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ORIGINAL RESEARCH

A Model to Predict the Risk of Lymph Node Metastasis in Breast Cancer Based on Clinicopathological Characteristics

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Background: Sentinel lymph node biopsy (SLNB) and axillary lymph node dissection (ALND) may cause lymphatic and nervous system side effects in patients with breast cancer. It is imperative to develop a model to evaluate the risk of sentinel lymph node metastasis to avoid unnecessary operation.

Patients and Methods: A total of 2705 cases of female breast cancer patients enrolled in this retrospective study. We divided into the training group (SLNB group) and the validation group (ALND group) to analyze the relathionship between lymph node metastasis and clinical-pathological factors. Logistic regression analysis was performed to verify the variables which involved in ALN metastasis and established a prediction model. ROC curves were employed to evaluate the predictive ability of the model.

Results: In the SLNB group, 9 variables, including pathological type, histological grade, tumor size, hormone receptor, HER-2, Ki-67, multifocality, and molecular subtypes, were related to breast cancer ALN metastasis. Clinically negative lymph nodes, favorable histologic type, tumor size <2 cm, and Ki-67 <15% were at very low risk for lymph node metastasis. The AUC of the validation group was 0.786.

Conclusion: We successfully establish a mathematics model to predict lymph node metastasis of breast cancer. Axillary surgery should be individual with preoperative clinical characteristics, especially for patients with a longer life expectancy.

Keywords: breast cancer, predict model, axillary lymph node metastasis, surgery

Introduction

Axillary lymph node status is one of the substantial prognostic factors for patients with breast cancer. It's a gold standard to guide the adjuvant treatment decisions.[1] Axillary lymph node dissection (ALND) is a common alternative to mastectomy in the treatment of metastatic breast cancer. However, ALND also brings many complications, including lymphedema, pain, numbness, infection, and limited shoulder movement.[2,3] As more and more breast cancer gets screen-detected at an early stage, sentinel lymph node biopsy (SLNB) has emerged as a most predominant tool to probe axillary lymph node status for patients who have clinically negative lymph nodes. Review from previous data, only 30% of patients with clinically negative lymph nodes will develop sentinel lymph node metastasis.[4] Although SLNB is a minimally invasive and well-tolerated surgical procedure, the short-term and long-term complications such as shoulder pain, upper limb edema, and arm numbness may also occur in patients after SLNB.[5–7] It is

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unreasonable for all the patients who have clinically negative lymph nodes to receive an SLNB.

As previously reported, the clinical-pathological predictors of axillary lymph node metastases are including: age,[8,9] tumor size,[8–11,13,18] primary tumor quadrant,[12] multifocality,[19] histologic grade,[8,14] pathological type,[8,13,20] receptor status,[8,21] molecular subtypes.[21] Notwithstanding, all the identified factors are independently correlated with axillary lymph node metastases. Pooling all of these predictors, alone or combined with others, has not been adopted for the selection of patients for whom ALND may be avoided.

Therefore, in this study, we were trying to figure out the correlation between clinical-pathological characteristics and axillary lymph node status in an extensive series of 2705 patients treated with conservative or ablative surgery for primary invasive breast cancer, determined the risk factors of ALN metastasis and establish a mathematics model to guide surgeons to perform SLNB on selective patients.

Patients and Methods

2705 patients who underwent surgical treatment between Jan 2008 and December 2018 at Fujian Medical University Union Hospital and Affiliated Sanming First Hospital of Fujian Medical University were enrolled in this study.

The inclusion criteria were as follows: (i) female; (ii) operable primary breast cancer underwent surgical treatment by tumorectomy or mastectomy; (iii) negative axillary lymph nodes confirmed by clinical and imaging examinations; (iv) SLN biopsy successfully performed and additional ALND performed; (v) Axillary lymph nodes were confirmed to be negative by histological or cytological biopsy before surgery; (vi) not pregnant; (vii) no neoadjuvant therapy and (viii) no previous history of axillary surgery. Patients who did not meet the above criteria were excluded.

The patients were divided into two groups according to the methods of axillary surgery: the SLNB group (training group) and the ALND group (validation group). In the SLNB group, patients with pathologically negative lymph nodes who underwent sentinel lymph node biopsy; in the ALND group, patients with pathologically positive lymph nodes who underwent SLNB and then received additional ALND.

The Ethics Committee approved the protocol of Fujian Medical University Union Hospital and Affiliated Sanming First Hospital of Fujian Medical University. This study was strictly conducted in accordance with the Declaration of Helsinki.

Data were collected on demographics materials and tumor clinical-pathological characteristics, including age, surgical procedure, clinical size, tumor location, postoperative pathological tumor size, pathological type, histological grade, clinical axillary lymph node status, estrogen receptor (E.R.) status, progesterone receptor (P.R.) status, Ki-67 index, human epidermal growth factor receptor 2 (HER-2) status, multifocality, postoperative axillary lymph node status, stage of the disease, molecular subtypes. All diagnostic slides of the tumors and lymph nodes were evaluated independently by two breast pathologists.

Statistical Analysis

The mean and S.D. were used to describe continuous variables. *t*-test was used for the comparison of continuous variables, and the chi-square test or Fisher's exact test was applied for comparison of categorical variables. Univariate logistic regression analysis was applied to study ALN metastasis-related variables; multivariate logistic regression analysis was used to verify the variables that were independent affecting factors of ALN metastasis and establish a prediction model for breast cancer ALN metastasis. ROC curves were employed to evaluate the predictive ability of the model.

The predicted value of transfer risk was segmented in the decimal system according to the verification queue data, and the average transfer risk of each segment was calculated. To further evaluated the clinical application value of the model, we considered a certain predictive risk cutoff value in the verification cohort. We calculated the corresponding accuracy and false-negative rate of the cutoff value to evaluate the screening indicators of patients with low-risk ALN metastasis.

All data analyses were via SPSS (version 11.0, Chicago, IL, USA, and R software (version 3.1.0, Vienna, Austria). A two-tailed p-value <0.05 was considered as statistically significant.

Results

Clinical-Pathologic Characteristics and Grouping of Patients

As 658 patients did not meet the inclusion criteria, we enrolled a total of 2047 patients, of which 1010 were assigned into the training cohort, and 1037 were assigned into the validation cohort. The baseline of clinical-pathological data between the two groups did not differ significantly ($p>0.05$). (Table 1).

Table 1 Baseline of the Clinical-Pathological Characteristics Between of Two Cohorts

Characteristics		Training	%	Validation	%	P-value
Number of patients		1010	49.3	1037	50.7	
Age		50.8±10.8		50.0±10.2		0.082
Tumor location[a]						0.069
	UOQ	469	53.0	438	49.8	
	LOQ	122	13.8	138	15.7	
	UIQ	169	19.1	179	20.4	
	LIQ	61	6.9	51	5.8	
	Central	46	5.2	47	5.3	
	Others*	18	2.0	26	3.0	
Clinical tumor size[b]						0.186
	≤2.0	639	63.3	624	60.2	
	>2.0	371	36.7	413	39.8	
Pathological type						0.102
	IDC	864	85.5	902	87.0	
	ILC	24	2.4	24	2.3	
	Others**	122	12.1	111	10.7	
Histologic grade						0.078
	I	62	6.1	88	8.5	
	II	521	51.6	572	55.2	
	III	319	31.6	299	28.8	
	N.A.***	108	10.7	78	7.5	
ER [c]						0.099
	Positive	788	78	777	74.9	
	Negative	222	22	260	25.1	
PR[c]						0.915
	Positive	661	65.4	681	65.7	
	Negative	349	34.6	356	34.3	
Ki-67						0.234
	<15%	244	24.2	298	28.7	
	15-30%	415	41.1	356	34.3	
	>30%	351	34.8	383	36.9	
HER-2 receptor status[d]						0.213
	Positive	222	22	252	24.3	
	Negative	788	78	785	75.7	
Multifocality						0.301
	Unifocal	956	94.7	967	93.3	
	Multifocal	50	5.0	67	6.5	
	Multicentric	4	0.4	3	0.3	
Lymph node status						0.053
	Negative	769	76.1	893	86.1	
	Positive	241	23.9	144	13.9	

(*Continued*)

Table 1 (Continued).

Characteristics		Training	%	Validation	%	P-value
Molecular subtype						0.110
	Luminal	788	78.0	777	74.9	
	HER-2+	91	9.0	122	11.8	
	TN	131	13	138	13.3	

Notes: [a]In the case of multifocal tumors or unifocal tumors involving more than one quadrant, the tumor locations are classified in the following priority order: upper outer quadrant (UOQ), central, lower outer quadrant (LOQ), lower inner lower quadrant (LIQ), and upper inner quadrant (UIQ). For example, the inner and central regions are divided into the central quadrant. The central and outer quadrants involved are classified as outer. If all quadrants are included, the tumor is classified as the outer upper quadrant. Others (other) are occult breast cancer or tumors that cannot be found by manual examination. [b]Clinical tumor size assessment by preoperative ultrasound. [c]The positivity of estrogen and progesterone receptors was defined as at least 10% or more immunostained cells. [d]Positivity for HER-2 was defined as HER-2 gene amplification using the fluorescence in situ hybridization by the HER-2/neu probe kit, or scoring >3 using the immunohistochemistry method. *Others: occult breast cancer or tumors that cannot be found by manual examination. **Others: mucinous carcinoma, infiltrating carcinoma with medullary characteristics, squamous cell carcinoma, papillary carcinoma, infiltrating micropapillary carcinoma, sieve carcinoma, medullary carcinoma, tubular carcinoma, etc. ***Some specific types of cancer are not histologically graded. N.A, not available.

Some Factors Were Involved in ALN Metastasis in the Training Cohort

Univariate logistic regression was performed to explore ALN metastasis-related variables. Pathological type, histologic grade, tumor size, hormone receptors, HER-2, Ki-67, multifocality, and molecular subtypes were attributed to ALN metastasis ($p < 0.05$) (Table 2).

Five clinical-pathological predictors, including Pathological type, HER-2, Ki-67, Hormone receptors, tumor size, were involved in the multivariate logistic regression model. (Table 3).

Establishment of Mathematics Model for ALN Metastasis

According to the results of multivariate analysis, the following 5 variables were included in the prediction model of ALN metastasis: pathological type, HER-2, Ki-67, hormone receptors, and tumor size. The weights of each variable in the model corresponded to different point values. Points for the following factors were added together to determine total points, which corresponded to the linear predictors and risk predictors of ALN metastasis: pathology (LDC=0; IDC=100; others=31), HER-2 (Positive=0; Negative=43), Ki-67 (High=0; Low=5; Moderate=55), Hormone receptors (HR-=0; HR+=32), size (≤2.0 cm=0; >2.0 cm=71) (Figure 1). The final logistic regression model for predicting lymph node metastasis listed as follows:

$$\ln(p/1-p) = -1.623 \times a2 - 1.167 \times a3 - 0.749 \times b1 + 0.939 \times c2 - 0.201 \times c3 - 0.502 \times d1 + 1.225 \times e1 - 2.537$$

where "p" represents the risk of ALN metastasis. "a" represents Histological type (a2=IDC; a3=others); "b" represents HER-2 status (b1=HER-2+); "c" represents Ki-67 expression (c2=low; c3=moderate); "d" represents Hormone receptors (d1=HER-2-); "e" represents tumor size (e1=size >2.0 cm).

We retrospectively utilized the model upon the patients in the training cohort (n=1010). The area under curve (AUC) value was 0.725 (Figure 2), suggesting the predictive ability of this model was formidable.

The Predictive Ability of the Prediction Model in the Validation Cohort

We utilized the model on the patients in the validation cohort. According to the ROC curve, the AUC value was 0.786 (Figure 3), indicating the model performed well in the validation cohort as well. To further evaluate the clinical value of the model under different risk of ALN metastasis, we selected 10 cutoffs according to the Youden's index. We calculated the number of patients, number of patients with ALN metastasis, sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of ALN metastasis under different predicted risk values. As shown in Table 4, this model is more appropriate for predicting the negative axillary lymph nodes with the negative predictive rate >90%. Only 5 patients (2.9%) had lymph node metastasis among 172 cases with a predicted risk of <10%. However, the model presented a poorer prediction of positive lymph nodes. As a result, our model was more applicable to predict negative lymph nodes.

Discussion

Sentinel lymph node biopsy has become the standard surgical procedure to determine the status of axillary lymph node metastasis in breast cancers with clinically negative lymph nodes. Of note, SLNB may result in

Table 2 Factors Associated with ALD Metastasis in Univariate Logistic Regression

Variables		Coefficient	Wald Value	P-value	OR	OR 95% CI	
						Lower	Upper
Age			7.399	0.193			
	35–44 VS <35	0.264	0.442	0.506	1.302	0.598	2.863
	45–54 VS <35	0.659	2.944	0.086	1.933	0.91	4.103
	55–64 VS <35	0.337	0.718	0.397	1.401	0.642	3.053
	65–74 VS <35	0.44	0.967	0.325	1.552	0.646	3.726
	>75 VS <35	−0.022	0.001	0.973	0.978	0.269	3.555
Pathological type			20.363	<0.001			
	ILC VS IDC	−0.564	2.917	0.088	0.569	0.298	1.087
	Other VS IDC	−0.737	17.943	<0.001	0.479	0.34	0.673
	Other VS ILC	−0.173	0.22	0.639	0.842	0.409	1.731
Histologic grade			26.987	<0.001			
	II V SI	0.546	9.971	0.002	1.727	1.23	2.425
	III V SI	0.741	17	<0.001	2.097	1.475	2.983
	NO V SI	−0.169	0.347	0.556	0.844	0.481	1.483
Clinical tumor size	>2.0 VS ≤2.0	0.493	9.896	0.002	1.637	1.204	2.225
Hormone receptors	HR- VS HR+	−0.519	7.016	0.008	0.595	0.405	0.874
HER2	HER-2+ VS HER-2-	−0.407	4.513	0.034	0.666	0.458	0.969
Ki-67			16.286	<0.001			
	15-30% VS <15%	0.551	8.221	0.004	1.735	1.19	2.529
	>30% VS <15%	−0.082	0.151	0.698	0.922	0.61	1.392
	15-30% VS >30%	0.322	10.132	0.001	1.38	1.132	1.682
Tumor location			5.449	0.364			
	LOQ VS UOQ	0.124	0.3	0.584	1.132	0.727	1.762
	UIQ VS UOQ	−0.382	2.996	0.083	0.683	0.443	1.052
	LIQ VS UOQ	−0.177	0.301	0.583	0.838	0.446	1.575
	Central VS UOQ	−0.379	0.965	0.326	0.684	0.321	1.459
	Other VS UOQ	0.341	0.446	0.504	1.407	0.517	3.828
Multifocality			4.011	0.135			
	Multifocal VS Unifocal	0.656	4.011	0.045	1.928	1.014	3.668
	Multicentric VS Unifocal	0.043	0.001	0.97	1.044	0.108	10.095
Molecular subtype			0.72	0.027			
	HER-2+ VS LM	−0.412	2.154	0.142	0.662	0.382	1.148
	TN VS LM	−0.598	5.637	0.018	0.55	0.336	0.901
	TN VS HER-2+	−0.185	0.266	0.606	0.831	0.411	1.68

many short-term or long-term complications. In this study, we successfully established a nomogram model for the prediction of breast cancer ALN metastasis. In our nomogram model, the histopathological type comes as the most weighted factor; Meanwhile, tumor size, Ki-67, HER-2 expression, and hormone receptors contribute to ALN metastasis.

Several studies demonstrated that age at diagnosis, tumor size, primary tumor quadrant, presence of multiple tumors, histologic grade, pathological type, ER/PR, HER-2 status, molecular subtypes, and other factors were related to ALN metastasis status.[8,22–24]

Viale et al,[23] studied data from 4351 patients and found favorable historical types (medullary, cribriform, tubular, mucinous) have a significantly lower risk of axillary lymph node metastasis than ductal. Similarly, a lower frequency of axillary nodal metastasis in invasive lobular carcinoma than in invasive duct carcinoma has been

Table 3 Factors Associated with ALD Metastasis in Multivariate Logistic Regression

Variables		Coefficient	SE	Wald Value	P value	OR	OR 95% CI	
							Lower	Upper
Pathological type				16.711	<0.001			
	ILC VS LDC	−1.623	0.776	4.374	0.036	0.197	0.043	0.903
	Other VS LDC	−1.167	0.324	12.968	<0.001	0.311	0.165	0.588
HER-2	HER-2+ VS HER2-	−0.749	0.240	9.761	0.002	0.473	0.295	0.756
Ki-67				35.650	<0.001			
	15–30% VS <15%	0.939	0.226	17.269	<0.001	2.558	1.643	3.985
	>30% VS <15%	−0.201	0.269	0.554	0.457	0.818	0.483	1.387
Hormone receptors	HR- VS HR+	−0.502	0.255	3.857	0.050	0.606	0.367	0.999
Tumor size	>2.0 VS ≤2.0	1.225	0.177	48.020	<0.001	3.403	2.407	4.812
Constant		−2.537	0.473	28.727	<0.001	0.079		

reported in several studies.[25] In our study, invasive ductal carcinoma indicated the most unfavorable outcome of ALN metastasis. The lowest rate of node positivity was observed in invasive lobular carcinoma.

Tumor size emerged as the most influential independent predictor of SLN metastases. This fact has been confirmed in some studies. Wada et al,[17] have reported that larger primary tumors (>2.0cm) were significantly associated with positive non-SLNs (NSLN+). In a series of 893 cases published by Cutuli et al.[18] The rate of lymph node metastases increased from 11% to 36% when the tumor size increased from 10 mm to 25 mm. In our multivariate model, the influence coefficient of tumor size is 1.225; the effect weight is just a little bit lower than the histological type. The figures are entirely in line with previous findings on the likelihood of axillary lymph node involvement after ALND according to tumor size.[8–15,19]

Ki-67 is a nuclear protein that is associated with cellular proliferation. Many studies[26,28] suggested that higher Ki-67 index results were significantly associated with more frequency of ALNM in breast cancer. In several studies, patients were categorized into two categories of above and below 20% for the Ki-67 index. Our

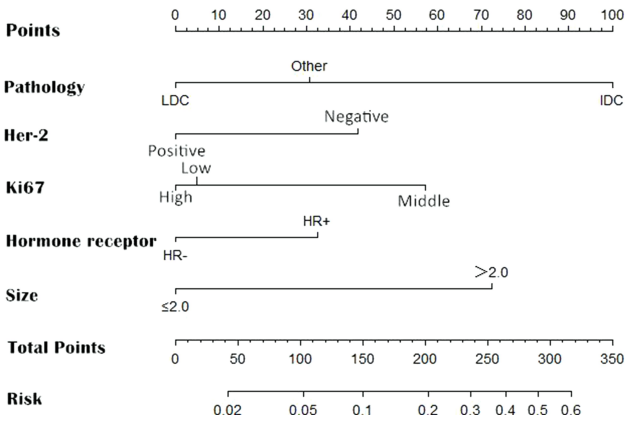

Figure 1 Nomogram for predicting the probability of axillary lymph node metastasis. There are a total of 8 rows in the nomogram. The behavioral variables are presented in rows 2 to 6, and points for each variable correspond to the scale in row 1. The points of these 5 variables were added to the total score shown in the balance in row 7, which relevant to the risk predictors of axillary lymph node metastasis in row 8.

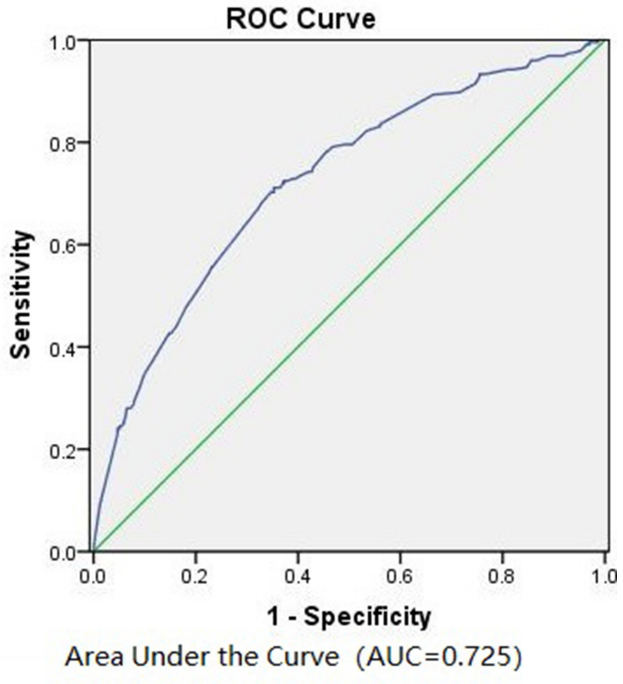

Figure 2 Receiver operating characteristic (ROC) curve calculation for the predictive model of the training cohort (n = 1010).

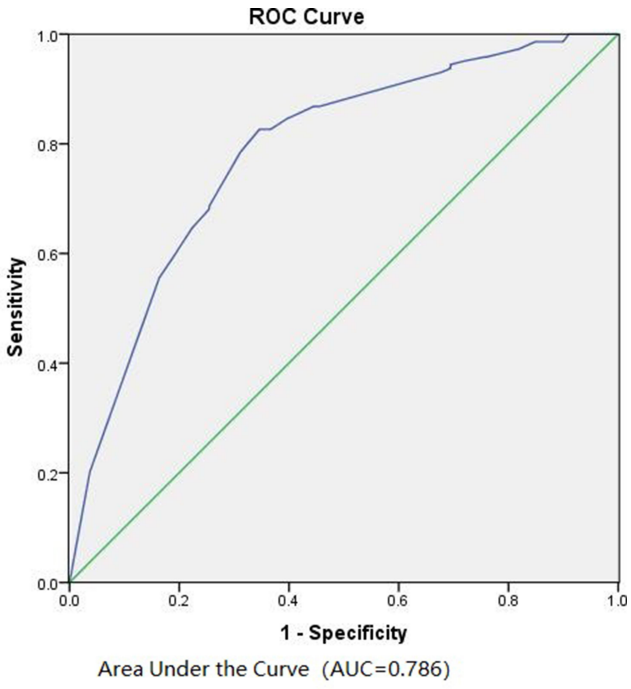

Figure 3 Receiver operating characteristic (ROC) curve calculation for the predictive model of the validation cohort (n = 1037).

study seems to indicate that moderately malignant tumors and low-grade malignant tumors are most prone to axillary lymph node metastasis.

There are many available nomogram models for predicting ALND metastasis. In 2007, MSKCC put forward a model that age, tumor size, tumor type, lymphovascular invasion, tumor location, multifocality, and estrogen and progesterone receptors were associated with SLN metastasis.[29] In 2012, Chen et al established an SCH model, and they identified age, tumor size, tumor location, tumor type, and lymphovascular invasion were independent predictors of SLN metastasis.[30]

Owing to skipping metastasis and unproficiency of doctors, SLNB has a false-negative probability of about 10%. We aimed to identify which patients had a low risk of both SLND and ALND metastasis and to protect them from invasive procedures. Therefore, we only targeted the study population to patients with clinically negative axillary lymph nodes. We used the clinical and pathological data of patients undergoing sentinel lymph node biopsy to create a model of axillary lymph node metastasis. Compared with the MSKCC and SCH nomogram, our model has the same AUC with fewer variables, and the false-negative rate is less than 10% in both training and validation groups.

Still, we have some limitations to this study. It would be unusual management in the validation group, patients who were clinically and radiologically node-negative, yet had ALND. As most of our data were over ten years, the SLNB had not been fully promoted in our centers at that time. However, only very few patients received ALND without SLNB enrolled in this analysis. We reported the majority of patients in the ALND group were those who had a positive for SLNB and continued to receive an ALND. Moreover, the data only came from two centers, and the nomogram still needs to be further validated in various patient populations to demonstrate its reproducibility.

In conclusion, our nomogram could serve as an acceptable and adoptable clinical tool in preoperative evaluation, especially for those who were clinically and radiologically node-negative to avoid an SLNB procedure safely—thus improving the quality of life of the patients without adverse effect on their survival rates.

Table 4 Accuracy of the Developed Model in the Validation Cohort

Predicted Risk	No. of Patients (%)	No. of Patients with ALN Metastasis	Sensitivity (%)	Specificity (%)	Accuracy (%)	Positive Predictive Rate (%)	Negative Predictive Rate (%)
<0.051	43 (4.15)	1	99.31	4.70	17.84	14.39	97.67
<0.082	105 (10.13)	3	97.92	11.42	23.43	15.13	97.14
<0.100	172 (16.59)	5	96.53	18.70	29.51	16.07	97.09
<0.142	313 (30.18)	12	91.67	33.71	41.76	18.23	96.17
<0.163	471 (45.42)	19	86.81	50.62	55.64	22.08	95.97
<0.205	503 (48.51)	20	86.11	54.09	58.53	23.22	96.02
<0.261	602 (58.05)	38	73.61	63.16	64.61	24.37	93.69
<0.313	737 (71.07)	50	65.28	76.93	75.31	31.33	93.22
<0.407	903 (87.08)	69	52.08	93.39	87.66	55.97	92.36
<0.487	920 (88.72)	75	47.92	94.62	88.14	58.97	91.85

The Statement of Consent Obtaining

The consent was obtained from the study participants before study commencement via signing the Informed Consent Form.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. Wenxin Chen and Yingming Sun made a language copy editing for the revised manuscript.

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Disclosure

The authors have declared that no competing interest exists.

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