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Nomogram predicting overall survival for invasive micropapillary carcinoma of the breast: a SEER-based population study.

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4 Nomogram predicting overall survival for invasive micropapillary carcinoma of the
5 breast: a SEER-based population study.
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Abstract

Background: The prognosis of invasive micropapillary carcinoma (IMPC) of the breast is determined by many clinicopathological factors. This study aims to identify prognostic factors and develop reliable nomogram to predict the overall survival (OS) in patients with IMPC.

Methods: The Surveillance, Epidemiology, and End Results (SEER) database was used to screen 754 eligible patients as the study cohort. The whole cohort was randomly divided into a training cohort (n=377) and a validation cohort (n=377). Log-rank test and Cox proportional hazards analysis were used to identify variables and construct a nomogram based on the training cohort. C-index and calibration curves were performed to evaluate the performance of the model in the training cohort and validation cohorts.

Results: Age at diagnosis, hormone receptors, number of positive regional nodes and clinical stage were independent prognostic factors for patients with IMPC. The calibration curves presented excellent consistency between the actual and nomogram-predict survival probabilities in the training and validation cohorts. The C-index values of the nomogram were 0.794 and 0.774 for OS in the training and validation cohorts, respectively.

Conclusion: The novel nomogram provides new insights of the risk of each prognostic factor and can assist doctors in predicting the 1-, 3-, and 5-year OS in patients with IMPC.

Keywords: Invasive micropapillary breast carcinoma; nomogram; prognosis; Surveillance, Epidemiology, and End Results

Strengths and limitations of this study

First, retrospective SEER data lack a pathologic review to identify the diagnosis for each case. Second, we cannot consider the types of systemic therapy administered to patients. Third, the relationship between the degree of micropapillary involvement and clinical outcomes among patients with IMPC remains unclear.

Background

Breast cancer is the most prevalent malignancy in women with 290,560 newly estimated diagnosed cases and 43,780 estimated deaths in the United States in 2022(1). The subtype invasive micropapillary carcinoma (IMPC) of the breast is characterized by aggressive potential for lymphovascular invasion and lymph node metastasis(2, 3) and accounts for less than 2% of all invasive breast cancers(4). This cancer type has varying classifications and has no available standardized treatment guidelines.

Considering the rarity of this disease, the conduct of clinical trials to evaluate prognostic factors and optimal treatments is difficult. A few studies have discussed the potential pathologic predictors of survival for IMPC(5-8). However, these published analyses of IMPC have been limited by size, thus leading to discrepancies in the reported prevalence of overall survival and significant prognostic indicators.

A nomogram, a simple visual prediction tool based on a prognostic model that includes related clinicopathological factors, allows doctors to access the probabilities of the clinical outcomes of particular individuals(9, 10). Moreover, compared to the American Joint Committee on Cancer (AJCC) TNM stage system, nomograms can provide a more precise estimation of prognosis for some malignancies(11, 12) and help clinicians to make decisions in complex situations in an alternative or novel standard(13, 14).

In this study, we investigated the Surveillance, Epidemiology, and End Results (SEER) database to determine the prognostic effect of clinicopathological factors on overall survival (OS) in patients with IMPC. A novel nomogram was constructed to predict the prognosis for patients with IMPC.

Methods

Study cohorts

The data for this study were obtained from 18 registries of the SEER program, and 1,480 patients diagnosed with IMPC of the breast between 1973 and 2013 were included. The inclusion criteria for the data screening were as follows: (1) female

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4 patients who accepted surgery treatment; (2) age older than 18 years; (3) diagnosis
5 confirmed by positive histology; (4) IMPC as the first and primary cancer determined
6 by international rules; (5) survival data with complete and available dates and more
7 than 0 days of survival; and (6) clear clinicopathological information for all the
8 variables of interest including age at diagnosis, race, marital status, primary site,
9 hormone receptors (HRs) [estrogen receptor (ER) and progesterone receptor (PR)],
10 tumor size, grade, laterality, number of positive regional nodes, surgery record, and
11 clinical stage (the 6th edition of AJCC system).
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19 Variables and definitions

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21 The following data were extracted for each patient from the database: age at
22 diagnosis, race (White, and other), marital status at diagnosis, laterality, clinical stage,
23 number of positive regional nodes, tumor size, tumor grade (well-differentiated,
24 moderately differentiated, poorly differentiated, undifferentiated or anaplastic),
25 hormone receptors (HR+ and HR-), surgery record, radiotherapy record, survival
26 months, and vital status. Marital status was classified as married or unmarried. The
27 latter included single, separated, divorced, widowed, and unmarried/domestic
28 partners. OS was defined as the time from diagnosis to death from any cause or to the
29 time of the last follow-up.
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38 Construction and validation of the nomogram

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40 We performed univariate and multivariate Cox regression analyses to determine
41 the prognostic value of the factors. The independent factors were used to build the
42 nomogram for the Wins by using the rms package in R software version 4.1.3. All the
43 significant independent factors in the training cohort were used to build a nomogram
44 to predict the survival rates. The nomogram was validated in the training and the
45 validation cohorts. We used the Harrell concordance index (C-index), the area under
46 the receiver operating characteristic (ROC) curve (AUC) and the calibration curve to
47 assess the discrimination of the nomogram.
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56 Statistical analysis

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58 Our study consolidated the descriptive characteristics of the training and
59 validation cohorts, respectively. Chi-square test or Fisher's exact test was used to
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confirm whether significant differences exist in the demographic and clinicopathological features between the training and validation cohorts. The variables were analyzed using Kaplan–Meier survival curves and log-rank tests to evaluate their effects on OS. The prognostic value of each variable was estimated through univariate and multivariate Cox regression analyses. All P values are two sided, and P values under .05 are reported as statistically significant. 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).

Results

Demographics and clinicopathological characteristics

From the SEER database, a total of 754 cases of IMPC were eligible for inclusion criteria. The eligible patients were randomly divided into the training cohort (n=377) and the validation cohort (n=377) by applying ‘create Data Partition’ function in the package of ‘caret’ from R version 4.1.3. The demographic and clinicopathological characteristics of the training and validation cohorts are shown in Table 1, and no statistically significant differences were found between the two cohorts. The estimated average OS values were 106.9 months (95% CI: 102.7-111.1 months) in the 377 patients with IMPC in the training cohort, and 108.2 months (95%CI: 104.4-112.1 months) in the validation cohort. The survival curve showed no significant differences between the two cohorts (Figure 1A, P= 0.786).

Table 1. Clinicopathologic characteristics of the training and validation cohorts.

Variables	Training cohort (n=377) (%)	Validation cohort (n=377) (%)	P value
Age (year)	58.73±13.19	59.90±12.94	0.22
Race			0.11
White	276 (73.2)	295 (78.2)	
Other	101 (26.8)	82 (21.8)	
Marital status			0.55
Unmarried	159 (42.2)	151 (40.1)	
Married	218 (57.8)	226 (59.9)	
Laterality			0.17
Left	205 (54.4)	186 (49.3)	
Right	172 (45.6)	191 (50.7)	

Grade				0.26
	I/II	236 (62.6)	221 (58.6)	
	III/IV	141 (37.4)	156 (41.4)	
HR status				0.55
	Positive	335 (88.9)	340 (90.2)	
	Negative	42 (11.1)	37 (9.8)	
Tumor size (mm)		24.44±22.78	24.71±21.93	0.87
	<20	223 (59.2)	204 (54.1)	0.29
	20-50	114 (30.2)	134 (35.5)	
	>50	40 (10.6)	39 (10.3)	
Number of positive regional nodes				0.99
	0	179 (47.5)	175 (46.4)	
	1-3	118 (31.3)	121 (32.1)	
	4-9	45 (11.9)	47 (12.5)	
	≥10	35 (9.3)	34 (9.0)	
Stage				0.73
	I	141 (37.4)	127 (33.7)	
	II	148 (39.2)	160 (42.4)	
	III	82 (21.8)	83 (22.0)	
	IV	6 (1.6)	7 (1.9)	
Surgery				0.34
	Conserving surgery	208 (55.2)	195 (51.7)	
	Mastectomy	169 (44.8)	182 (48.3)	
Radiotherapy				0.06
	Yes	238 (63.1)	213 (56.5)	
	No	139 (36.9)	164 (43.5)	

Univariate and multivariate Cox proportional hazards analyses

The hazard ratios for OS according to all variables in the univariate or multivariate Cox proportional hazards model are listed in Tables 2 and 3. According to the results of univariate analysis, we found that the race, marital status, laterality, and radiotherapy were not significant factors for OS. After excluding the aforementioned variables, age at diagnosis, grade, HR status, tumor size, number of positive regional nodes, clinical stage, and surgery were determined as prognostic factors in the multivariate Cox proportional hazards model for the OS analysis. As shown in Table 3, age at diagnosis could be a negative prognostic factor for the OS of patients with IMPC. The HR negative subtype exhibited higher risk of death. Compared with patients with IMPC and negative regional node, patients with positive

regional nodes suffered from higher risk of poor prognosis. Interestingly, the subgroups of stages II and III had a significantly lower risk than the stage I group.

Construction and validation of the nomograms.

Table 2. Univariate analysis of OS in the training cohort.

Variables	HR	95% CI	P value
Age (year)	1.035	1.005-1.065	0.023
Race			
White		reference	
Other	1.202	0.529-2.732	0.660
Marital status			
Unmarried		reference	
Married	0.721	0.343-1.512	0.386
Laterality			
Left		reference	
Right	0.915	0.435-1.923	0.816
Grade			
I/II		reference	
III/IV	2.180	1.030-4.611	0.042
HR status			
Positive		reference	
Negative	4.150	1.914-8.998	<0.001
Tumor size (mm)			<0.001
<20		reference	
20-50	1.931	0.728-5.119	0.186
>50	7.960	3.339-18.973	<0.001
Number of positive regional nodes			<0.001
0		reference	
1-3	1.679	0.609-4.632	0.317
4-9	3.145	0.998-9.914	0.050
≥10	8.350	3.016-23.115	<0.001
Stage			<0.001
I		reference	
II	1.040	0.365-2.967	0.941
III	3.529	1.262-8.419	0.015
IV	19.576	4.982-76.921	<0.001
Surgery			
Conserving surgery		reference	
Mastectomy	2.530	1.144-5.596	0.022
Radiotherapy			
Yes		reference	
No	0.780	0.368-1.649	0.515

Table 3. Multivariate analysis of OS in the training cohort.

Variables	HR	95% CI	P value
Age (year)	1.054	1.020-1.090	0.020
Grade			
I/II		reference	
III/IV	1.159	0.504-2.666	0.728
HR status			
Positive		reference	
Negative	5.368	2.084-13.830	0.001
Tumor size (mm)			
<20		reference	
20-50	2.292	0.631-8.322	0.208
>50	4.807	0.919-25.153	0.063
Number of positive regional nodes			
0		reference	
1-3	18.314	1.387-241.811	0.027
4-9	10.340	1.044-102.388	0.046
≥10	26.776	3.300-23.115	0.002
Stage			
I		reference	
II	0.057	0.004-0.802	0.034
III	0.096	0.100-0.964	0.046
IV	0.211	0.170-2.641	0.228
Surgery			
Conserving surgery		reference	
Mastectomy	1.119	0.393-3.190	0.833

The nomogram for 1-, 3-, and 5-year OS was developed by using the multivariate Cox proportional hazards models as the final prognostic models after factor selection (Figure 1B). The nomogram was internally validated in the training cohort and externally validated in the validation cohort. The AUC values of the ROC curve, which exhibited the discrimination capacity, were 0.830 and 0.764 in the training (Figure 1C) and validation cohorts (Figure 1D), respectively. Moreover, compared with the discriminative ability of the sixth edition AJCC TNM staging classification, the discriminative ability of the nomogram was significantly superior in the training and validation cohorts ($P < 0.001$). The results indicated that the nomogram can efficiently predict OS in patients with IMPC. The calibration plots

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4 also showed great consistency between the actual and nomogram-predicted survival
5 rates in the training (Figure 2A) and testing cohorts (Figure 2B). The C-index values
6 of the nomogram for OS were 0.794 in the training cohort and 0.774 in the validation
7 cohort.
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11 12 13 Discussion

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15 Invasive micropapillary carcinoma of breast, which was first described by
16 Siriaungkul and Tavassoli in 1993(4), is a rare variant of invasive breast carcinoma
17 (IDC). Histologically, it is a subtype characterized by small papillary structures that
18 lack true central fibrovascular cores and lie within empty stromal spaces(15, 16).
19 Historically, standard IDC treatment was used to treat patients with IMPC. However,
20 notable differences in histological characters and prognosis exist between IMPC and
21 IDC(17); as such, treating IMPC as IDC would be inappropriate. Accurate predictions
22 of prognosis of patients with IMPC patients could effectively help clinicians to take
23 proper treatment modalities. This study aims to build a nomogram capable of
24 predicting the prognosis of IMPC based on a larger population database of the
25 Surveillance, Epidemiology, and End Results (SEER) program.
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37 In this study, we equally divided 754 patients with IMPC from the SEER
38 database into two cohorts. We developed an effective nomogram that contains four
39 independent prognostic factors including age at diagnosis, HR, number of positive
40 regional nodes, and clinical stage. The nomogram, derived from the Cox regression
41 model to predict the 1-, 3-, and 5-year OS of patients with IMPC, was verified to have
42 good discrimination capacity. Moreover, the nomogram showed better prediction
43 ability for OS than that of the sixth edition AJCC TNM staging classification (AUCs
44 in the ROC curve: 0.830 and 0.651 in the training cohort and 0.764 and 0.633 in the
45 validation cohort, respectively).
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55 Hormone receptors play important role in prognosis of breast cancer(18, 19). A
56 previous study showed that the 5-year OS was 59% in 100 patients with IMPC with a
57 mean age of 50 years and 46% HR positivity(7). In another study, 72 patients with
58 IMPC with a mean age of 46 years and 75% HR positivity had 86% 5-year OS(5). In
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4 comparison, our study population was older (mean age of 59.3 years) and had a higher
5 percentage of HR positivity (89.5%). The higher HR positivity in the present study
6 may contribute to the better 5-year OS (91.1%)(20). The Cox-regression analysis
7 result also proved that HR negativity could lead to significantly poor OS in patients
8 with IMPC (HR 5.368; 95%CI 2.084–13.830; P=0.001).
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13 Lymph node metastasis is widely considered as an unfavorable prognostic factor
14 in clinical practice(21, 22). Axillary lymph node metastasis is commonly seen in
15 patients with IMPC at first diagnosis. The rate of lymphatic and lymph nodal spread
16 ranged from 33% to 95%(4, 15, 23, 24). The value and necessity of sentinel lymph
17 node biopsy (SLNB) or axillary dissection in patients with IMPC remains
18 controversial. Walsh et al. found that regional lymph nodes can be involved even at
19 early stage of IMPC lesions. The team highly recommended a thorough regional
20 lymph node examination to patients with IMPC (16). However, Paterakos et al. were
21 skeptical to the utility of SLNB for patients with IMPC due to the high frequency of
22 multiple positive regional lymph nodes(25). In the present study, we found that
23 patients with IMPC with even one positive regional lymph node would suffer higher
24 risk than patients with negative lymph node. Patients with IMPC and 10 or more
25 positive lymph nodes are at the highest risk (OR 26.776; 95%CI 3.300-23.115;
26 P=0.002). Thus, axillary dissection, or SLNB at minimum, should be performed to
27 correctly assess the risk and adopt suitable treatment regimens for patients with
28 IMPC.
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45 This study has some limitations. First, retrospective SEER data lack a pathologic
46 review to identify the diagnosis for each case. Second, we cannot consider the types
47 of systemic therapy administered to patients. Hormonal blockade therapy and
48 chemotherapy could significantly affect the outcome of patients. Third, the
49 relationship between the degree of micropapillary involvement and clinical outcomes
50 among patients with IMPC remains unclear. Although some previous small case
51 series studies have revealed that an increasing percentage of micropapillary
52 component was not associated with more lymph node metastasis and worse
53 survival(23, 26), it need to be further validated in large-scale studies.
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Conclusions

In conclusion, age at diagnosis, HR status, number of positive regional nodes, and clinical stage were independent prognostic factors for patients with IMPC. We constructed a nomogram to predict OS in patients with IMPC based on a large-scale population from the SEER database. This accessible nomogram will help doctors to adopt proper treatment regimens in clinical practice.

List of abbreviations

invasive micropapillary carcinoma (IMPC)
overall survival (OS)
Surveillance, Epidemiology, and End Results (SEER)
American Joint Committee on Cancer (AJCC)
hormone receptors (HRs)
estrogen receptor (ER)
progesterone receptor (PR)
receiver operating characteristic (ROC)
area under the curve (AUC)
invasive breast carcinoma (IDC)

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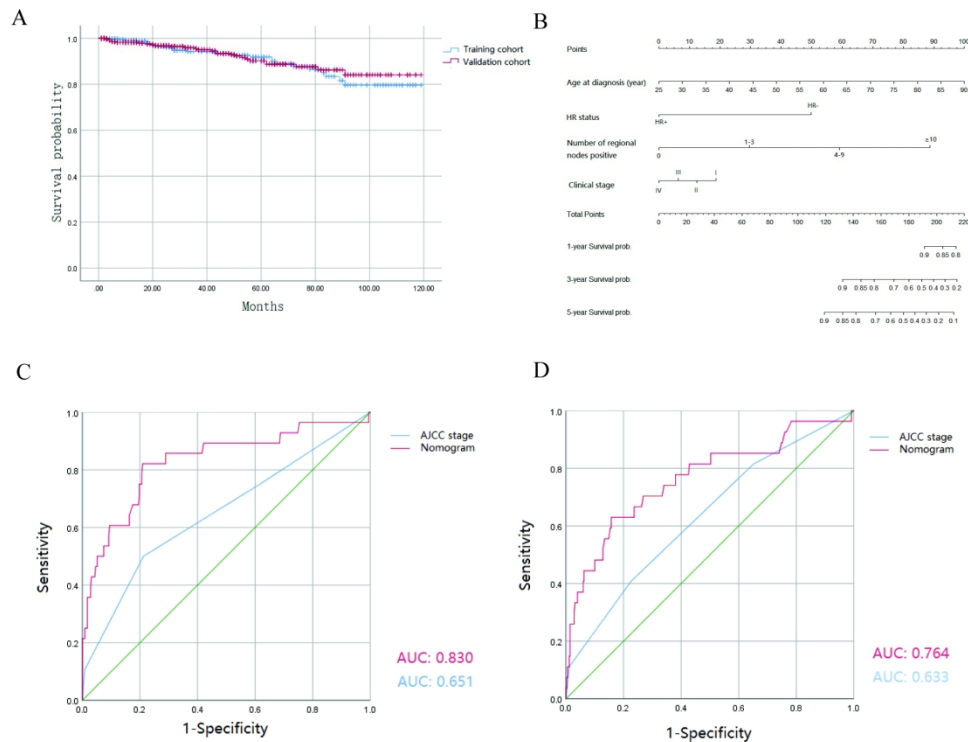


Figure 1A. Kaplan-Meier survival curves of the patients with IMPC in the training and validation cohorts.
Notes: The survival curves showed no significant differences between the 2 cohorts ($P=0.786$).

Figure 1B. Nomogram for predicting 1-, 3-, 5-year OS for patients with the prognosis factors.
Notes: The total points are calculated by summing up the points for each factor. The predicted probability of OS can be obtained by projecting the location of the total points to the bottom scales. Abbreviations: OS= overall survival.

Figure 1C and Figure 1D. ROC curves for discrimination in the training and validation cohorts.
Notes: (Figure 1C) In the training cohort, the AUC of the ROC curve of the nomogram and the sixth edition AJCC TNM staging classification was 0.830 and 0.651, respectively ($P<0.001$). (Figure 1D) In the validation cohort, the AUC of the ROC curve of the nomogram and the sixth edition AJCC TNM staging classification was 0.764 and 0.633, respectively ($P<0.001$). Abbreviations: AJCC= American Joint Committee on Cancer; AUC= area under the curve; ROC= receiver operating characteristic.

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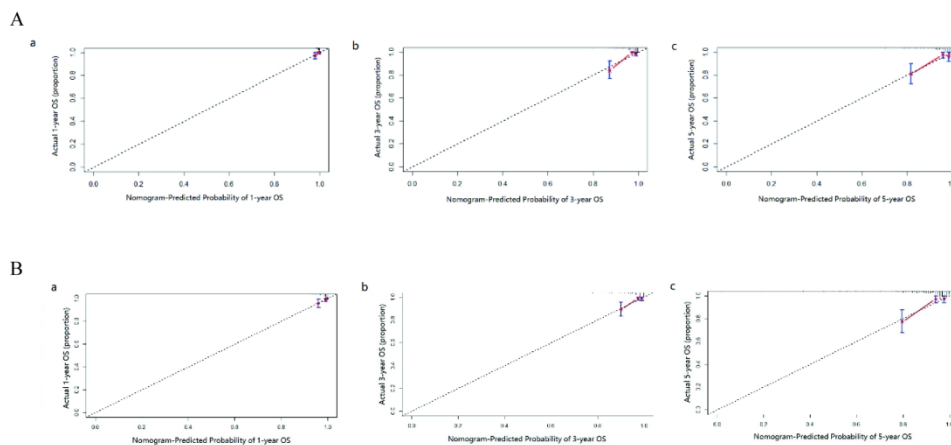


Figure 2. Calibration curves for predictions for the 1-year (a), 3-year (b), 5-year (c) OS in the training cohort (Figure 2A) and in the testing cohort (Figure 2B).
 Notes: (Figure 2A) The nomogram-predicted probability of OS is plotted on the X-axis, and the actual OS is plotted on the Y-axis. (Figure 2B) The nomogram-predicted probability of OS is plotted on the X-axis, and the actual OS is plotted on the Y-axis.

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Nomogram predicting overall prognosis for invasive micropapillary carcinoma of the breast: a SEER-based population study.

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4 Nomogram predicting overall prognosis for invasive micropapillary carcinoma of the
5 breast: a SEER-based population study.
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Abstract

Objectives The prognosis of invasive micropapillary carcinoma (IMPC) of the breast is determined by many clinicopathological factors. This study aims to identify prognostic factors and develop reliable nomogram to predict the overall survival (OS) in patients with IMPC.

Design Log-rank test and Cox proportional hazards analysis were used to identify variables and construct a nomogram based on the training cohort. C-index and calibration curves were performed to evaluate the performance of the model in the training cohort and validation cohorts.

Setting We collected the patient data from the Surveillance, Epidemiology, and End Results (SEER) database. This database holds data related to the cancer incidence from 18 population-based cancer registries in the United States.

Participants The SEER database was used to screen 754 eligible patients as the study cohort. The whole cohort was randomly divided into a training cohort (n=377) and a validation cohort (n=377).

Results Age at diagnosis, hormone receptors, number of positive regional lymph-nodes and clinical stage were independent prognostic factors for patients with IMPC. The calibration curves presented excellent consistency between the actual and nomogram-predict survival probabilities in the training and validation cohorts. The C-index values of the nomogram were 0.794 and 0.774 for OS in the training and validation cohorts, respectively.

Conclusions The novel nomogram provides new insights of the risk of each prognostic factor and can assist doctors in predicting the 1-, 3-, and 5-year OS in patients with IMPC.

Keywords: Invasive micropapillary breast carcinoma; nomogram; prognosis; Surveillance, Epidemiology, and End Results

Strengths and limitations of this study

The data was downloaded from the SEER database, which provides a representative population-based cohort.

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4 Prognostic factors were determined by univariate and multivariate Cox proportional
5 hazards regression analyses and used to develop nomograms to predict 1-, 3-, and
6 5-year overall survival of patients with invasive micropapillary carcinoma (IMPC).
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9 To compare the accuracy of the nomograms with that of American Joint Committee
10 on Cancer 6 staging, we used the Harrell concordance index (C-index), the area
11 under the receiver operating characteristic (ROC) curve (AUC) and the calibration
12 curve to assess the discrimination of the nomograms.
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17 This research was a retrospectively large-sample study, the casual basis of this
18 research was difficult to conclude.
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21 The diagnosis of IMPC in each case cannot be validated by pathologic assessments,
22 and the relationship between the degree of micropapillary involvement and clinical
23 outcomes among patients with IMPC yet to be determined.
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Introduction

Breast cancer is the most prevalent malignancy in women with 290,560 newly estimated diagnosed cases and 43,780 estimated deaths in the United States in 2022¹. The special type invasive micropapillary carcinoma (IMPC) of the breast is characterized by aggressive potential for lymphovascular invasion and lymph node metastasis and accounts for less than 2% of all invasive breast cancers²⁻⁴. 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 carcinoma⁵⁻⁷. This cancer type has varying classifications and has no available standardized treatment guidelines.

Considering the rarity of this disease, the conduct of clinical trials to evaluate prognostic factors and optimal treatments is difficult. A few studies have discussed the potential pathologic predictors of survival for IMPC⁸⁻¹⁵. However, these published analyses of IMPC have been limited by size, thus leading to discrepancies in the reported prevalence of overall survival and significant prognostic indicators.

A nomogram, a simple visual prediction tool based on a prognostic model that includes related clinicopathological factors, allows doctors to access the probabilities of the clinical outcomes of particular individuals^{16 17}. Moreover, compared to the American Joint Committee on Cancer (AJCC) TNM stage system, nomograms can provide a more precise estimation of prognosis for some malignancies^{18 19} and help clinicians to make decisions in complex situations in an alternative or novel standard^{20 21}.

In this study, we investigated the Surveillance, Epidemiology, and End Results (SEER) database to determine the prognostic effect of clinicopathological factors on overall survival (OS) in patients with IMPC. A novel nomogram was constructed to predict the prognosis for patients with IMPC.

Methods

Study cohorts

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4 The data for this study were obtained from 18 registries of the SEER program,
5 and 1,480 patients diagnosed with IMPC of the breast between 1973 and 2013 were
6 included. The inclusion criteria for the data screening were as follows: (1) female
7 patients who accepted surgery treatment; (2) age older than 18 years; (3) diagnosis
8 confirmed by histopathological report; (4) IMPC as the first and primary cancer
9 determined by international rules; (5) survival data with complete and available
10 dates and more than 0 days of survival; and (6) clear clinicopathological information
11 for all the variables of interest including age at diagnosis, race, marital status,
12 primary site, hormone receptors (HRs) [estrogen receptor (ER) and progesterone
13 receptor (PR)], tumor size, grade, laterality, number of positive regional lymph-nodes,
14 surgery record, and clinical stage (the 6th edition of AJCC system).

25 Variables and definitions

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27 The following data were extracted for each patient from the database: age at
28 diagnosis, race (white and others), marital status at diagnosis, laterality, clinical stage,
29 number of positive regional lymph-nodes, tumor size, tumor grade
30 (well-differentiated, moderately differentiated, poorly differentiated,
31 undifferentiated or anaplastic), hormone receptors (HR+ and HR-), surgery record,
32 radiotherapy record, survival months, and vital status. Marital status was classified
33 as married or unmarried. The latter included single, separated, divorced, widowed,
34 and unmarried/domestic partners. OS was defined as the time from diagnosis to
35 death from any cause or to the time of the last follow-up.

44 Construction and validation of the nomogram

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46 We performed univariate and multivariate Cox regression analyses to
47 determine the prognostic value of the factors. The independent factors were used to
48 build the nomogram for the Wins by using the rms package in R software version
49 4.1.3. All the significant independent factors in the training cohort were used to
50 build a nomogram to predict the survival rates. The nomogram was validated in the
51 training and the validation cohorts. We used the Harrell concordance index (C-index),
52 the area under the receiver operating characteristic (ROC) curve (AUC) and the
53 calibration curve to assess the discrimination of the nomogram.
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Statistical analysis

Our study consolidated the descriptive characteristics of the training and validation cohorts, respectively. Chi-square test or Fisher's exact test was used to confirm whether significant differences exist in the demographic and clinicopathological features between the training and validation cohorts. The variables were analyzed using Kaplan–Meier survival curves and log-rank tests to evaluate their effects on OS. The prognostic value of each variable was estimated through univariate and multivariate Cox regression analyses. All P values are two sided, and P values under .05 are reported as statistically significant. 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).

Results

Demographics and clinicopathological characteristics

From the SEER database, a total of 754 cases of IMPC were eligible for inclusion criteria. The eligible patients were randomly divided into the training cohort (n=377) and the validation cohort (n=377) by applying 'create Data Partition' function in the package of 'caret' from R version 4.1.3. The demographic and clinicopathological characteristics of the training and validation cohorts are shown in Table 1, and no statistically significant differences were found between the two cohorts. The estimated average OS values were 106.9 months (95% CI: 102.7-111.1 months) in the 377 patients with IMPC in the training cohort, and 108.2 months (95%CI: 104.4-112.1 months) in the validation cohort. The survival curve showed no significant differences between the two cohorts (Figure1, P= 0.786).

Table 1. Clinicopathologic characteristics of the training and validation cohorts.

Variables	Training cohort (n=377) (%)	Validation cohort (n=377) (%)	P value
Age (year)	58.73±13.19	59.90±12.94	0.22
Race			0.11
White	276 (73.2)	295 (78.2)	
Other	101 (26.8)	82 (21.8)	
Marital status			0.55

	Unmarried	159 (42.2)	151 (40.1)	
	Married	218 (57.8)	226 (59.9)	
Laterality				0.17
	Left	205 (54.4)	186 (49.3)	
	Right	172 (45.6)	191 (50.7)	
Grade				0.26
	I/II	236 (62.6)	221 (58.6)	
	III/IV	141 (37.4)	156 (41.4)	
HR status				0.55
	Positive	335 (88.9)	340 (90.2)	
	Negative	42 (11.1)	37 (9.8)	
Tumor size (mm)		24.44±22.78	24.71±21.93	0.87
	<20	223 (59.2)	204 (54.1)	0.29
	20-50	114 (30.2)	134 (35.5)	
	>50	40 (10.6)	39 (10.3)	
Number of positive regional nodes				0.99
	0	179 (47.5)	175 (46.4)	
	1-3	118 (31.3)	121 (32.1)	
	4-9	45 (11.9)	47 (12.5)	
	≥10	35 (9.3)	34 (9.0)	
Stage				0.73
	I	141 (37.4)	127 (33.7)	
	II	148 (39.2)	160 (42.4)	
	III	82 (21.8)	83 (22.0)	
	IV	6 (1.6)	7 (1.9)	
Surgery				0.34
	Conserving surgery	208 (55.2)	195 (51.7)	
	Mastectomy	169 (44.8)	182 (48.3)	
Radiotherapy				0.06
	Yes	238 (63.1)	213 (56.5)	
	No	139 (36.9)	164 (43.5)	

Univariate and multivariate Cox proportional hazards analyses

The hazard ratios for OS according to all variables in the univariate or multivariate Cox proportional hazards model are listed in Tables 2 and 3. According to the results of univariate analysis, we found that the race, marital status, laterality, and radiotherapy were not significant factors for OS. After excluding the aforementioned variables, age at diagnosis, grade, HR status, tumor size, number of positive regional lymph-nodes, clinical stage, and surgery were determined as

prognostic factors in the multivariate Cox proportional hazards model for the OS analysis. As shown in Table 3, age at diagnosis could be a negative prognostic factor for the OS of patients with IMPC. The HR negative special type exhibited higher risk of death. Compared with patients with IMPC and negative regional node, patients with positive regional lymph-nodes suffered from higher risk of poor prognosis. Interestingly, the subgroups of stages II and III had a significantly lower risk than the stage I group.

Table 2. Univariate analysis of OS in the training cohort.

Variables	HR	95% CI	P value
Age (year)	1.035	1.005-1.065	0.023
Race			
White		reference	
Other	1.202	0.529-2.732	0.660
Marital status			
Unmarried		reference	
Married	0.721	0.343-1.512	0.386
Laterality			
Left		reference	
Right	0.915	0.435-1.923	0.816
Grade			
I/II		reference	
III/IV	2.180	1.030-4.611	0.042
HR status			
Positive		reference	
Negative	4.150	1.914-8.998	<0.001
Tumor size (mm)			<0.001
<20		reference	
20-50	1.931	0.728-5.119	0.186
>50	7.960	3.339-18.973	<0.001
Number of positive regional nodes			<0.001
0		reference	
1-3	1.679	0.609-4.632	0.317
4-9	3.145	0.998-9.914	0.050
≥10	8.350	3.016-23.115	<0.001
Stage			<0.001
I		reference	
II	1.040	0.365-2.967	0.941
III	3.529	1.262-8.419	0.015
IV	19.576	4.982-76.921	<0.001
Surgery			

Conserving surgery			reference	
	Mastectomy	2.530	1.144-5.596	0.022
Radiotherapy				
	Yes		reference	
	No	0.780	0.368-1.649	0.515

Table 3. Multivariate analysis of OS in the training cohort.

Variables	HR	95% CI	P value	
Age (year)	1.054	1.020-1.090	0.020	
Grade				
	I/II	reference		
	III/IV	1.159	0.504-2.666	0.728
HR status				
	Positive	reference		
	Negative	5.368	2.084-13.830	0.001
Tumor size (mm)				
	<20	reference		
	20-50	2.292	0.631-8.322	0.208
	>50	4.807	0.919-25.153	0.063
Number of positive regional nodes				
	0	reference		
	1-3	18.314	1.387-241.811	0.027
	4-9	10.340	1.044-102.388	0.046
	≥10	26.776	3.300-23.115	0.002
Stage				
	I	reference		
	II	0.057	0.004-0.802	0.034
	III	0.096	0.100-0.964	0.046
	IV	0.211	0.170-2.641	0.228
Surgery				
	Conserving surgery		reference	
	Mastectomy	1.119	0.393-3.190	0.833

Construction and validation of the nomograms.

The nomogram for 1-, 3-, and 5-year OS was developed by using the multivariate Cox proportional hazards models as the final prognostic models after factor selection (Figure 2). The nomogram was internally validated in the training cohort and externally validated in the validation cohort. The AUC values of the ROC curve, which exhibited the discrimination capacity, were 0.830 and 0.764 in the

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4 training and validation cohorts, respectively (Figure 3). Moreover, compared with
5 the discriminative ability of the sixth edition AJCC TNM staging classification, the
6 discriminative ability of the nomogram was significantly superior in the training and
7 validation cohorts ($P < 0.001$). The results indicated that the nomogram can
8 efficiently predict OS in patients with IMPC. The calibration plots also showed great
9 consistency between the actual and nomogram-predicted survival rates in the
10 training and testing cohorts (Figure 4, Figure 5). The C-index values of the nomogram
11 for OS were 0.794 in the training cohort and 0.774 in the validation cohort.
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21 Patient and public involvement

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23 No patient involved.
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27 Discussion

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29 Invasive micropapillary carcinoma of breast, which was first described by
30 Siriaungkul and Tavassoli in 1993⁴, is a rare variant of invasive breast carcinoma (IBC).
31 Histologically, it is a special type characterized by small papillary structures that lack
32 true central fibrovascular cores and lie within empty stromal spaces^{22 23}. Historically,
33 standard IBC treatment was used to treat patients with IMPC. However, notable
34 differences in histological characters and prognosis exist between IMPC and IBC²⁴; as
35 such, treating IMPC as IBC would be inappropriate. Accurate predictions of prognosis
36 of patients with IMPC patients could effectively help clinicians to take proper
37 treatment modalities. This study aims to build a nomogram capable of predicting the
38 prognosis of IMPC based on a larger population database of the Surveillance,
39 Epidemiology, and End Results (SEER) program.
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50 In this study, we equally divided 754 patients with IMPC from the SEER
51 database into two cohorts. We developed an effective nomogram that contains four
52 independent prognostic factors including age at diagnosis, HR, number of positive
53 regional lymph-nodes, and clinical stage. The nomogram, derived from the Cox
54 regression model to predict the 1-, 3-, and 5-year OS of patients with IMPC, was
55 verified to have good discrimination capacity. Moreover, the nomogram showed
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4 better prediction ability for OS than that of the sixth edition AJCC TNM staging
5 classification (AUCs in the ROC curve: 0.830 and 0.651 in the training cohort and
6 0.764 and 0.633 in the validation cohort, respectively).
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10 Hormone receptors play important role in prognosis of breast cancer^{25 26}. A
11 previous study showed that the 5-year OS was 59% in 100 patients with IMPC with a
12 mean age of 50 years and 46% HR positivity¹⁰. In another study, 72 patients with
13 IMPC with a mean age of 46 years and 75% HR positivity had 86% 5-year OS⁸. In
14 comparison, our study population was older (mean age of 59.3 years) and had a
15 higher percentage of HR positivity (89.5%). The higher HR positivity in the present
16 study may contribute to the better 5-year OS (91.1%)²⁷. The Cox-regression analysis
17 result also proved that HR negativity could lead to significantly poor OS in patients
18 with IMPC (HR 5.368; 95%CI 2.084–13.830; P=0.001).
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27 Lymph node metastasis is widely considered as an unfavorable prognostic
28 factor in clinical practice^{28 29}. Axillary lymph node metastasis is commonly seen in
29 patients with IMPC at first diagnosis. The rate of lymphatic and lymph nodal spread
30 ranged from 33% to 95%^{4 22 30 31}. The value and necessity of sentinel lymph node
31 biopsy (SLNB) or axillary dissection in patients with IMPC remains controversial.
32 Walsh et al. found that regional lymph nodes can be involved even at early stage of
33 IMPC lesions. The team highly recommended a thorough regional lymph node
34 examination to patients with IMPC²³. However, Paterakos et al. were skeptical to the
35 utility of SLNB for patients with IMPC due to the high frequency of multiple positive
36 regional lymph nodes³². In the present study, we found that patients with IMPC with
37 even one positive regional lymph node would suffer higher risk than patients with
38 negative lymph node. Patients with IMPC and 10 or more positive lymph nodes are
39 at the highest risk (OR 26.776; 95%CI 3.300-23.115; P=0.002). Thus, axillary
40 dissection, or SLNB at minimum, should be performed to correctly assess the risk
41 and adopt suitable treatment regimens for patients with IMPC.
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56 This study has some limitations. First, retrospective SEER data lack a pathologic
57 review to identify the diagnosis for each case. Second, we cannot consider the types
58 of systemic therapy administered to patients. Hormonal blockade therapy and
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4 chemotherapy could significantly affect the outcome of patients. Third, the
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6 relationship between the degree of micropapillary involvement and clinical
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8 outcomes among patients with IMPC remains unclear. Although some previous small
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10 case series studies have revealed that an increasing percentage of micropapillary
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12 component was not associated with more lymph node metastasis and worse
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14 survival^{30 33}, it need to be further validated in large-scale studies.

17 Conclusions

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19 In conclusion, age at diagnosis, HR status, number of positive regional
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21 lymph-nodes, and clinical stage were independent prognostic factors for patients
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23 with IMPC. We constructed a nomogram to predict OS in patients with IMPC based
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25 on a large-scale population from the SEER database. This accessible nomogram will
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27 help doctors to adopt proper treatment regimens in clinical practice.

31 List of abbreviations

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invasive micropapillary carcinoma (IMPC)

overall survival (OS)

Surveillance, Epidemiology, and End Results (SEER)

American Joint Committee on Cancer (AJCC)

hormone receptors (HRs)

estrogen receptor (ER)

progesterone receptor (PR)

receiver operating characteristic (ROC)

area under the curve (AUC)

invasive breast carcinoma (IBC)

Jianpeng Liu and Wei Xi contributed equally.

Contributors: Jianpeng Liu and Wei Xi designed and conducted the study. Jiahao Zhou provide suggestions in revision. Wei Gao analysed the data. Qiaolin Wu drafted the manuscript. Jianpeng Liu are responsible for the critical revision. All authors have approved the final version of the manuscript. Qiaolin Wu responsible for the overall content as the guarantor.

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12 writing of the manuscript.
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17 Conflict of interest: The authors declare that they have no conflict of interest.
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21 Patient and public involvement: Patients and/or the public were not involved in the
22 design, or conduct, or reporting, or dissemination plans of this research.
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27 Patient consent for publication: Not Applicable.
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31 Ethics statements: Not Applicable.
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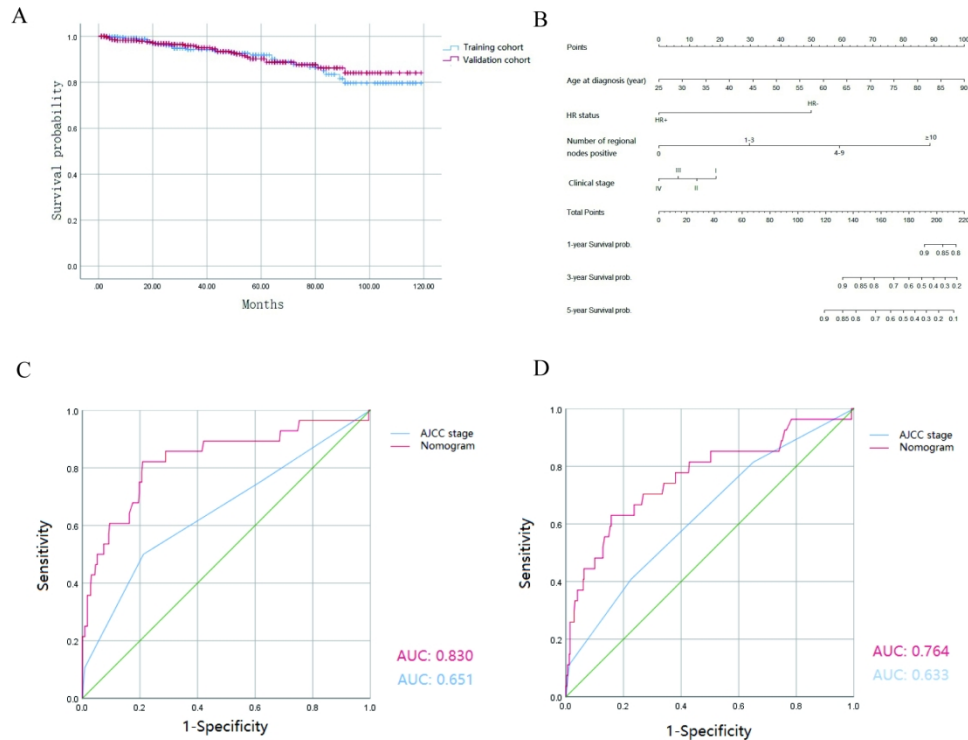


Figure 1A. Kaplan-Meier survival curves of the patients with IMPC in the training and validation cohorts.
Notes: The survival curves showed no significant differences between the 2 cohorts ($P=0.786$).

Figure 1B. Nomogram for predicting 1-, 3-, 5-year OS for patients with the prognosis factors.
Notes: The total points are calculated by summing up the points for each factor. The predicted probability of OS can be obtained by projecting the location of the total points to the bottom scales. Abbreviations: OS= overall survival.

Figure 1C and Figure 1D. ROC curves for discrimination in the training and validation cohorts.
Notes: (Figure 1C) In the training cohort, the AUC of the ROC curve of the nomogram and the sixth edition AJCC TNM staging classification was 0.830 and 0.651, respectively ($P<0.001$). (Figure 1D) In the validation cohort, the AUC of the ROC curve of the nomogram and the sixth edition AJCC TNM staging classification was 0.764 and 0.633, respectively ($P<0.001$). Abbreviations: AJCC= American Joint Committee on Cancer; AUC= area under the curve; ROC= receiver operating characteristic.

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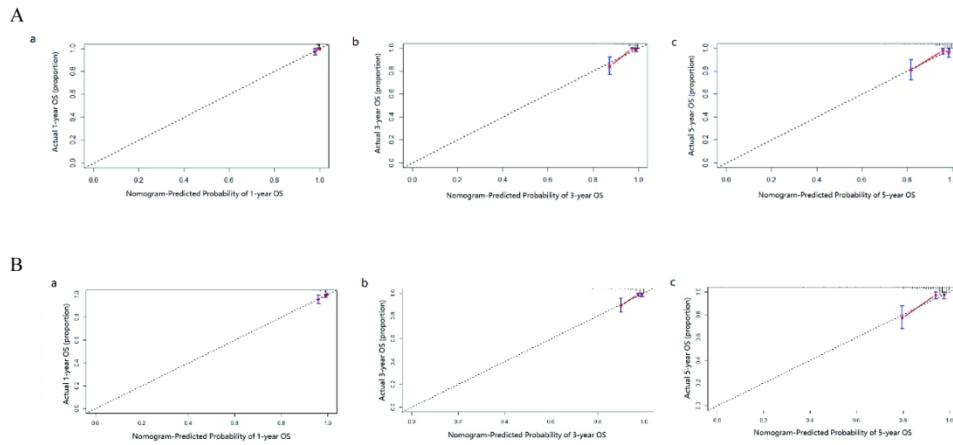


Figure 2. Calibration curves for predictions for the 1-year (a), 3-year (b), 5-year (c) OS in the training cohort (Figure 2A) and in the testing cohort (Figure 2B).
 Notes: (Figure 2A) The nomogram-predicted probability of OS is plotted on the X-axis, and the actual OS is plotted on the Y-axis. (Figure 2B) The nomogram-predicted probability of OS is plotted on the X-axis, and the actual OS is plotted on the Y-axis.

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4 Nomogram predicting overall prognosis for invasive micropapillary carcinoma of the
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Abstract

Objectives The prognosis of invasive micropapillary carcinoma (IMPC) of the breast is determined by many clinicopathological factors. This study aims to identify prognostic factors and develop reliable nomogram to predict the overall survival (OS) in patients with IMPC.

Design Log-rank test and Cox proportional hazards analysis were used to identify variables and construct a nomogram based on the training cohort. C-index and calibration curves were performed to evaluate the performance of the model in the training cohort and validation cohorts.

Setting We collected the patient data from the Surveillance, Epidemiology, and End Results (SEER) database. This database holds data related to the cancer incidence from 18 population-based cancer registries in the United States.

Participants The SEER database was used to screen 754 eligible patients as the study cohort. The whole cohort was randomly divided into a training cohort (n=377) and a validation cohort (n=377).

Results Age at diagnosis, hormone receptors, number of positive regional lymph-nodes and clinical stage were independent prognostic factors for patients with IMPC. The calibration curves presented excellent consistency between the actual and nomogram-predict survival probabilities in the training and validation cohorts. The C-index values of the nomogram were 0.794 and 0.774 for OS in the training and validation cohorts, respectively.

Conclusions The novel nomogram provides new insights of the risk of each prognostic factor and can assist doctors in predicting the 1-, 3-, and 5-year OS in patients with IMPC.

Keywords: Invasive micropapillary breast carcinoma; nomogram; prognosis; Surveillance, Epidemiology, and End Results

Strengths and limitations of this study

- The data was downloaded from the SEER database, which provides a representative population-based cohort.

- Prognostic factors were determined by univariate and multivariate Cox proportional hazards regression analyses and used to develop nomograms to predict 1-, 3-, and 5-year overall survival of patients with invasive micropapillary carcinoma (IMPC).
- We used the Harrell concordance index (C-index), the area under the receiver operating characteristic (ROC) curve (AUC) and the calibration curve to assess the discrimination of the nomograms.
- This research was a retrospectively large-sample study, the casual basis of this research was difficult to conclude.

Introduction

Breast cancer is the most prevalent cancer in women and one of the most rapidly increasing human malignancies worldwide. In the USA, the number of newly estimated diagnosed cases and deaths were 290,560 and 43,780, respectively, in 2022¹. The invasive micropapillary carcinoma (IMPC) of the breast, which characterized by aggressive lymphovascular invasion and metastasis, accounting for less than 2% of all invasive breast cancers²⁻⁵. 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 carcinoma⁶⁻⁸. This cancer type has varying classifications and has no available standardized treatment guidelines.

Considering the rarity of this disease, the conduct of clinical trials to evaluate prognostic factors and optimal treatments is difficult. A few studies have discussed the potential pathologic predictors of survival for IMPC^{5 9-16}. However, the discrepancies caused by the limited IMPC cases in the reported prevalence of overall survival and significant clinicopathological factors were difficult to exclude.

A nomogram, a simple visual prediction tool based on a prognostic model that includes related clinicopathological factors, allows doctors to access the probabilities of the clinical outcomes of particular individuals^{17 18}. Moreover, compared to the American Joint Committee on Cancer (AJCC) TNM stage system, nomograms can provide a more precise estimation of prognosis for some malignancies^{19 20} and help clinicians to make decisions in complex situations in an alternative or novel standard²¹⁻²³.

In this study, we investigated the Surveillance, Epidemiology, and End Results (SEER) database to evaluate the prognostic clinicopathological indicators on overall survival (OS) in patients with IMPC. A novel nomogram was constructed to predict the prognosis for patients with IMPC.

Methods

Study cohorts

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4 The data for this study were obtained from 18 registries of the SEER program,
5 and 1,480 patients diagnosed with IMPC of the breast between 1973 and 2013 were
6 included. The personal information from the SEER database is untracked and
7 unavailable. The inclusion criteria for the data screening were as follows: (1) female
8 patients who accepted surgery treatment; (2) age older than 18 years; (3) diagnosis
9 confirmed by histopathological report; (4) IMPC as the first and primary cancer
10 determined by international rules; (5) survival data with complete and available
11 dates and more than 0 days of survival; and (6) clear clinicopathological information
12 for all the variables of interest including age at diagnosis, race, marital status,
13 primary site, hormone receptors (HRs) [estrogen receptor (ER) and progesterone
14 receptor (PR)], tumor size, grade, laterality, number of positive regional lymph-nodes,
15 surgery record, and clinical stage (the 6th edition of AJCC system).

26 27 Variables and definitions

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29 The following data were extracted for each patient from the database: age at
30 diagnosis, race (white and others), marital status at diagnosis, laterality, clinical stage,
31 number of positive regional lymph-nodes, tumor size, tumor grade
32 (well-differentiated, moderately differentiated, poorly differentiated,
33 undifferentiated or anaplastic), hormone receptors (HR+ and HR-), surgery record,
34 radiotherapy record, survival months, and vital status. Marital status was classified
35 as married or unmarried. The latter included single, separated, divorced, widowed,
36 and unmarried/domestic partners. OS was defined as the time from diagnosis to
37 death from any cause or to the time of the last follow-up.

46 47 Construction and validation of the nomogram

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49 The univariate and multivariate Cox regression analyses were performed to
50 determine the potential prognostic factors. The independent factors were used to
51 build the nomogram for the Wins by using the rms package in R software version
52 4.1.3. And the annual survival rates were analysed by using the survival and rms
53 packages in R software. All the significant independent factors in the training cohort
54 were used to build a nomogram to predict the survival rates. The nomogram was
55 validated in the training and the validation cohorts. We used the Harrell
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4 concordance index (C-index), the area under the receiver operating characteristic
5 (ROC) curve (AUC) and the calibration curve to assess the discrimination of the
6 nomogram.
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9 Statistical analysis

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11 Our study consolidated the descriptive characteristics of the training and
12 validation cohorts, respectively. Chi-square test or Fisher's exact test was used to
13 confirm whether significant differences exist in the demographic and
14 clinicopathological features between the training and validation cohorts. The
15 variables were analyzed using Kaplan–Meier survival curves and log-rank tests to
16 evaluate their effects on OS. The ROC-AUC calculation was performed by the
17 function of "ROC curve" in SPSS version 26.0. All P values are two sided, and P values
18 under .05 are considered as statistically significant. The SEER data were extracted
19 using SEERStat 8.4.0, and statistical analyses were performed using SPSS version 26.0
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33 Patient and public involvement

34 No patient involved.
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38 Results

39 Demographics and clinicopathological characteristics

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41 From the SEER database, a total of 754 cases of IMPC were eligible for inclusion
42 criteria. The eligible patients were randomly divided into the training cohort (n=377)
43 and the validation cohort (n=377) by applying 'create Data Partition' function in the
44 package of 'caret' from R version 4.1.3. The demographic and clinicopathological
45 characteristics of the training and validation cohorts are shown in Table 1, and no
46 statistically significant differences were found between the two cohorts. The
47 estimated average OS values were 106.9 months (95% CI: 102.7-111.1 months) in
48 the 377 patients with IMPC in the training cohort, and 108.2 months (95%CI:
49 104.4-112.1 months) in the validation cohort. The survival curve showed no
50 significant differences between the two cohorts (Figure 1A, P= 0.786).
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Table 1. Clinicopathologic characteristics of the training and validation cohorts.

Variables	Training cohort (n=377) (%)	Validation cohort (n=377) (%)	P value
Age (year)	58.73±13.19	59.90±12.94	0.22
Race			0.11
White	276 (73.2)	295 (78.2)	
Other	101 (26.8)	82 (21.8)	
Marital status			0.55
Unmarried	159 (42.2)	151 (40.1)	
Married	218 (57.8)	226 (59.9)	
Laterality			0.17
Left	205 (54.4)	186 (49.3)	
Right	172 (45.6)	191 (50.7)	
Grade			0.26
I/II	236 (62.6)	221 (58.6)	
III/IV	141 (37.4)	156 (41.4)	
HR status			0.55
Positive	335 (88.9)	340 (90.2)	
Negative	42 (11.1)	37 (9.8)	
Tumor size (mm)	24.44±22.78	24.71±21.93	0.87
<20	223 (59.2)	204 (54.1)	0.29
20-50	114 (30.2)	134 (35.5)	
>50	40 (10.6)	39 (10.3)	
Number of positive regional nodes			0.99
0	179 (47.5)	175 (46.4)	
1-3	118 (31.3)	121 (32.1)	
4-9	45 (11.9)	47 (12.5)	
≥10	35 (9.3)	34 (9.0)	
Stage			0.73
I	141 (37.4)	127 (33.7)	
II	148 (39.2)	160 (42.4)	
III	82 (21.8)	83 (22.0)	
IV	6 (1.6)	7 (1.9)	
Surgery			0.34
Conserving surgery	208 (55.2)	195 (51.7)	
Mastectomy	169 (44.8)	182 (48.3)	
Radiotherapy			0.06
Yes	238 (63.1)	213 (56.5)	
No	139 (36.9)	164 (43.5)	

Univariate and multivariate Cox proportional hazards analyses

The hazard ratios for OS according to all variables in the univariate or multivariate Cox proportional hazards model are listed in Tables 2 and 3. According to the results of univariate analysis, we found that the race, marital status, laterality, and radiotherapy were not significant factors for OS. After excluding the aforementioned variables, age at diagnosis, grade, HR status, tumor size, number of positive regional lymph-nodes, clinical stage, and surgery were determined as prognostic factors in the multivariate Cox proportional hazards model for the OS analysis. As shown in Table 3, age at diagnosis could be a negative prognostic factor for the OS of patients with IMPC. The HR negative special type exhibited higher risk of death. Compared with patients with IMPC and negative regional node, patients with positive regional lymph-nodes suffered from higher risk of poor prognosis. Interestingly, the subgroups of stages II and III had a significantly lower risk than the stage I group.

Table 2. Univariate analysis of OS in the training cohort.

Variables	HR	95% CI	P value
Age (year)	1.035	1.005-1.065	0.023
Race			
White		reference	
Other	1.202	0.529-2.732	0.660
Marital status			
Unmarried		reference	
Married	0.721	0.343-1.512	0.386
Laterality			
Left		reference	
Right	0.915	0.435-1.923	0.816
Grade			
I/II		reference	
III/IV	2.180	1.030-4.611	0.042
HR status			
Positive		reference	
Negative	4.150	1.914-8.998	<0.001
Tumor size (mm)			<0.001
<20		reference	
20-50	1.931	0.728-5.119	0.186
>50	7.960	3.339-18.973	<0.001
Number of positive regional nodes			<0.001
0		reference	

	1-3	1.679	0.609-4.632	0.317
	4-9	3.145	0.998-9.914	0.050
	≥10	8.350	3.016-23.115	<0.001
Stage				<0.001
	I		reference	
	II	1.040	0.365-2.967	0.941
	III	3.529	1.262-8.419	0.015
	IV	19.576	4.982-76.921	<0.001
Surgery				
	Conserving surgery		reference	
	Mastectomy	2.530	1.144-5.596	0.022
Radiotherapy				
	Yes		reference	
	No	0.780	0.368-1.649	0.515

Table 3. Multivariate analysis of OS in the training cohort.

Variables	HR	95% CI	P value	
Age (year)	1.054	1.020-1.090	0.020	
Grade				
	I/II	reference		
	III/IV	1.159	0.504-2.666	0.728
HR status				
	Positive	reference		
	Negative	5.368	2.084-13.830	0.001
Tumor size (mm)				
	<20	reference		
	20-50	2.292	0.631-8.322	0.208
	>50	4.807	0.919-25.153	0.063
Number of positive regional nodes				
	0	reference		
	1-3	18.314	1.387-241.811	0.027
	4-9	10.340	1.044-102.388	0.046
	≥10	26.776	3.300-23.115	0.002
Stage				
	I	reference		
	II	0.057	0.004-0.802	0.034
	III	0.096	0.100-0.964	0.046
	IV	0.211	0.170-2.641	0.228
Surgery				
	Conserving surgery	reference		
	Mastectomy	1.119	0.393-3.190	0.833

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4 Construction and validation of the nomograms.

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6 The nomogram for 1-, 3-, and 5-year OS was developed by using the
7 multivariate Cox proportional hazards models as the final prognostic models after
8 factor selection (Figure 1B). The nomogram was internally validated in the training
9 cohort and externally validated in the validation cohort. The AUC values of the ROC
10 curve, which exhibited the discrimination capacity, were 0.830 and 0.764 in the
11 training and validation cohorts, respectively (Figure 1C and Figure 1D). Moreover,
12 compared with the discriminative ability of the sixth edition AJCC TNM staging
13 classification, the discriminative ability of the nomogram was significantly superior in
14 the training and validation cohorts ($P < 0.001$). The results indicated that the
15 nomogram can efficiently predict OS in patients with IMPC. The calibration plots also
16 showed great consistency between the actual and nomogram-predicted survival
17 rates in the training and testing cohorts (Figure 2A and Figure 2B). The C-index values
18 of the nomogram for OS were 0.794 in the training cohort and 0.774 in the validation
19 cohort.
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35 Discussion

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37 Invasive micropapillary carcinoma of breast is a rare variant of invasive breast
38 carcinoma (IBC)⁴. Histologically, it is a special type characterized by small papillary
39 structures that lack true central fibrovascular cores and lie within empty stromal
40 spaces^{24 25}. Historically, patients with IMPC were usually treated with standard IBC
41 treatment. However, notable differences in histological characters and prognosis
42 exist between IMPC and IBC²⁶; as such, treating IMPC as IBC would be inappropriate.
43 Accurate predictions of prognosis of patients with IMPC patients could effectively
44 help clinicians to take proper treatment modalities. This study aims to build a
45 nomogram capable of predicting the prognosis of IMPC based on a larger population
46 database of the Surveillance, Epidemiology, and End Results (SEER) program.
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56 In this study, we equally divided 754 patients with IMPC from the SEER
57 database into two cohorts. We developed an effective nomogram that contains four
58 independent prognostic factors including age at diagnosis, HR, number of positive
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3 regional lymph-nodes, and clinical stage. The nomogram, derived from the Cox
4 regression model to predict the 1-, 3-, and 5-year OS of patients with IMPC, was
5 verified to have good discrimination capacity. Moreover, the nomogram showed
6 better prediction ability for OS than that of the sixth edition AJCC TNM staging
7 classification (AUCs in the ROC curve: 0.830 and 0.651 in the training cohort and
8 0.764 and 0.633 in the validation cohort, respectively).
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15 Hormone receptors play important role in prognosis of breast cancer^{27 28}. A
16 previous study showed that the 5-year OS was 59% in 100 patients with IMPC with a
17 mean age of 50 years and 46% HR positivity¹². In another study, 72 patients with
18 IMPC with a mean age of 46 years and 75% HR positivity had 86% 5-year OS¹⁰. In
19 comparison, our study population was older (mean age of 59.3 years) and had a
20 higher percentage of HR positivity (89.5%). The higher HR positivity in the present
21 study may contribute to the better 5-year OS (91.1%)²⁹. The Cox-regression analysis
22 result also proved that HR negativity could lead to significantly poor OS in patients
23 with IMPC (HR 5.368; 95%CI 2.084–13.830; P=0.001).
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33 Lymph node metastasis is widely considered as an unfavorable prognostic
34 factor in clinical practice^{30 31}. Axillary lymph node metastasis is commonly seen in
35 patients with IMPC at first diagnosis. The rate of lymphatic and lymph nodal spread
36 ranged from 33% to 95%^{4 24 32 33}. The value and necessity of sentinel lymph node
37 biopsy (SLNB) or axillary dissection in patients with IMPC remains controversial.
38 Walsh et al. found that regional lymph nodes can be involved even at early stage of
39 IMPC lesions. The team highly recommended a thorough regional lymph node
40 examination to patients with IMPC²⁵. However, Paterakos et al. were skeptical to the
41 utility of SLNB for patients with IMPC due to the high frequency of multiple positive
42 regional lymph nodes³⁴. In the present study, we found that patients with IMPC with
43 even one positive regional lymph node would suffer higher risk than patients with
44 negative lymph node. Patients with IMPC and 10 or more positive lymph nodes are
45 at the highest risk (OR 26.776; 95%CI 3.300-23.115; P=0.002). Thus, axillary
46 dissection, or SLNB at minimum, should be performed to correctly assess the risk
47 and adopt suitable treatment regimens for patients with IMPC.
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4 This study has some limitations. First, retrospective SEER data lack a pathologic
5 review to identify the diagnosis for each case. Second, we cannot consider the types
6 of systemic therapy administered to patients. Hormonal blockade therapy and
7 chemotherapy could significantly affect the outcome of patients. Third, the
8 relationship between the degree of micropapillary involvement and clinical
9 outcomes among patients with IMPC remains unclear. Although some previous small
10 case series studies have revealed that an increasing percentage of micropapillary
11 component was not associated with more lymph node metastasis and worse
12 survival^{32 35}, it need to be further validated in large-scale studies.
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23 Conclusions

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25 In conclusion, age at diagnosis, HR status, number of positive regional
26 lymph-nodes, and clinical stage were independent prognostic factors for patients
27 with IMPC. We constructed a nomogram to predict OS in patients with IMPC based
28 on a large-scale population from the SEER database. This accessible nomogram will
29 help doctors to adopt proper treatment regimens in clinical practice.
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37 List of abbreviations

38 invasive micropapillary carcinoma (IMPC)
39 overall survival (OS)
40 Surveillance, Epidemiology, and End Results (SEER)
41 American Joint Committee on Cancer (AJCC)
42 hormone receptors (HRs)
43 estrogen receptor (ER)
44 progesterone receptor (PR)
45 receiver operating characteristic (ROC)
46 area under the curve (AUC)
47 invasive breast carcinoma (IBC)
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54 Jianpeng Liu and Wei Xi contributed equally.

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56
57 Contributorship statement: Jianpeng Liu and Wei Xi designed and conducted the
58 study. Jiahao Zhou provide suggestions in revision. Wei Gao analysed and
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4 interpreted the data. Wei Xi drafted, revised, finalised and submitted the manuscript.
5
6 Jianpeng Liu are responsible for the critical revision. Qiaolin Wu approved the
7
8 submission of the manuscript. Qiaolin Wu has full responsibility for the overall
9
10 content as the guarantor, had access to the data and controlled the decision to
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12 publish.

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20
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29 writing of the manuscript.
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33 Patient consent for publication: Not Applicable.
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37 Ethics statements: This study was reviewed by the Ethics Committee in Clinical
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39 Research of the First Affiliated Hospital of Wenzhou Medical University. The data are
40
41 anonymous, and the requirement for informed consent was therefore waived.
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45 Data sharing statement: Data are available in a public, open access repository. Data
46
47 are fully accessible at <https://seer.cancer.gov/data-software/>. The datasets used in
48
49 this study are available from the corresponding author on reasonable request. The
50
51 corresponding author has full access to all the data used in this study and had final
52
53 responsibility for the decision to submit the study for publication.
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4 Figure legend

5 Figure 1A. Kaplan-Meier survival curves of the patients with IMPC in the training and
6 validation cohorts.
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9 Notes: The survival curves showed no significant differences between the 2 cohorts
10 (P= 0.786).
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15 Figure 1B. Nomogram for predicting 1-, 3-, 5-year OS for patients with the prognosis
16 factors.
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19 Notes: The total points are calculated by summing up the points for each factor. The
20 predicted probability of OS can be obtained by projecting the location of the total
21 points to the bottom scales. Abbreviations: OS= overall survival.
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27 Figure 1C and Figure 1D. ROC curves for discrimination in the training and validation
28 cohorts.
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31 Notes: (Figure 1C) In the training cohort, the AUC of the ROC curve of the nomogram
32 and the sixth edition AJCC TNM staging classification was 0.830 and 0.651,
33 respectively (P < 0.001). (Figure 1D) In the validation cohort, the AUC of the ROC
34 curve of the nomogram and the sixth edition AJCC TNM staging classification was
35 0.764 and 0.633, respectively (P < 0.001). Abbreviations: AJCC= American Joint
36 Committee on Cancer; AUC= area under the curve; ROC= receiver operating
37 characteristic.
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47 Figure 2. Calibration curves for predictions for the 1-year (a), 3-year (b), 5-year (c) OS
48 in the training cohort (Figure 2A) and in the testing cohort (Figure 2B).
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51 Notes: (Figure 2A) The nomogram-predicted probability of OS is plotted on the X-axis,
52 and the actual OS is plotted on the Y-axis. (Figure 2B) The nomogram-predicted
53 probability of OS is plotted on the X-axis, and the actual OS is plotted on the Y-axis.
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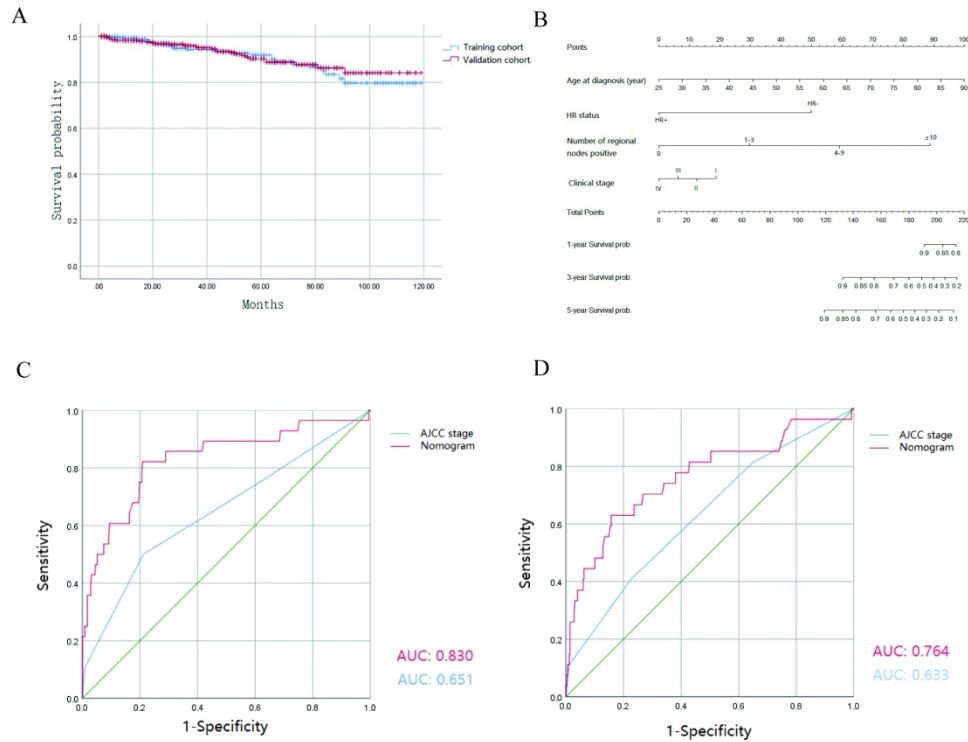


Figure 1A. Kaplan-Meier survival curves of the patients with IMPC in the training and validation cohorts.
 Notes: The survival curves showed no significant differences between the 2 cohorts (P= 0.786).

Figure 1B. Nomogram for predicting 1-, 3-, 5-year OS for patients with the prognosis factors.
 Notes: The total points are calculated by summing up the points for each factor. The predicted probability of OS can be obtained by projecting the location of the total points to the bottom scales. Abbreviations: OS= overall survival.

Figure 1C and Figure 1D. ROC curves for discrimination in the training and validation cohorts.
 Notes: (Figure 1C) In the training cohort, the AUC of the ROC curve of the nomogram and the sixth edition AJCC TNM staging classification was 0.830 and 0.651, respectively (P<0.001). (Figure 1D) In the validation cohort, the AUC of the ROC curve of the nomogram and the sixth edition AJCC TNM staging classification was 0.764 and 0.633, respectively (P<0.001). Abbreviations: AJCC= American Joint Committee on Cancer; AUC= area under the curve; ROC= receiver operating characteristic.

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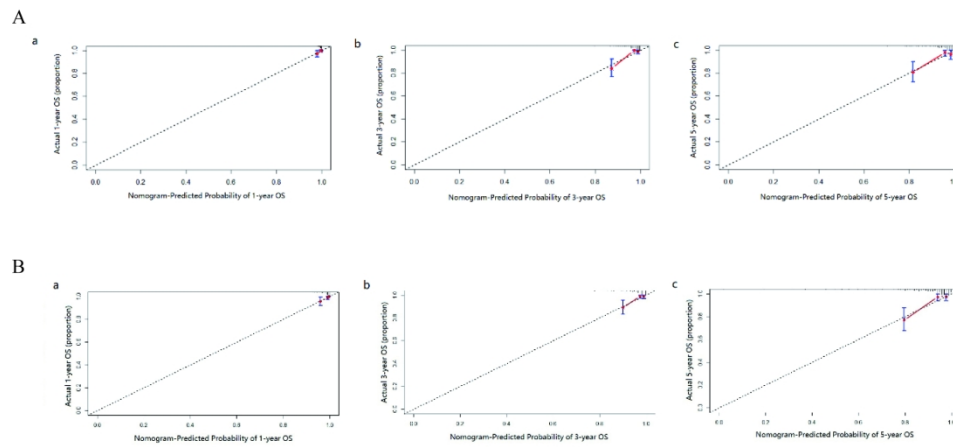


Figure 2. Calibration curves for predictions for the 1-year (a), 3-year (b), 5-year (c) OS in the training cohort (Figure 2A) and in the testing cohort (Figure 2B).

Notes: (Figure 2A) The nomogram-predicted probability of OS is plotted on the X-axis, and the actual OS is plotted on the Y-axis. (Figure 2B) The nomogram-predicted probability of OS is plotted on the X-axis, and the actual OS is plotted on the Y-axis.

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(b) For matched studies, give matching criteria and number of exposed and unexposed	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	5
		(b) Describe any methods used to examine subgroups and interactions	5
		(c) Explain how missing data were addressed	5
		(d) If applicable, explain how loss to follow-up was addressed	5
		(e) Describe any sensitivity analyses	5
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	6
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	6
		(c) Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	Report numbers of outcome events or summary measures over time	8
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10
		(b) Report category boundaries when continuous variables were categorized	10
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.