, Fasani R, Botteri E, Brito JAD, Maisonneuve P, Vento AR, Viale G: **Metaplastic carcinoma of the breast, an unusual disease with worse prognosis: the experience of the European Institute of Oncology and review of the literature.***Breast Cancer Res Tr* 2007, **101**:349-353.
25. Jung S, Kim HY, Nam B, Min SY, Lee SJ, Park C, Kwon Y, Kim E, Ko KL, Shin KH: **Worse prognosis of metaplastic breast cancer patients than other patients with triple-negative breast cancer.***Breast Cancer Res Tr* 2010, **120**:627-637.
26. Yamaguchi R, Horii R, Maeda I, Suga S, Makita M, Iwase T, Oguchi M, Ito Y, Akiyama F: **Clinicopathologic study of 53 metaplastic breast carcinomas: their elements and prognostic implications.***Hum Pathol* 2010, **41**:679-685.
27. Bae SY, Lee SK, Koo MY, Hur SM, Choi M, Cho DH, Kim S, Choe J, Lee JE, Kim J: **The prognoses of metaplastic breast cancer patients compared to those of triple-negative breast cancer patients.***Breast Cancer Res Tr* 2011, **126**:471-478.
28. Tseng WH, Martinez SR: **Metaplastic breast cancer: to radiate or not to radiate?***Ann Surg Oncol* 2011, **18**:94-103.
29. Lee H, Jung S, Ro JY, Kwon Y, Sohn JH, Park IH, Lee KS, Lee S, Kim SW, Kang HS: **Metaplastic breast cancer: clinicopathological features and its prognosis.***J Clin Pathol* 2012, **65**:441-446.

30. Lester TR, Hunt KK, Nayeemuddin KM, Bassett RL, Gonzalez-Angulo AM, Feig BW, Huo L, Rourke LL, Davis WG, Valero V: **Metaplastic sarcomatoid carcinoma of the breast appears more aggressive than other triple receptor-negative breast cancers.***Breast Cancer Res Tr* 2012, **131**:41-48.
31. Kwong N, Medici M, Angell TE, Liu X, Marqusee E, Cibas ES, Krane JF, Barletta JA, Kim MI, Larsen PR: **The influence of patient age on thyroid nodule formation, multinodularity, and thyroid cancer risk.***The Journal of Clinical Endocrinology & Metabolism* 2015, **100**:4434-4440.
32. Shen W, Sakamoto N, Yang L: **Cancer-specific mortality and competing mortality in patients with head and neck squamous cell carcinoma: a competing risk analysis.***Ann Surg Oncol* 2015, **22**:264-271.
33. Skillington SA, Kallogjeri D, Lewis JS, Piccirillo JF: **Prognostic importance of comorbidity and the association between comorbidity and p16 in oropharyngeal squamous cell carcinoma.***JAMA Otolaryngology–Head & Neck Surgery* 2016, **142**:568-575.
34. Wray CJ, Phatak UR, Robinson EK, Wiatek RL, Rieber AG, Gonzalez A, Ko TC, Kao LS: **The effect of age on race-related breast cancer survival disparities.***Ann Surg Oncol* 2013, **20**:2541-2547.
35. Pezzi CM, Patel-Parekh L, Cole K, Franko J, Klimberg VS, Bland K: **Characteristics and treatment of metaplastic breast cancer: analysis of 892 cases from the National Cancer Data Base.***Ann Surg Oncol* 2007, **14**:166-173.
36. Moulder S, Moroney J, Helgason T, Wheler J, Booser D, Albarracin C, Morrow PK, Koenig K, Kurzrock R: **Responses to liposomal Doxorubicin, bevacizumab, and temsirolimus in metaplastic carcinoma of the breast: biologic rationale and implications for stem-cell research in breast cancer.***J Clin Oncol* 2011, **29**:e572-e575.
37. Nagao T, Kinoshita T, Hojo T, Tsuda H, Tamura K, Fujiwara Y: **The differences in the histological types of breast cancer and the response to neoadjuvant chemotherapy: the relationship between the outcome and the clinicopathological characteristics.***The Breast* 2012, **21**:289-295.
38. Ong CT, Campbell BM, Thomas SM, Greenup RA, Plichta JK, Rosenberger LH, Force J, Hall A, Hyslop T, Hwang ES: **Metaplastic breast cancer treatment and outcomes in 2500 patients: a retrospective analysis of a national oncology database.***Ann Surg Oncol* 2018, **25**:2249-2260.
39. Leyrer CM, Berriochoa CA, Agrawal S, Donaldson A, Calhoun BC, Shah C, Stewart R, Moore HC, Tendulkar RD: **Predictive factors on outcomes in metaplastic breast cancer.***Breast Cancer Res Tr* 2017, **165**:499-504.
40. Han M, Salamat A, Zhu L, Zhang H, Clark BZ, Dabbs DJ, Carter GJ, Brufsky AM, Jankowitz RC, Puhalla SL: **Metaplastic breast carcinoma: a clinical-pathologic study of 97 cases with subset analysis of response to neoadjuvant chemotherapy.***Modern Pathol* 2019:1.
41. Zhang Y, Lv F, Yang Y, Qian X, Lang R, Fan Y, Liu F, Li Y, Li S, Shen B: **Clinicopathological features and prognosis of metaplastic breast carcinoma: experience of a major Chinese cancer center.***Plos One* 2015, **10**:e131409.

Tables

Table 1. Characteristics of the training and validation cohorts.

Variables	All patients (N=1835)		Training set (n=1223)		Validation set (n=612)	
	N	%	N	%	N	%
Age						
<60	908	49.5	617	50.4	291	47.5
≥60	927	50.5	606	49.6	321	52.5
Race						
White	1414	77.1	945	77.3	469	76.6
Black	295	16.1	202	16.5	93	15.2
Others	126	6.9	76	6.2	50	8.2
Marital						
Single	268	14.6	181	14.8	87	14.2
Married	1567	85.4	1042	85.2	525	85.8
Grade						
G1	86	4.7	56	4.6	30	4.9
G2	239	13.0	159	13.0	80	13.1
G3	1425	77.7	945	77.3	480	78.4
G4	85	4.6	63	5.2	22	3.6
ER						
negative	1504	82.0	1014	82.9	490	80.1
positive	331	18.0	209	17.1	122	19.9
PR						
negative	1591	86.7	1069	87.4	522	85.3
positive	244	13.3	154	12.6	90	14.7
Stage ajcc7						
I	428	23.3	298	24.4	130	21.2
II	1122	61.1	732	59.9	390	63.7
III	285	15.5	193	15.8	92	15.0
Stage_T						

T1	478	26.0	325	26.6	153	25.0
T2	960	52.3	636	52.0	324	52.9
T3	285	15.5	186	15.2	99	16.2
T4	112	6.1	76	6.2	36	5.9
Stage_N						
N0	1392	75.9	925	75.6	467	76.3
N1	308	16.8	204	16.7	104	17.0
N2	83	4.5	60	4.9	23	3.8
N3	52	2.8	34	2.8	18	2.9
Surg prim site						
Lumpectomy	771	42.0	514	42.0	257	42.0
Mastectomy	1064	58.0	709	58.0	355	58.0
Chemotherapy						
No/unknown	594	32.4	389	31.8	205	33.5
Yes	1241	67.6	834	68.2	407	66.5
Radiation						
No/unknown	940	51.2	624	51.0	316	51.6
Yes	895	48.8	599	49.0	296	48.4

Table 2. Univariate and multivariate analyses of variables associated with OS

Variables	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P value	HR (95%CI)	P value
Age				
<60	Reference			
≥60	1.786(1.436-2.221)	<0.001	1.653(1.307-2.089)	<0.001
Race		0.791		
Black	Reference			
White	0.923(0.684-1.246)	0.601		
Other	1.088(0.705-1.682)	0.703		
Marital				
Married	Reference			
Single	0.842(0.631-1.124)	0.244		
Grade		0.004		
G1	Reference			
G2	2.023(0.904-4.531)	0.087		
G3	2.584(1.220-5.474)	0.013		
G4	3.819(1.677-8.695)	0.001		
ER				
negative	Reference			
positive	0.933(0.689-1.264)	0.656		
PR				
negative	Reference			
positive	0.861(0.612-1.212)	0.392		
Stage ajcc7		<0.001		0.002
I	Reference			
II	2.421(1.686-3.476)	<0.001	3.506(1.731-7.101)	<0.001
III	8.743(5.987-12.767)	<0.01	4.403(1.786-10.855)	0.001
Stage_T		<0.001		<0.001
T1	Reference			

T2	1.776(1.280-2.464)	0.001	0.585(0.316-1.084)	0.088
T3	5.175(3.631-7.376)	<0.001	1.595(0.835-3.047)	0.157
T4	9.686(6.491-14.453)	<0.001	2.467(1.148-5.299)	0.021
Stage_N		<0.001		0.006
N0	Reference			
N1	1.901(1.463-2.469)	<0.001	1.220(0.878-1.695)	0.235
N2	3.767(2.602-5.453)	<0.001	2.265(1.286-3.991)	0.005
N3	5.174(3.433-7.798)	<0.001	2.409(1.396-4.155)	0.002
Surg prim site				
Lumpectomy	Reference			
Mastectomy	2.581(2.020-3.298)	<0.001	1.202(0.899-1.607)	0.213
Chemotherapy				
No/unknown	Reference			
Yes	0.657(0.529-0.816)	<0.001	0.689(0.538-0.882)	0.003
Radiation				
No/unknown	Reference			
Yes	0.656(0.528-0.814)	<0.001	0.666(0.530-0.836)	<0.001

Table 3. Univariate and multivariate analyses of variables associated with CSS

Variables	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P value	HR (95%CI)	P value
Age				
<60	Reference			
≥60	1.185(0.925-1.517)	0.179		
Race				
Black	Reference			
White	0.916(0.648-1.297)	0.622		
Other	1.054(0.633-1.755)	0.839		
Marital				
Married	Reference			
Single	0.745(0.541-1.026)	0.071		
Grade		0.001		0.409
G1	Reference			
G2	1.495(0.561-3.984)	0.421	1.086(0.405-2.913)	0.870
G3	2.826(1.164-6.863)	0.022	1.438(0.585-3.534)	0.428
G4	3.988(1.510-10.531)	0.005	1.754(0.655-4.698)	0.264
ER				
negative	Reference			
positive	0.923(0.651-1.309)	0.654		
PR				
negative	Reference			
positive	0.870(0.588-1.289)	0.489		
Stage ajcc7		<0.001		0.003
I	Reference			
II	3.306(2.019-5.414)	<0.001	4.240(1.809-9.939)	0.001
III	14.131(8.556-23.339)	<0.001	5.619(1.959-16.115)	0.001
Stage_T		<0.001		<0.001
T1	Reference			

T2	2.137(1.400-3.262)	<0.001	0.582(0.286-1.183)	0.135
T3	7.345(4.727-11.415)	<0.001	1.810(0.866-3.781)	0.115
T4	14.008(8.662-22.654)	<0.001	2.606(1.119-6.066)	0.026
Stage_N		<0.001		<0.001
N0	Reference			
N1	2.423(1.807-3.250)	<0.001	1.299(0.893-1.890)	0.171
N2	4.516(3.000-6.798)	<0.001	2.150(1.163-3.973)	0.015
N3	6.595(4.230-10.283)	<0.001	2.659(1.467-4.820)	0.001
Surg prim site				
Lumpectomy	Reference			
Mastectomy	2.720(2.038-3.630)	<0.001	1.216(0.871-1.698)	0.251
Chemotherapy				
No/unknown	Reference			
Yes	1.041(0.796-1.360)	0.772		
Radiation				
No/unknown	Reference			
Yes	0.757(0.591-0.970)	0.028	0.645(0.501-0.830)	0.001

Table 4. The C-index of nomogram for OS and CSS in patients with MBC

Survival	Training cohort		Validation cohort	
	HR	95% CI	HR	95% CI
OS	0.759	0.746-0.772	0.754	0.734-0.774
CSS	0.766	0.751-0.781	0.752	0.728-0.776

Figures

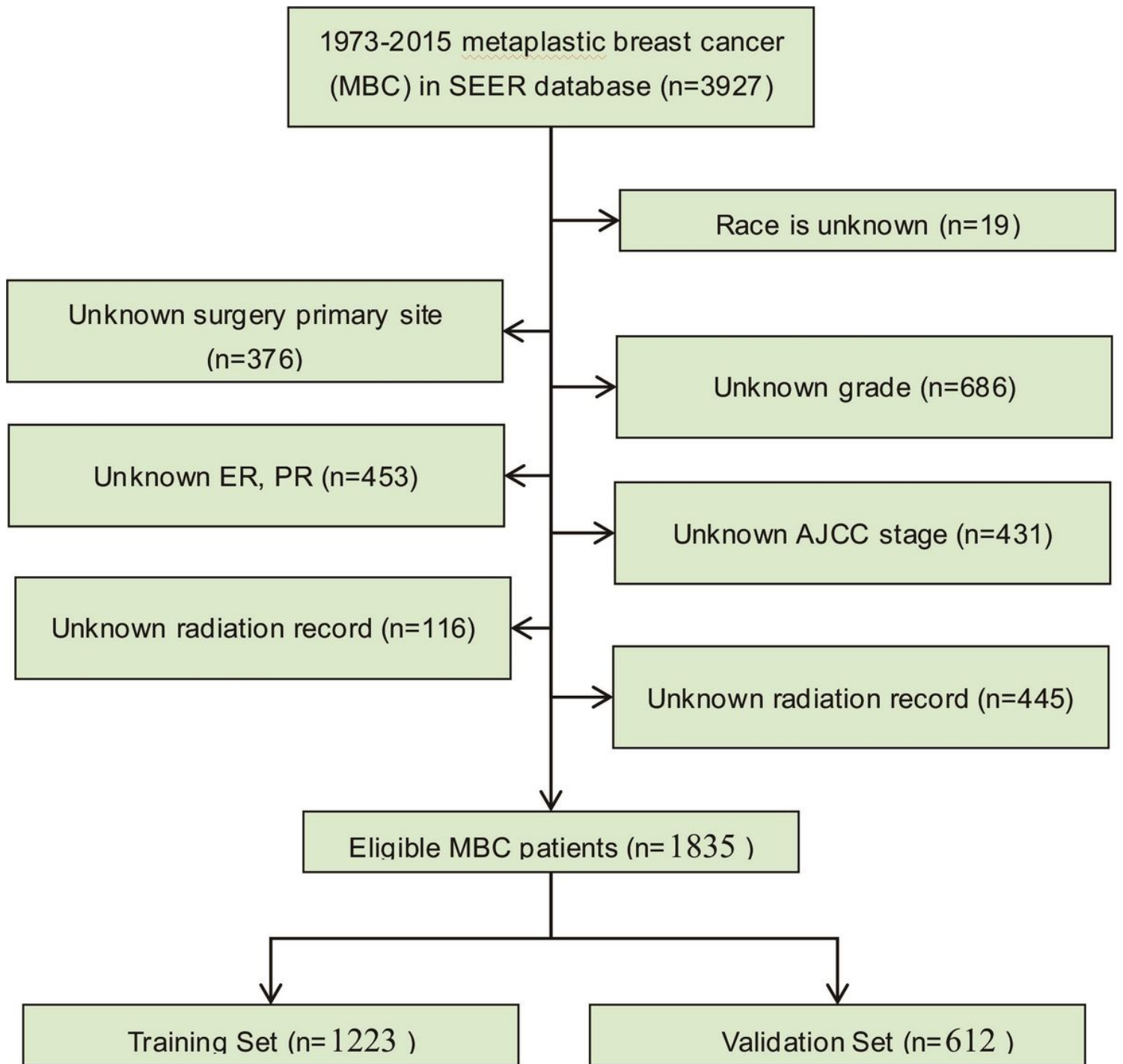
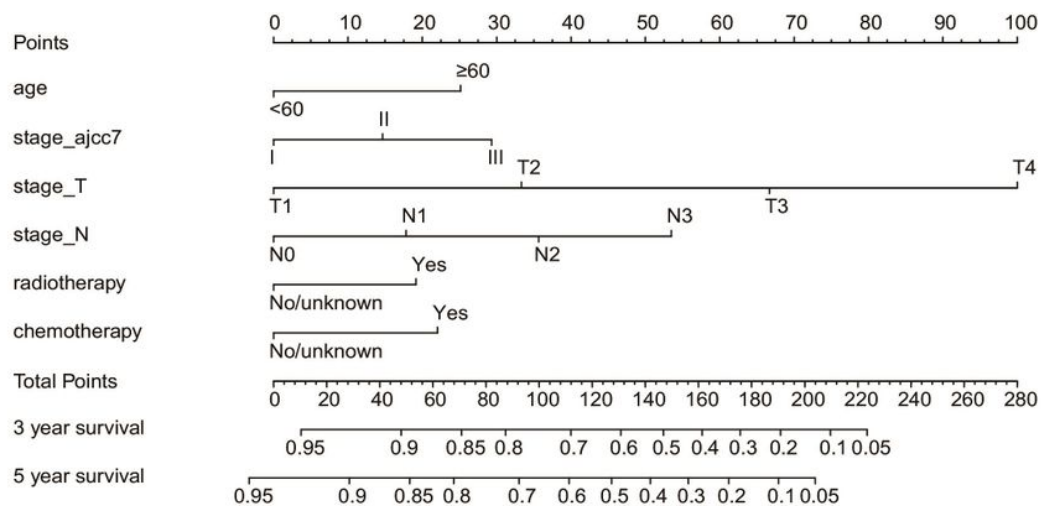
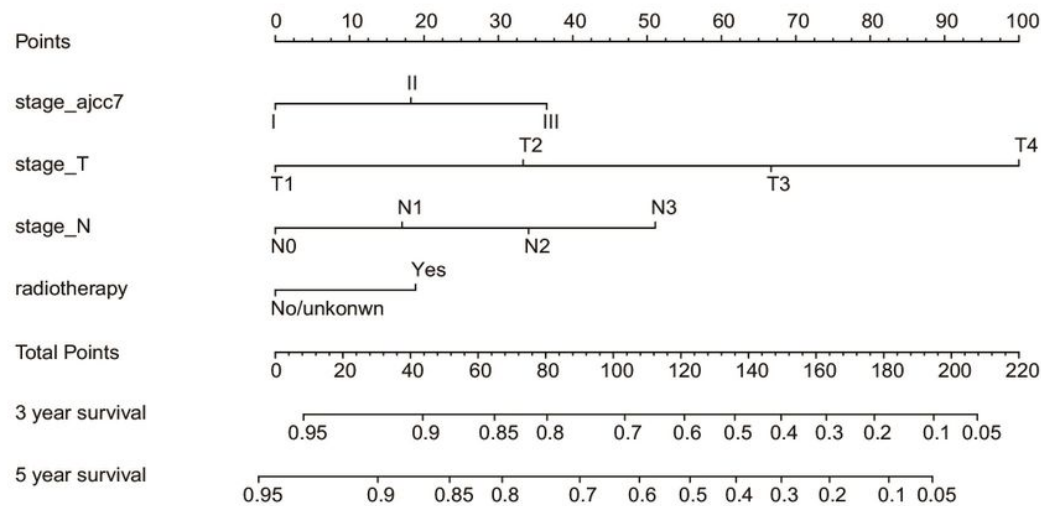


Figure 1

Flow chart of patient selection.



(a)



(b)

Figure 2

Nomograms for predicting the 3-, and 5-year (a) overall survival and (b) cancer-specific survival of MBC.

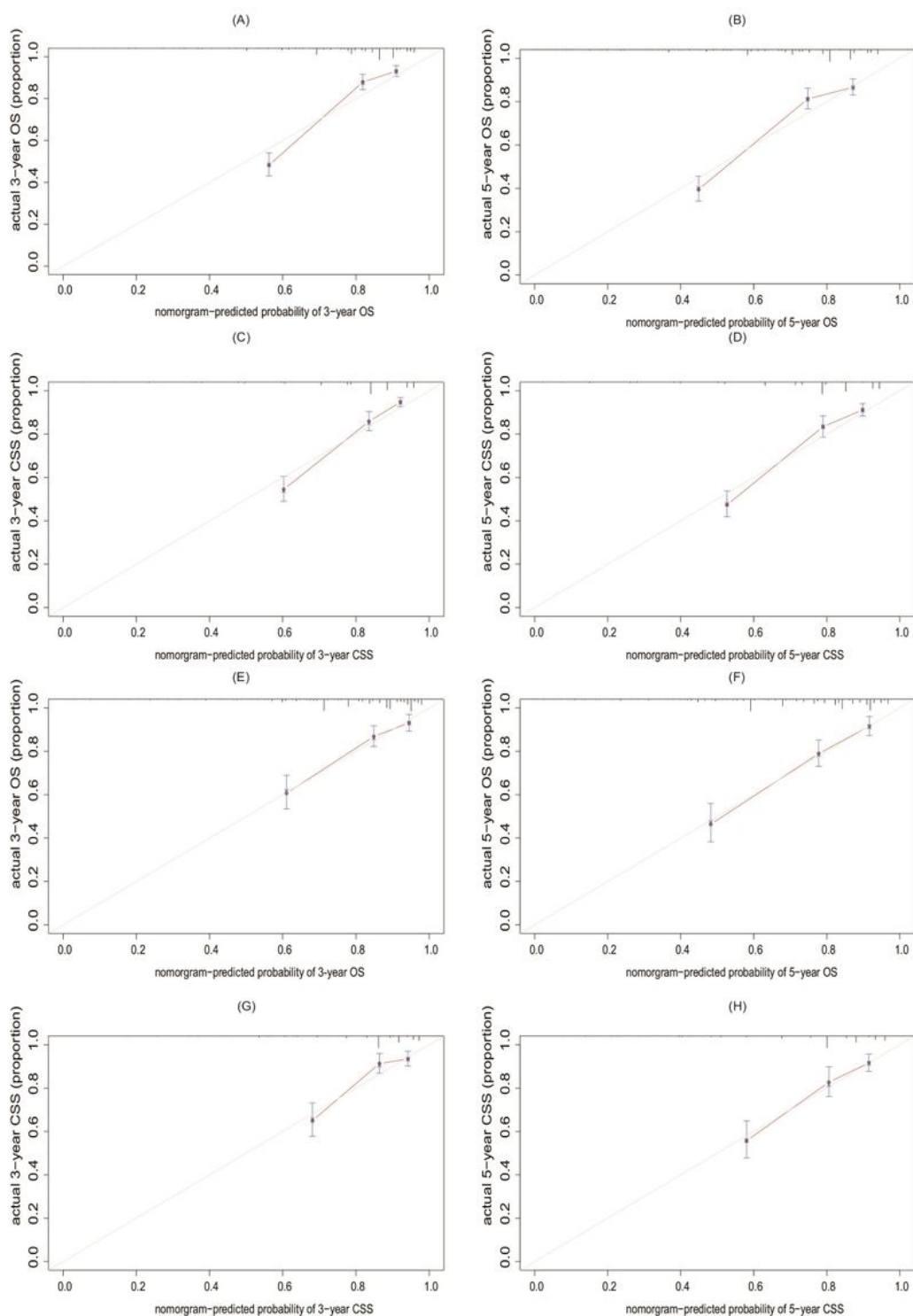


Figure 3

The calibration curves for predictions survival of MBC patients. The overall survival (A, B) and cancer-specific survival (C, D) in the training cohort at 3 and 5 years after diagnosis, and the overall survival (E, F) and cancer-specific survival (G, H) in the validation cohort at 3 and 5 years after diagnosis.