A prognostic nomogram based on lymph node ratio for postoperative vulvar squamous cell carcinoma from the Surveillance, Epidemiology, and End Results database: a retrospective cohort study

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Background: Vulvar carcinoma is a rare gynecological malignancy. The most commonly used staging system for vulvar cancer is the 2009 International Federation of Gynecology and Obstetrics (FIGO) staging system. Nevertheless, it does not incorporate many indispensable prognostic parameters, which prominently influence vulvar cancer patient survival. Thus, the development of a prediction model for evaluating survival prognosis in postoperative vulvar squamous cell cancer patients is of vital importance.

Methods: Data from 2,166 patients with pathologically confirmed diagnosis of vulvar squamous cell carcinoma from 2004 to 2015 were acquired from the Surveillance, Epidemiology, and End Results (SEER) database. Thirty percent of the patients were randomly assigned to the validation group, and the remainder were used to develop the nomogram. Parameters that significantly correlated with overall survival (OS) were used to create the nomogram. Concordance index (C-index), calibration curve, and decision curve analysis (DCA) were used to assess the predictive accuracy and discriminability of the nomogram model. Additionally, the C-index and DCA of the nomogram and the FIGO staging system were compared.

Results: Following multivariate analysis of the training cohort, independent factors for OS, including race, age at diagnosis, marital status, FIGO stage, tumor diameter, and lymph node ratio (LNR), were included in the nomogram model. The calibration curve indicated a high correlation between the nomogram-predicted and observed survival probability. The C-index of the nomogram in the training cohort was 0.772 (95% CI: 0.752–0.792), statistically superior to the C-index value of the FIGO staging system (0.676, 95% CI: 0.654–0.698). In DCA, compared to the FIGO staging system, this nomogram showed a greater net benefit and a wider range of threshold probability. Results were verified by an internal validation cohort.

Conclusions: Our nomogram, based on LNR, showed superior prognostic predictive accuracy compared with the FIGO staging system for predicting OS in postoperative vulvar squamous cell carcinoma patients.

Keywords: Lymph node ratio (LNR); prognostic nomogram; vulvar cancer

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Introduction

Vulvar carcinoma is a rare malignant gynecologic tumor that accounts for 4–5% of all gynecological malignancies in the United States, with an estimated incidence of 6,190 new cases and 1,200 deaths in 2018 alone (1). Vulvar squamous cell carcinoma, the most common pathological subtype, is generally thought to occur in postmenopausal women. However, in recent years, due to the increase in human papillomavirus (HPV) infections worldwide, the average age of onset has decreased (2). Generally, lymph node (LN) involvement is considered a significant factor in the therapeutic decision-making and prognosis of vulvar carcinoma (3). Radical vulvectomy with complete inguinofemoral lymphadenectomy remains the standard approach for the management of vulvar cancer in lymph node-positive patients. The number of positive lymph nodes (PLNs) was included in the 2009 International Federation of Gynecology and Obstetrics (FIGO) staging system (4). The five-year overall survival (OS) rate ranges from 30% to 58.5% for lymph node-positive patients, whereas it ranges from 64.7% to 90.9% in lymph node-negative patients (5-7). The OS of LN-positive patients varies greatly depending on the extent of LN involvement. However, clinicians demonstrated that the number of PLNs might not adequately reflect LN involvement in clinical practice, because the degree of intraoperative LN evaluation influences the number of involved resected lymph nodes (RLNs) and the detection rate of LN metastases. Therefore, if surgical detection of LN is limited in LN-positive patients, it is possible that cases of LN metastasis could be overlooked.

The lymph node ratio (LNR) is defined as the ratio of the number of PLNs to the total number of RLNs, which reflects not only the burden of lymph node metastasis but also the degree of operative LN evaluation. The LNR has emerged as a vital independent prognostic factor for survival outcomes, and is superior to evaluation based on LN status in solid tumor malignancies, including cervical (8), endometrial (9), ovarian (10), breast (11), esophageal (12), gastric (13), and colorectal cancers (14). In two retrospective multicenter cohort trial analyses of the VULCAN (15) and the AGO CaRE-1 trial datasets (16), LNR appeared to be a consistent, independent prognostic parameter in vulvar cancer patients, and outperformed the number of PLNs in survival analyses.

The most commonly used staging system for vulvar cancer is the FIGO score staging system. Nevertheless, studies have shown that the FIGO staging system does not incorporate many indispensable prognostic parameters, which can greatly influence vulvar squamous cell cancer patient survival, such as patient characteristics, tumor cell differentiation, LNR, HPV status, and additional factors relevant to molecular pathways of prognosis (17-21). Thus, it is vital to develop a prediction model for evaluating survival prognosis in vulvar squamous cell cancer patients that incorporates tumor status as well as patient characteristics.

Nomogram-based statistical methods are intuitive statistical tools that quantify risk. They have advantages over traditional staging systems for many carcinomas, and have been generally implemented in oncologic prognosis-associated clinical practices (22,23). Here, we developed a nomogram using LNR, based on the assumption that this is a vital prognostic parameter and is superior to PLNs in survival prediction for vulvar squamous cell carcinoma patients. Furthermore, this nomogram may show superior prognostic predictive accuracy compared with the current FIGO staging system.

We present the following article in accordance with STROBE guideline checklist (available at http://dx.doi.org/10.21037/atm-20-3240).

Methods

Data source and collection

In this retrospective cohort study, patients diagnosed with vulvar cancer between 2004 and 2015 were included from the Surveillance, Epidemiology, and End Results (SEER) database. Methods of data collection and follow-up of patients are available on the SEER database. Inclusion criteria were as follows: histopathologically proven vulvar squamous cell carcinoma; and surgical treatment included lymphadenectomy. Exclusion criteria were: a history of other malignancies; a history of neoadjuvant anticancer therapy or sentinel lymph node biopsy; unexplained mortality; and unknown variables, such as race/ethnicity, age of diagnosis, tumor grade, FIGO stage, tumor diameter, marital status, number of PLNs, and number of RLNs.

Based on the aforementioned criteria, a total of 2,166 vulvar squamous cell carcinoma patients were included in this study. Thirty percent of the patients were randomly assigned to the validation group, and the remainder were used to develop the nomograms (training cohort, N=1,518; validation cohort, N=648). The flow chart for detailed patient selection is presented in *Figure 1*.
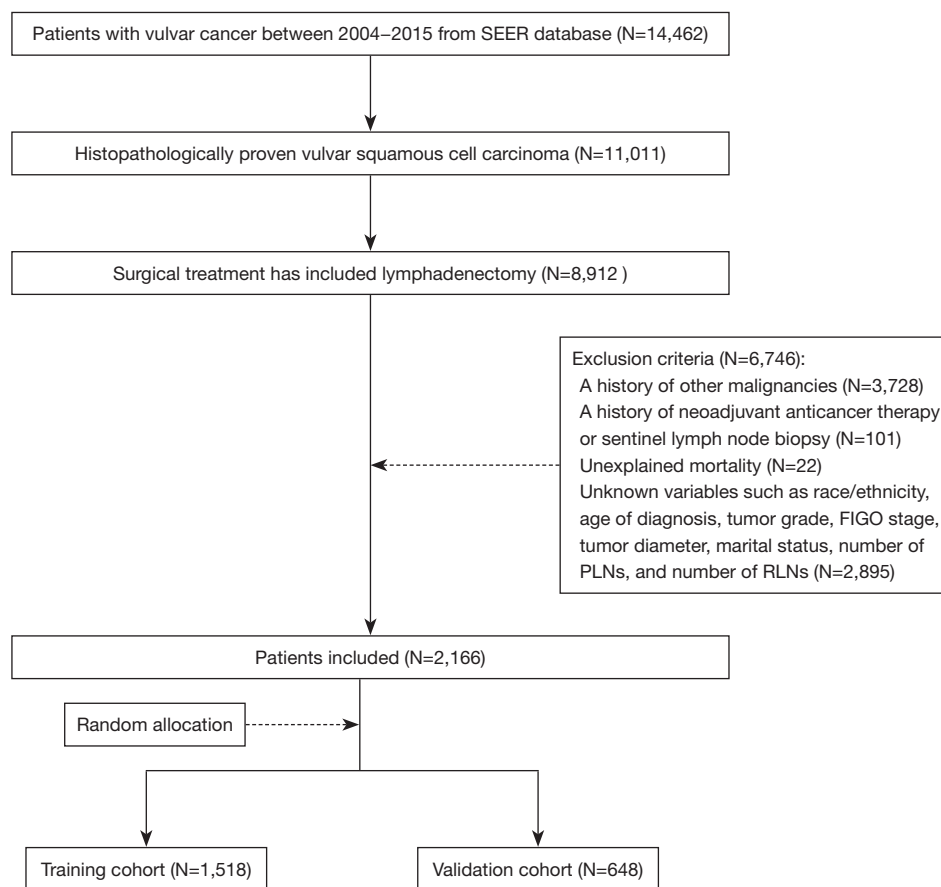
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┌─────────────────────────────────────────────────────────────┐
│ Patients with vulvar cancer between 2004–2015 from SEER      │
│ database (N=14,462)                                           │
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                              ▼
┌─────────────────────────────────────────────────────────────┐
│ Histopathologically proven vulvar squamous cell carcinoma    │
│ (N=11,011)                                                    │
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│ Surgical treatment has included lymphadenectomy (N=8,912 )   │
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                              │       ┌──────────────────────────────────────┐
                              │       │ Exclusion criteria (N=6,746):         │
                              │       │  A history of other malignancies      │
                              │       │  (N=3,728)                            │
                              │       │  A history of neoadjuvant anticancer  │
                              │       │  therapy or sentinel lymph node       │
                              │◄------│  biopsy (N=101)                       │
                              │       │  Unexplained mortality (N=22)         │
                              │       │  Unknown variables such as race/      │
                              │       │  ethnicity, age of diagnosis, tumor   │
                              │       │  grade, FIGO stage, tumor diameter,   │
                              │       │  marital status, number of PLNs, and  │
                              │       │  number of RLNs (N=2,895)             │
                              │       └──────────────────────────────────────┘
                              ▼
┌─────────────────────────────────────────────────────────────┐
│ Patients included (N=2,166)                                  │
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┌──────────────────┐          │
│ Random allocation │----------▶│
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                     ┌─────────┴──────────┐
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         ┌──────────────────────┐  ┌──────────────────────┐
         │ Training cohort       │  │ Validation cohort     │
         │ (N=1,518)             │  │ (N=648)               │
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Figure 1 Flow chart of patient selection. FIGO, International Federation of Gynecology and Obstetrics; LNR, lymph node ratio; PLNs, number of positive lymph nodes; RLNs, number of resected lymph nodes.

Prognostic variables

The following clinical variables were extracted: race/ethnicity (black, white, or others); age at diagnosis (<50, 50–64, or >64 years); tumor grade (I, well differentiated; II, moderately differentiated; or III, poorly differentiated/undifferentiated); tumor diameter (<4, or ≥4 cm); FIGO stage (I, II, III or IV); and marital status (single, married, divorced, widowed, or others). The number of PLNs was subdivided into four groups: zero, one, two, and three or more. The LNR was stratified into the following three risk groups, according to LNR as previously published in the report from Gynecologic Oncology Group (GOG) protocol #37 (24): 0.0, 0.0–0.2, and >0.2. The outcome of this study was OS; overall survival was defined as the interval from the surgical date to date of death from any cause or last follow-up.

Statistical analysis

Count and percentage were used to describe categorical measurements, whereas mean and range were used to present continuous measurements. The chi-square or Fisher's exact test was used to compare the categorical measurements, while t test or Mann-Whitney U test was used to compare continuous variables with an abnormal distribution. The Kaplan-Meier method was used to depict survival curves. Cox regression analysis was conducted for multivariate analyses. A nomogram was formulated with potential risk factors ($P<0.05$) based on results from the multivariate analysis. The concordance index (C-index), calibration curve, and decision curve analysis (DCA) were calculated to evaluate the predictive performance. DCA was performed to test the clinical usefulness of the model. The predictive performance was validated using an independent

internal cohort. Additionally, the predictive ability of the nomogram was compared with the FIGO staging system by calculating the C-index and constructing the DCA model. A larger C-index and wider range of threshold probability indicated a superior prognostic prediction. All statistical analyses and graph construction were performed using R (version 3.5.1; www.r-project.org). P value <0.05 was defined as statistically significant.

Results

Patient characteristics

Overall, 2,166 postoperative patients diagnosed with vulvar squamous cell carcinoma between 2004 and 2015 from the SEER database were included. The main clinical characteristics and baseline demographic of the study subjects are summarized in *Table 1*.

Independent Prognostic Factor for OS

Univariate and multivariate analyses were performed to identify factors that were significantly correlated with OS (*Table 2*). In the training cohort, race, age at diagnosis, marital status, tumor grade, FIGO stage, tumor diameter, and LNR were significantly associated with OS by Univariate analysis (P<0.05). Further multivariate analysis indicated that race, age at diagnosis, marital status, FIGO stage, tumor diameter, and LNR were independent risk factors for OS (P<0.05).

Survival analysis of Kaplan-Meier curves demonstrated a significant correlation between poorer OS and the group with an LNR greater than 0.2 compared to groups with lower LNR, in both the training and validation cohorts (*Figure 2*).

Construction and validation of the Prognostic Nomogram

Based on the multivariate analysis results, the prognostic nomogram was formulated to predict the 3- and 5-year OS in the training cohort (*Figure 3*). In the training cohort, a C-index of 0.772 (95% CI: 0.752–0.792) was observed for the nomogram. For the validation cohort, the C-index was 0.784 (95% CI: 0.75–0.813). Calibration plots for the OS nomogram validation indicated a high correlation between the predicted and observed probabilities of survival at 3- or 5-year post-surgery for both the training (*Figure 4A,B*) and validation cohorts (*Figure 4C,D*).

Comparison with the FIGO staging system

In the training cohort, the C-index of the nomogram cohort was 0.772 (95% CI: 0.752–0.792), statistically higher than that of the FIGO staging system (0.676, 95% CI: 0.654–0.698). The C-index of our model (0.784, 95% CI: 0.755–0.813) remained superior to that of the FIGO staging system (0.693, 95% CI: 0.660–0.726) in the validation cohort.

In DCA, our nomogram presented a greater net benefit as well as a wider field of threshold probability compared to the FIGO staging system, both in the training cohort (*Figure 5A,B*) and the validation cohort (*Figure 5C,D*), indicating that our model has superior predictive ability in predicting OS at 3- or 5-year. A higher threshold probability results in a more robust estimation of decision results. The results indicated that our formulated nomogram is a better predictive method for survival of patients with squamous cell vulvar cancer.

Conclusions

The FIGO score staging system is commonly used for vulvar cancer. However, controversies remain regarding the FIGO system, as a large number of additional risk factors have proven to be prognostic parameters for vulvar cancer patients. Consequently, the FIGO staging system appears to have lost its effectiveness in evaluating the prognosis of vulvar cancer. Moreover, the FIGO staging system was not specifically developed for postoperative prognostic prediction in squamous cell vulvar cancer patients, the most common type of vulvar cancer; thus, the predictive prognostic accuracy for these patients who then undergo surgery may be affected.

A nomogram is a quantitative hierarchical prediction model that has shown robust ability in survival prediction in many carcinomas (25,26). Therefore, as the predominant treatment of vulvar carcinoma, specifically squamous cell carcinoma, is surgery, we constructed a prognostic nomogram for postoperative vulvar squamous cell cancer patients.

In this study, we assessed 2,166 patients with postoperative vulvar squamous cell cancer. In the univariate and multivariate analyses, LNR was considered as an independent predictive factor for prognosis, as was race, age at diagnosis, marital status, FIGO staging system, and tumor diameter. Finally, a nomogram based on these factors was formulated. The nomogram had advantages in survival prediction, and the

Table 1 Demographic and clinicopathologic characteristics of patients with squamous cell carcinoma of vulva diagnosed between 2004 and 2015 from SEER database

Variables	All (N=2,166)		Training cohort (N=1,518)		Validation cohort (N=648)	
	N	%	N	%	N	%
Age of diagnosis (year)						
<50	385	17.77	271	17.85	114	17.59
50–64	660	30.47	476	31.36	184	28.40
>64	1121	51.75	771	50.79	350	54.01
Race						
Black	162	7.48	114	7.51	48	7.41
White	1930	89.10	1359	89.53	571	88.12
Others	74	3.42	45	2.96	29	4.48
Marital status						
Single	404	18.65	278	18.31	126	19.44
Married	938	43.31	663	43.68	275	42.44
Divorced	268	12.37	189	12.45	79	12.19
Widowed	523	24.15	367	24.18	156	24.07
Others	33	1.52	21	1.38	12	1.85
Tumor grade						
I	547	25.29	391	25.81	156	24.07
II	1169	54.05	822	54.26	347	53.55
III	447	20.67	302	19.93	145	22.38
Tumor diameter (cm)						
<4	1482	68.42	1045	68.84	437	67.44
≥4	684	31.58	473	31.16	211	32.56
FIGO stage						
I	1085	50.09	780	51.38	305	47.07
II	310	14.31	228	15.02	82	12.65
III	729	33.66	489	32.21	240	37.04
IV	42	1.94	21	1.38	21	3.24
LNR						
0	1404	63.64	1015	65.15	389	60.03
0–0.2	405	18.36	277	17.78	128	19.75
>0.2	397	18.00	266	17.07	131	20.22
PLN						
Mean (range)	0.87	0–40	0.77	0–40	1.1	0–23
RLNs						
Mean (range)	10.20	1–66	10.22	1–66	10.14	1–43

FIGO, International Federation of Gynecology and Obstetrics; LNR, lymph node ratio; PLNs, number of positive lymph nodes; RLNs, number of resected lymph nodes.

Table 2 Univariate and multivariate analyses of prognostic factors associated with overall survival of patients with squamous cell carcinoma of vulva in the training cohort

Variables	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Age of diagnosis (year)				
<50	1		1	
50–64	1.627 (1.126–2.350)	0.010*	1.516 (1.043–2.204)	0.029*
>64	6.168 (4.459–8.532)	<0.001***	5.349 (3.807–7.516)	<0.001***
Race				
Black	1		1	
White	2.019 (1.362–2.992)	<0.001***	1.259 (0.841–1.883)	0.049*
Others	2.255 (1.269–4.009)	0.006**	1.010 (0.558–1.827)	0.975
Marital status				
Single	1		1	
Married	1.207 (0.932–1.564)	0.155	1.006 (0.772–1.309)	0.967
Divorced	1.201 (0.858–1.681)	0.285	1.097 (0.782–1.538)	0.593
Widowed	2.867 (2.214–3.712)	<0.001***	1.350 (1.028–1.774)	0.031*
Others	0.808 (0.327–1.995)	0.643	0.832 (0.296–2.335)	0.727
Tumor grade				
I	1		1	
II	1.374 (1.116–1.691)	0.003**	1.104 (0.891–1.367)	0.368
III	1.804 (1.419–2.293)	<0.001***	1.195 (0.929–1.538)	0.165
Tumor diameter (cm)				
<4	1		1	
≥4	1.871 (1.588–2.204)	<0.001***	1.432 (1.209–1.696)	<0.001***
FIGO stage				
I	1		1	
II	1.313 (1.018–1.694)	0.036*	1.255 (0.970–1.623)	0.083
III	3.341 (2.793–3.996)	<0.001***	1.193 (0.343–4.154)	0.782
IV	7.331 (4.405–12.202)	<0.001***	2.692 (0.847–8.558)	0.043*
LNR				
0	1		1	
0–0.2	2.338 (1.918–2.851)	<0.001***	1.917 (0.553–6.651)	0.305
>0.2	4.896 (4.019–5.964)	<0.001***	3.953 (1.156–13.514)	0.028*

*, P<0.05; **, P<0.01; ***, P<0.001. FIGO, International Federation of Gynecology and Obstetrics; LNR, lymph node ratio.
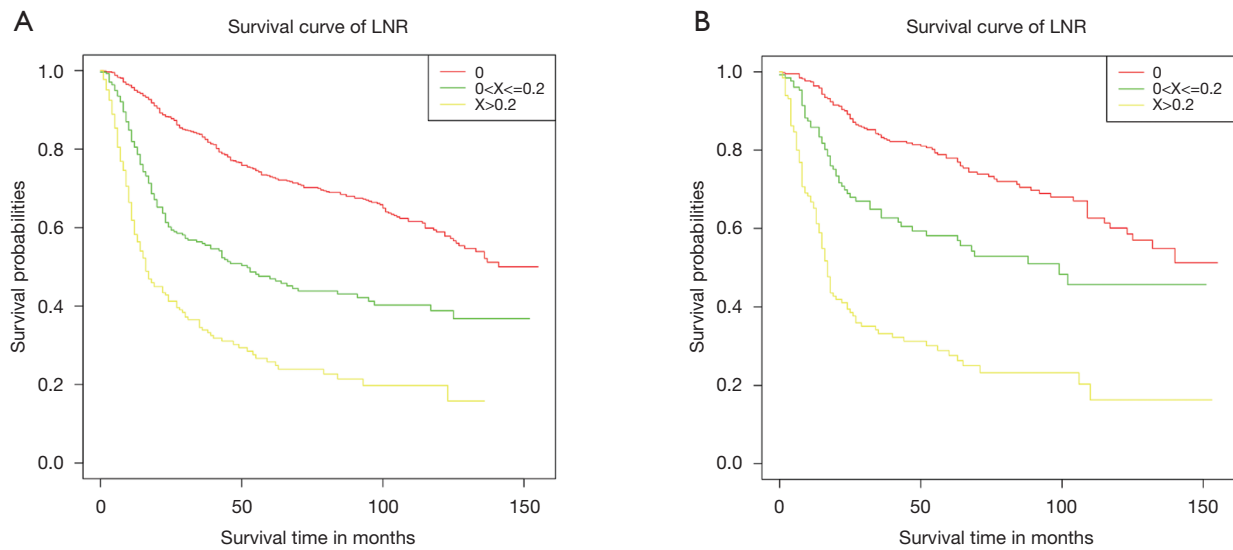
Figure 2 Kaplan-Meier survival curves for patients with vulvar squamous cell carcinoma in the training cohort (A) and validation cohort (B) according to LNR. LNR, lymph node ratio.
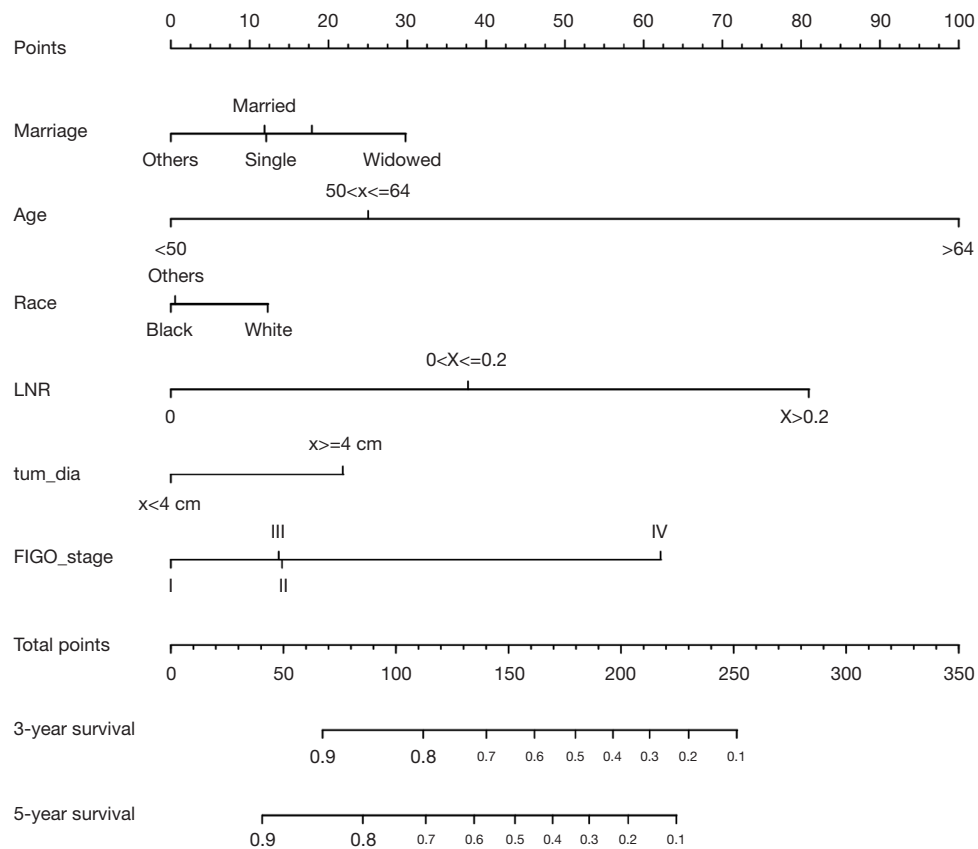

Figure 3 Overall survival-predicting nomogram for postoperative vulvar squamous cell carcinoma. LNR, lymph node ratio; tum_dia, tumor diameter; FIGO, International Federation of Gynecology and Obstetrics.
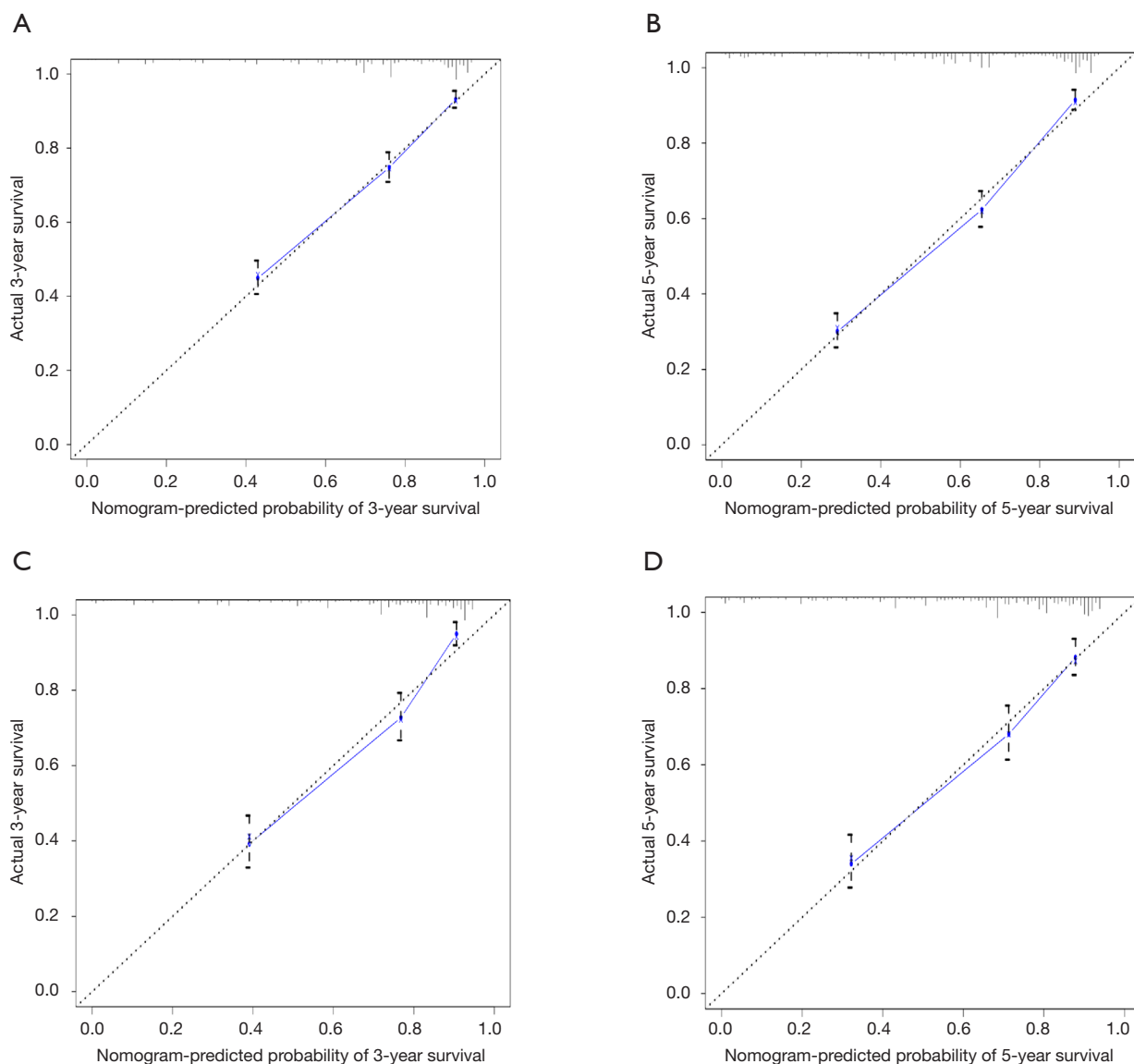
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Figure 4 The calibration curve of the nomogram for predicting overall survival at 3- (A) and 5-year (B) in the training cohort, and at 3- (C) and 5-year (D) in the validation cohort. The nomogram-predicted probability of overall survival is plotted on the x-axis and the actual probability is on the y-axis.

C-index (0.772 and 0.784 for the training and validation cohorts, respectively), and the calibration curve, and DCA supported its predictive performance. Compared with the FIGO staging system, the nomogram demonstrated advanced efficiency for prognostic prediction.

In contrast to the FIGO staging system, tumor diameter and lymph node status remained in this model, and race, age at diagnosis, and marital status were further included in our formulated nomogram. Lymph node status is perceived

to be one of the most significant factors for predicting OS and progression-free survival (PFS) in vulvar cancer patients (3,27). However, the lymph node status of the FIGO staging system failed to adequately reflect the extent of disease, due to the influence of surgical operation, and the number of examined PLNs remained defective as a crucial predictive factor. Kunos *et al.* (24) first described LNR for prognostic assessment in patients with vulvar cancer. Patients with an LNR value >0.2 had an increased likelihood of contralateral
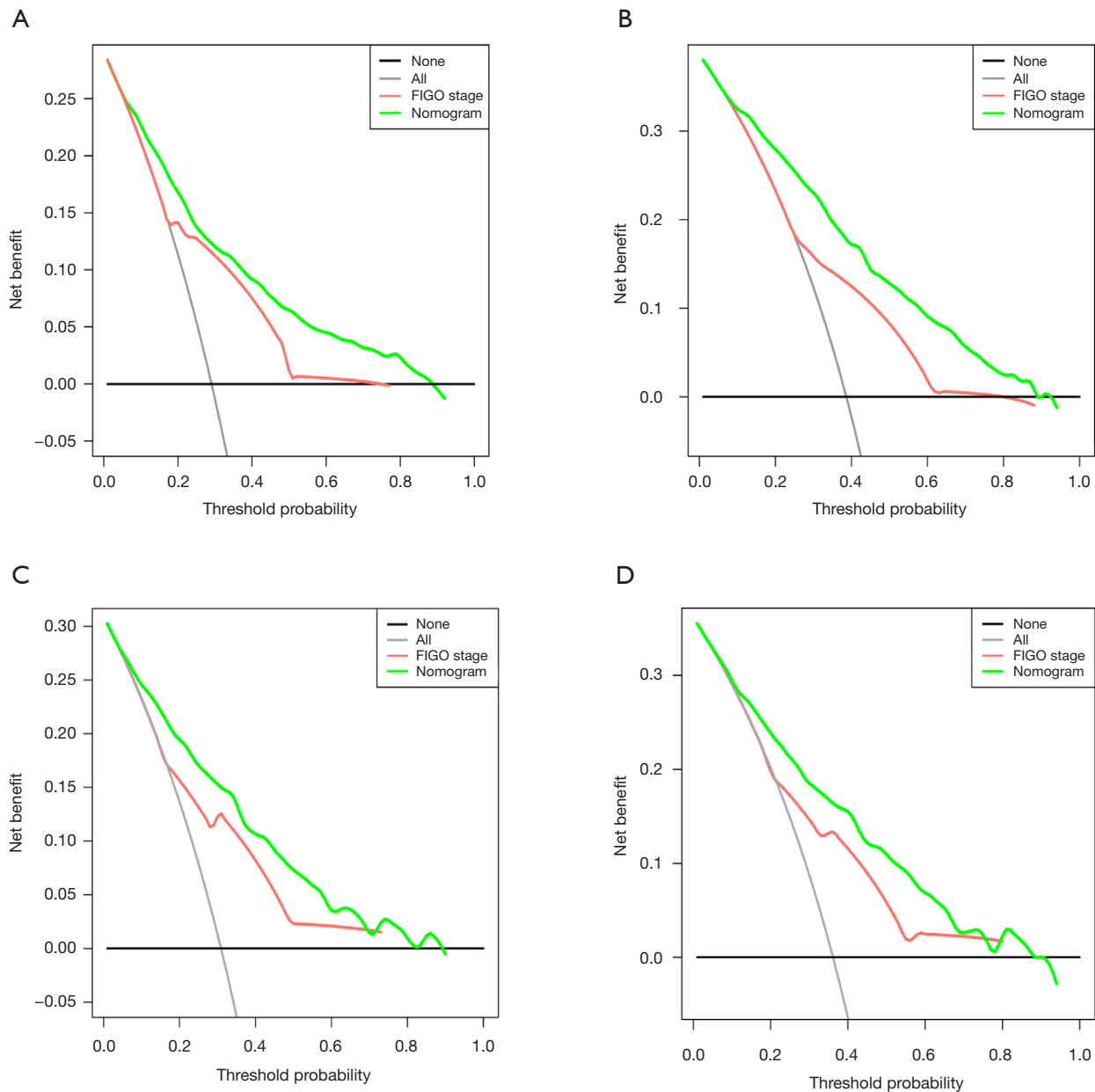
Figure 5 Decision curve analysis for postoperative vulvar squamous cell carcinoma using nomogram and FIGO staging system in terms of the 3- (A) and 5-year (B) overall survival in the training cohort, and the 3- (C) and 5-year (D) overall survival in the validation cohort. The x-axis represents the threshold probability. The y-axis measures the net benefit. The threshold probability is where the expected benefit of treatment balances the expected benefit of avoiding treatment. The nomograms resulted in a superior net benefit to the FIGO staging system, with a wide range of threshold probabilities. FIGO, International Federation of Gynecology and Obstetrics.

PLNs, recurrence, and cancer-specific death compared with patients with an LNR value ≤0.2. The prognostic significance of LNR was confirmed through a study of 1,047 patients who underwent surgery, including inguinal lymph node resection for vulvar squamous cell cancer, from a multicenter retrospective trial (the AGO CaRE-1 trial) (16). Our results suggest that a high LNR was relevant to poor OS, and agreed with the AGO CaRE-1 trial results.

From a clinical point of view, these findings are persuasive, as LNR reflects not only the nodal disease burden, but also the quality and extent of lymphadenectomy.

In addition, previous studies demonstrated that age is a vital prognostic factor (28). Our multivariate analyses revealed that older age was an independent risk parameter, indicating that senior patients had poorer overall survival. This study also revealed that widowed patients had poorer outcomes than non-widowed patients, which concurs with a study showing an increased risk of cancer mortality in widows with vulvar cancer (19). Widowed cancer patients may suffer greater depression, anxiety, and distress than their non-widowed counterparts, and are less likely to receive surgical treatment and chemotherapy, potentially contributing to poorer cancer control. These findings indicate a need for social support and personalized care among widowed patients. Additionally, the important role of race in relation to survival was emphasized in previous analyses. Rauh-Hain *et al.* (18) reported that African-American patients had improved survival compared to white patients, consistent with our results.

The most common staging system for vulvar carcinoma is the FIGO staging system; thus, we compared the prognostic nomogram and the FIGO staging system via the C-index and DCA. We discovered that the C-index of our nomogram for predicting OS in the training cohort was 0.772 (95% CI: 0.752–0.792), which was statistically superior to that of the FIGO staging system (0.676, 95% CI: 0.654–0.698), as was the result in the validation cohort. However, high prediction accuracy does not guarantee preferable clinical application (29). Therefore, in the present study, we used DCA to demonstrate that the nomogram obtained wider ranges of DCA and yielded better clinical validity and applicability.

In this study, the nomogram, consisting of six easily accessible variables, could conveniently provide a precise estimation of the individual survival rates to healthcare providers and patients. Additionally, it could facilitate the choice of postoperative treatment decision-making, such as adjuvant radiation, chemotherapy, or target-directed therapy. Moreover, this nomogram could assist in the formulation and adjustments of follow-up intervals for the purpose of achieving individualized disease monitoring. Another potential use of the nomogram could be to identify patients at high risk of death, allowing them to participate in clinical trials evaluating novel treatments for patients with an extremely poor prognosis.

While the current study makes sense in clinical practice, there are limitations that should be acknowledged. First, there is an inevitable selection bias due to using retrospective data from the SEER database, where the ethnic homogeneity of the patient population was a methodological limitation of our study. In addition, some prognostic factors, such as surgical tumor-free margin, serum tumor markers, and vascular infiltration, which may influence prognosis of postoperative vulvar cancer patients, are not available in the SEER database. Finally, although the prognostic nomogram model performed well in the current study, further validation is required in additional cohorts to enhance reliability. However, conducting a multicenter, large-scale prospective clinical trial of this rare disease remains a major challenge.

The formulated prognostic nomogram accurately and objectively predicted OS of vulvar squamous cell carcinoma. This may have a superior prognostic capability for patients with postoperative vulvar squamous cell carcinoma compared to the currently utilized FIGO staging system. Further studies to validate and improve this model are warranted.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the STROBE guideline checklist. Available at http://dx.doi.org/10.21037/atm-20-3240

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-3240). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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