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Establishment and validation of a nomogram for predicting overall survival in patients with vulvar carcinoma based on the SEER database

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Abstract: ***Background:*** *Vulvar carcinoma (VC) is a rare female gynecological malignancy, and optimizing prognostic factors for VC requires large-scale research containing various clinical indicators of patients. Our study attempted to develop and validate a detailed survival nomogram for predicting the overall survival (OS) probability in patients diagnosed with VC.* ***Methods:*** *Patients diagnosed with VC between 2004 and 2015 were extracted from the Surveillance, Epidemiology, and End Results (SEER) database. Univariate and multivariate Cox regression analyses were performed followed by the construction of the nomogram for OS. The performance of this model was evaluated using the concordance index (C-index), area under the time-dependent receiver operating characteristics curve (AUC), net reclassification improvement (NRI), integrated discrimination improvement (IDI), calibration plots and decision curve analysis (DCA). In addition, the C-index, AUC and DCA of the model and the 2009 International Federation of Gynecology and Obstetrics (FIGO) staging system were compared.* ***Results:*** *A total of 6275 patients were randomly assigned to the training cohort (n=4392) and the validation cohort (n=1883). Multivariate analysis identified independent prognostic factors ($p<0.05$) for OS, including histological type, age, surgery, T stage, N stage, M stage, grade, summary stage, chemotherapy, race, marital status and size. Finally, a nomogram was constructed to predict the 3-, 5-, and 8-year OS probabilities for patients with VC, and the C-index, NRI, IDI and calibration plotting all showed that the model has good discrimination. Additionally, the nomogram also showed better clinical validity of the DCA and AUC compared to that of the FIGO system.* ***Conclusions:*** *We developed and validated a nomogram for individual OS prediction in patients with VC. While further validation is required, this nomogram may be a useful comprehensive prognostic tool to give patients a better idea of prognosis during counseling.*

Keywords: *Vulvar carcinoma, Nomogram, FIGO, Overall survival, SEER, Prognostic*

1. Introduction

Vulvar carcinoma (VC) is a rare malignant tumor representing 3–5% of all gynecological cancers. The incidence rate of in situ and invasive VC has increased significantly in the United States in recent decades [1], and there were 45,420 new cases and 17,427 deaths from VC, accounting for 0.2% of all cancers worldwide from the latest data of the International Agency for Research on Cancer in 2020 [2]. It is distributed in the skin, mucous membranes and accessory tissues of the vulva, and the main pathological types are squamous cell carcinoma (SCC), adenocarcinoma, basal cell carcinoma, malignant melanoma, sarcoma, and metastatic carcinoma, accounting for 0.3% of all new cancers in the United States in 2019 [3]. In high-income countries, human papillomavirus (HPV) infection related to VC can increase the burden of this disease [4]. Vulvar intraepithelial neoplasia is its precancerous lesion, and 80%

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of cases of untreated high-grade intraepithelial neoplasia of the vulva can progress to external negative invasive carcinoma. For patients with early-stage VC, the current standard treatment is inguinofemoral lymph node dissection in the groin or radical excision of the tumor with a sentinel node procedure according to depth of invasion and tumor size [5]. References to the staging of VC include the 2009 Federation of International Gynecologic Oncology (FIGO) and tumor-node-metastasis (TNM) staging of the Union for International Cancer Control (UICC). At present, FIGO staging is mostly used to evaluate the prognosis of patients with VC [6]. However, fewer large-scale patient reports limit the data regarding the efficacy of guideline-based strategies. Meanwhile, more researchers are realizing that the limitations of the FIGO system should not be ignored, and several individual factors, such as patient characteristics, lymph node ratio, tumor size, and surgery, can also affect the prognosis of patients with VC [7,8,9].

A nomogram is a useful comprehensive prognostic tool to provide tailored individual prognostic information by incorporating significant demographic characteristics and clinical treatment features and presenting simple visualized results of statistical analysis [10]. Due to developments in research and oncology practice, approaches to cancer control include monitoring cancer occurrence by histopathologic and molecular subtypes. The Surveillance, Epidemiology, and End Results (SEER) database provides histopathologic cancer subtypes and shows an advantage in cancer research [11]. A recent study reported prognostic nomograms for patients with primary vulvar melanoma and SCC that could potentially guide the oncological prognosis of patients with VC based on the SEER database [9,12], which provides helpful estimation of the individual survival rate for patients with VC. Herein, we collected the baseline characteristics, different types of histopathology, detailed TNM staging information, clinical information, and follow-up data of patients with VC registered between 2004 and 2015 based on the SEER database, focusing on various histopathologic types (as well as the TNM stage of VC) and analyzing the underlying risk factors for prognosis. Finally, we demonstrated the discriminative ability and clinical practicality of the nomogram by comparing it with the FIGO staging system to identify whether it is better for predicting patient prognosis.

2. Methods

2.1. Patient selection

In this retrospective study, data sources for patients diagnosed with VC between 2004 and 2015 were included from the SEER database. The SEER database is a large population-based cancer outcome database that includes 21 cancer registries, representing approximately 30% of the US population [10], which does not include personally identifiable information, so it was not necessary to obtain informed patient consent. We used the name "12333-Nov2019" to assess demographic characteristics, tumor pathological information, treatment information and follow-up survival outcomes. The inclusion criteria were as follows: (1) diagnosis of VC (the site record ICD-O-3 [third revision of the International Classification of Diseases for Oncology/WHO 2008 of "Vulva"] and the ICD-O-3 histology/behavior codes of "8070/3, 8090/3, 8091/3, 8092/3, 8093/3, 8094/3, 8140/3, and 8720/3") and (2) defining cause of death and survival time after diagnosis. The exclusion criteria were as follows: (1) patients with no prognostic data; (2) patients with unknown race, summary stage, or surgery data; or (3) patients without Tx, Nx, or Mx data. Overall survival (OS) was the primary outcome of this study, and OS was defined as the interval from randomization to death due to any cause.

2.2. Variable classification

Clinical variables were extracted, including age at diagnosis, race, marital status, primary site, summary stage, histology, grade, size, Federation of International Gynecologic Oncology (FIGO) stage, T stage, N stage, M stage, surgery, chemotherapy, radiation, survival time and survival status. The primary site was classified as the labium, clitoris and vulva (including codes C51.0 Labium majus, C51.1 Labium minus, C51.2 Clitoris, C51.8 Overlapping lesion of vulva and C51.9 Vulva). Histology type was classified as SCC, basal cell carcinoma, adenocarcinoma and malignant melanoma (including ICD-0-3 codes 8070/3, 8090/3, 8091/3, 8092/3, 8093/3, 8094/3, 8140/3 and 8720/3). Grade was classified as I/II (I was defined as a well-differentiated tumor and II was defined as a moderately differentiated tumor), III/IV (III was defined as a poorly differentiated tumor and IV was defined as an undifferentiated tumor), and unknown. Tumor size was classified as <4 cm, ≥4 cm and unknown. To reduce censored data, we included unknown grade and size data. Surgery was classified as with surgery and without surgery. Chemotherapy was classified as chemotherapy and no/unknown chemotherapy, which were delimited from the SEER database. Radiation was classified as with radiation and without radiation. Surgery,

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chemotherapy and radiation were regarded as single variables termed treatment. The tumor staging referred to in this study was based on the AJCC (6th edition), which is applicable to the SEER database for patients diagnosed with VC in 2004–2015.

2.3. Statistical analysis

R software (version 3.6.3, http://www.r-project.org) was used to randomly divide these patients into a training cohort and validation cohort. A log-rank test was used to demonstrate whether there were statistically significant inter-group differences. SPSS statistics software (version 25.0, IBM SPSS, Chicago, IL, USA) was used to describe the baseline characteristics of the patients in both cohorts. Categorical variables are summarized as frequencies and percentages. Cox regression was used to identify factors associated with OS from VC, and these factors were used to establish a nomogram for predicting the 3-, 5-, and 8-year OS probabilities for VC. The Kaplan-Meier method was used to depict survival curves. The ROC and C-index are widely used to evaluate the discrimination ability of the nomogram, but their increment is not obvious when comparing two present models [13]. The NRI is mainly used to compare the predictive powers of new and old models at a set tangent level, while the IDI considers different tangent lines, which can be used to assess the overall improvement of the model [14,15]. Therefore, the NRI and IDI were applied, and the Z test was used to assess the differences. Calibration plots were employed to visually reflect the difference between the two models, and the DCA curve was used to evaluate the clinical validity of the model. The R packages we used were as follows: survival, rms, foreign, survival ROC, nricens, and DCA packages. A p-value < 0.05 was considered to be significant.

3. Result

3.1. Patient characteristics

As shown in the flowchart (Fig. 1), 6275 patients with VC were included; the median follow-up time was 41 months (IQR=18-80 months), the median age at diagnosis was 67 years (range: 19–85+ years) and the 3-, 5-, and 8-year OS rates were 53.75%, 35.79%, and 17.61%, respectively. After randomly dividing these patients into 2 cohorts, we applied the log-rank test, which showed that there was no significant difference between these 2 cohorts (p=0.9). The demographic and clinical characteristics of these 2 cohorts of patients are summarized in Table 1.

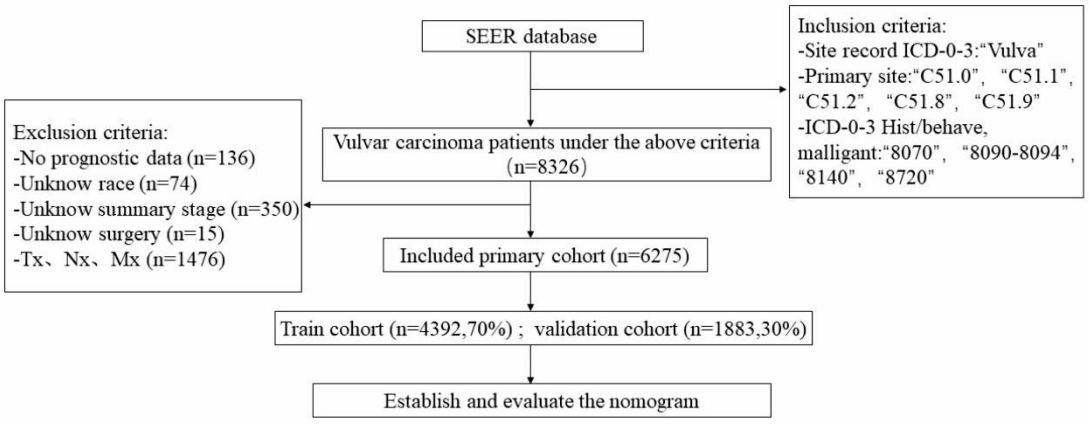

Fig. 1 Flowchart of sample selection.

Table 1 Demographic and Clinical Characteristics of the 2 Cohorts of patients.

Variable		Training Cohort	Validation Cohort	χ^2	*P*
Number of Patients n (%)		4392(70)	1883(30)		
Age n(%)	<50 years	682(15.53)	303(16.09)	0.316	0.854
	[50,65) years	1303(29.76)	555(29.47)		
	≥65 years	2407(54.81)	1025(54.43)		
Race n(%)	White	3856(87.80)	1655(87.89)	1.792	0.408

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	Black	390(8.88)	155(8.23)		
	Other	146(3.32)	73(3.88)		
Marital status n(%)	Married	3401(77.44)	1465(77.80)	0.355	0.837
	Unmarried	722(16.44)	310(16.46)		
	Unknown	269(6.12)	108(5.74)		
Primary site n(%)	Labium	625(14.23)	241(12.80)	2.292	0.318
	Clitoris	71(1.62)	30(1.59)		
	Vulva	3696(84.15)	1612(85.61)		
Histology style n(%)	Squamous cell carcinoma	3858(87.84)	1611(85.56)	6.823	0.078
	Malignant melanoma	200(4.55)	96(5.10)		
	Adenocarcinoma	69(1.57)	33(1.75)		
	Basal cell carcinoma	265(6.03)	143(7.59)		
Grade	I/II	2524(57.47)	1065(56.56)	1.753	0.416
	III/IV	659(15.00)	270(14.34)		
	Unknown	1209(27.53)	548(29.10)		
FIGO	I	1887(42.96)	823(43.71)	0.652	0.885
	II	1449(32.99)	618(32.82)		
	III	753(17.14)	309(16.41)		
	IV	303(6.90)	133(7.06)		
Summary stage	Localized	2655(60.45)	1158(61.50)	0.825	0.662
	Regional	1505(34.27)	623(33.09)		
	Distant	232(5.28)	102(5.42)		
Surgery	Yes	3738(85.11)	1605(85.24)	0.017	0.897
	No	654(14.89)	278(14.76)		
Radiation	Yes	1238(28.19)	508(26.98)	0.960	0.327
	No	3154(71.81)	1375(73.02)		
Chemotherapy	Yes	717(16.33)	297(15.77)	0.297	0.586
	No/unknown	3675(83.67)	1586(84.23)		
Size	<4cm	2855(65.00)	1204(63.94)	1.910	0.385
	≥4cm	1071(24.39)	457(24.27)		
	Unknown	466(10.61)	222(11.79)		
T	T1	2023(46.06)	883(46.89)	0.987	0.804
	T2	1518(34.56)	637(33.83)		
	T3	664(15.12)	276(14.66)		
	T4	187(4.26)	87(4.62)		
N	N0	3442(78.37)	1482(78.70)	0.423	0.935
	N1	662(15.07)	285(15.14)		
	N2	275(6.26)	110(5.84)		
	N3	13(0.30)	6(0.32)		
M	M0	4247(96.70)	1821(99.35)	0.000	0.986
	M1	145(3.30)	62(0.65)		

3.2. Prognostic factors of VC

As shown in Table 2, univariate and multivariate Cox regression analyses were used to identify prognostic factors for OS in the training cohort. Interestingly, age at diagnosis, race, marital status, histological type, tumor grade, tumor size, summary stage, surgery status, chemotherapy status, T stage, N stage and M stage were all identified as related to OS (p<0.05) in the multivariate Cox regression analysis. Survival analysis of Kaplan-Meier curves demonstrated that the histological type of malignant melanoma, grade III/ IV and higher FIGO, T, N, M stage were prognostic factors for poorer OS in patients

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with VC in the training cohort (p<0.001).

Table 2 Univariate and multivariate analysis of prognostic factors for overall survival in the training cohort.

		Univariate analysis	Multivariable analysis	
Variable		*P* value	HR(95%CL)	*P* value
Age	<50		Reference	
	[50,65)	0.001	1.6558(1.2335-2.2226)	< 0.001
	≥65	< 0.001	3.3154(2.5196-4.3626)	< 0.001
Race	White		Reference	
	Black	0.030	1.3337(1.0351-1.7187)	0.025
	Other		1.0701(0.7294-1.5699)	
Marital	Married		Reference	
	Unmarried	0.017	0.7589(0.6065-0.9496)	0.016
	Unknown		0.7910(0.5520-1.1334)	
Histological type	Squamous cell carcinoma		Reference	
	Malignant melanoma	< 0.001	2.0630(1.4016-3.0365)	< 0.001
	Adenocarcinoma		0.8640(0.5284-1.4128)	
	Basal cell carcinoma	< 0.001	0.1287(0.0408-0.4060)	< 0.001
Grade	I/ II		Reference	
	III/ IV	< 0.001	1.3614(1.1391-1.6272)	< 0.001
	Unknown	< 0.001	0.6479(0.5157-0.8142)	< 0.001
Summary stage	Localized		Reference	
	Regional	< 0.001	1.6711(1.3236-2.1099)	< 0.001
	Distant		1.4450(0.8512-2.4531)	
Surgery	Yes		Reference	
	No	< 0.001	3.0194(2.4484-3.7236)	< 0.001
Chemotherapy	Yes		Reference	
	No/unknown	< 0.001	1.5896(1.3017-1.9412)	< 0.001
Size	<4cm		Reference	
	≥4cm	0.018	1.2481(1.0402-1.4975)	0.017
	Unknown		1.2297(0.9551-1.5832)	
T stage	T1		Reference	
	T2	< 0.001	2.3922(1.9067-3.0030)	< 0.001
	T3	< 0.001	2.1381(1.5934-2.8692)	< 0.001
	T4	< 0.001	3.0384(2.0252-4.5584)	< 0.001
N stage	N0		Reference	
	N1	< 0.001	1.8383(1.4889-2.2698)	< 0.001
	N2	< 0.001	2.9008(2.2650-3.7152)	< 0.001
	N3		2.1958(0.9641-5.0009)	
M stage	M0		Reference	
	M1	< 0.001	2.2582(1.3938-3.6589)	< 0.001

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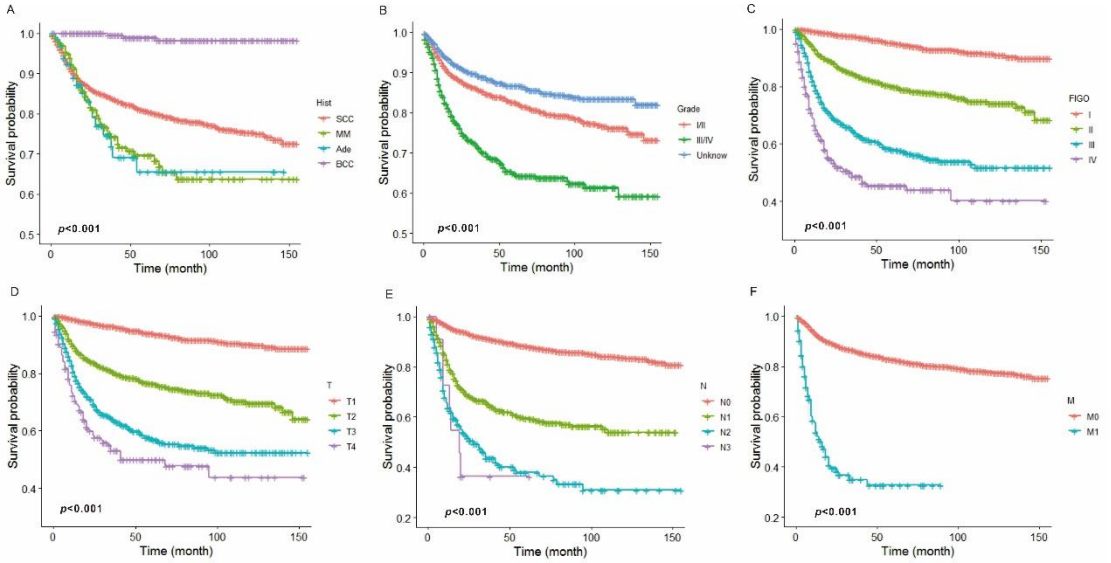

Fig. 2 Kaplan-Meier survival curves for patients with vulvar carcinoma in the training cohort according to Hist(a), Grade(b), FIGO(c), T(d), N(e), M(f). Hist, histological type; SCC, Squamous cell carcinoma; MM, Squamous cell carcinoma; Ade, Adenocarcinoma; BCC, Basal cell carcinoma; T, T stage; N, N stage; M, M stage.

3.3. Nomogram construction

Fig. 3 shows the nomogram we finally established using the training cohort, which is a graph that can be used to comprehensively predict the 3-, 5-, and 8-year OS probabilities for patients with VC based on the related factors. Histological type played the most important role in OS, followed by age at diagnosis, surgery status, T stage, N stage, M stage, tumor grade, summary stage, chemotherapy status, race, marital status and tumor size. Adding the scores of these twelve factors for an individual patient with VC yields the total scores predicting their 3-, 5-, and 8-year OS probabilities.

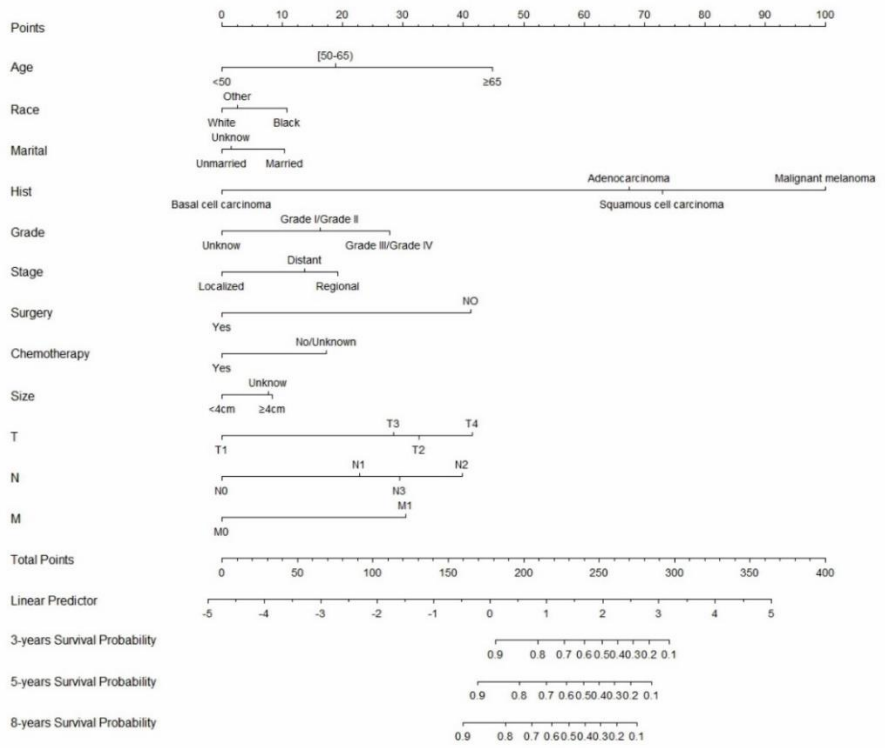

Fig. 3 Nomogram predicting 3-, 5-, and 8-years OS probability. Hist-Histological type; Hist, histological type; T, T stage; N, N stage; M, M stage.

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3.4. Evaluating the nomogram

The C-index of the nomogram model was 0.841 in the training cohort and 0.843 in the validation cohort, which was higher than that of the FIGO model (0.771 in the training cohort and 0.797 in the validation cohort). We plotted the 3-, 5-, and 8-year ROC curves, and the 3-, 5-, and 8-year AUCs of the nomogram model were 0.871, 0.862, and 0.852 (in the training cohort), respectively, and 0.876, 0.855, and 0.833 (in the validation cohort), respectively, which were higher than those of the FIGO model (0.813, 0.791, and 0.755 in the training cohort, respectively, and 0.775, 0.813, and 0.791 in the validation cohort, respectively) (Fig. 4). The NRI values for the 3-, 5-, and 8-year OS probabilities were 0.497 (95% CL = 0.439-0.602), 0.481 (95% CL = 0.433-0.619) and 0.523 (95% CL= 0.435-0.634) in the training cohort, respectively ($p < 0.001$), and 0.305 (95% CL = 0.140-0.484), 0.296 (95% CL = 0.124-0.446) and 0.265 (95% CL = 0.120-0.471) in the validation cohort, respectively ($p < 0.001$). The IDI values for 3-, 5-, and 8-year OS probabilities were 0.098, 0.109 and 0.115 in the training cohort, respectively ($p < 0.001$), and 0.061, 0.081 and 0.082 in the validation cohort, respectively ($p < 0.001$). Fig. 5 shows that the calibration plots for the 3-, 5-, and 8-year OS probabilities for the model are very close to the standard lines, indicating that the model has a good degree of calibration. Fig. 6 shows that the survival probability curves of the new model are all higher than those of the FIGO model, indicating that the net benefits of using the nomogram we established to predict the 3-, 5-, and 8-year OS probabilities of VC are significantly higher than those of the FIGO model.

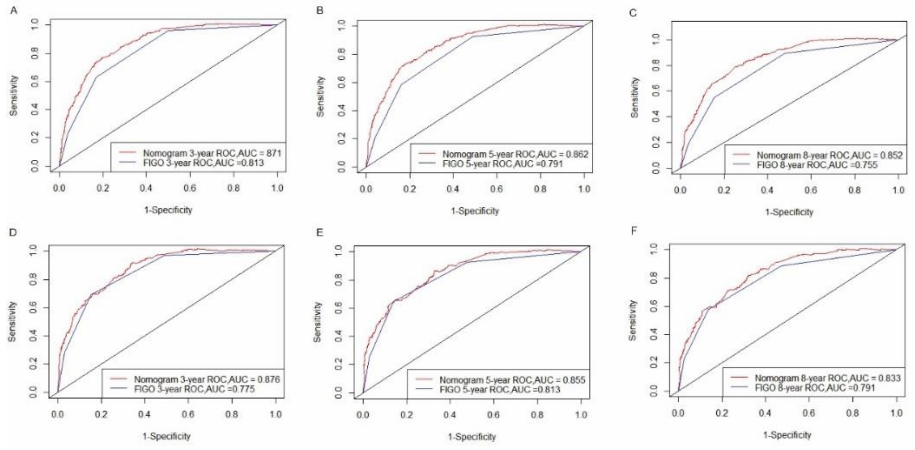

Fig. 4 The area under the ROC curve (AUC) for 3-, 5-, and 8-years OS probability of the training cohort (A), (B), (C) and validation cohort (D), (E), (F).

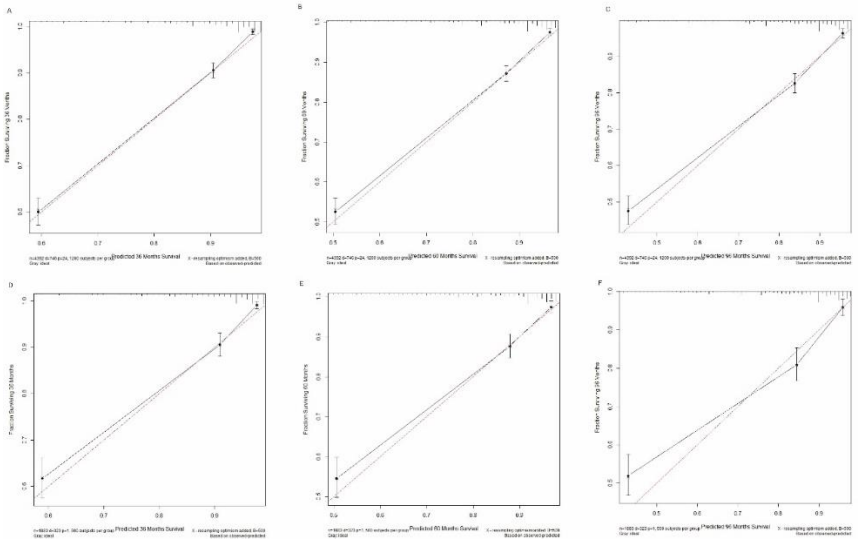

Fig. 5 Calibration curves for 3-, 5-, and 8-years OS probability depict the calibration of each model in terms of the agreement between the predicted probabilities and observed outcomes of the training cohort (A,B,C) and validation cohort (D, E, F).

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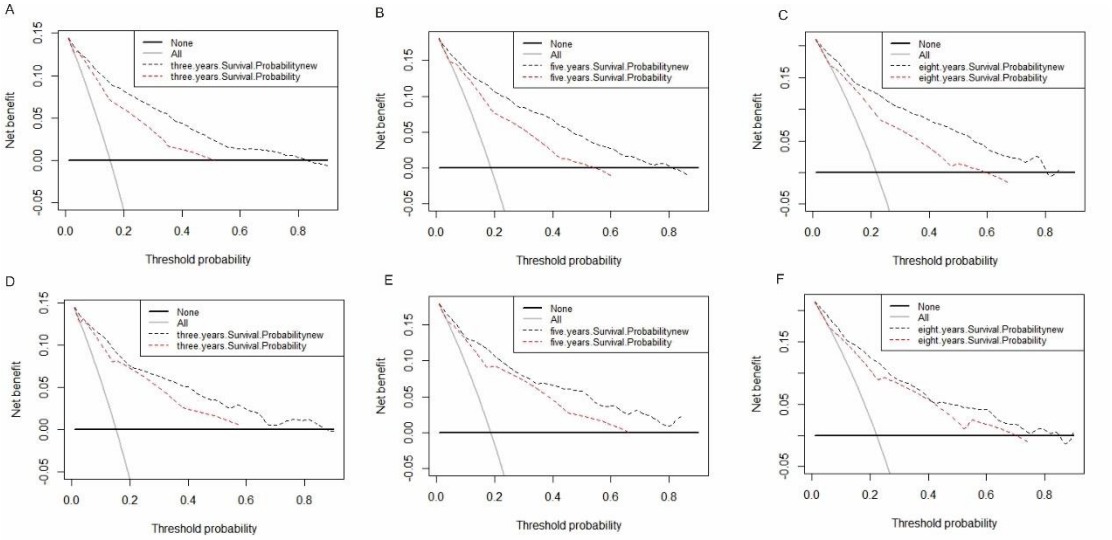

Fig. 6 Decision curve analysis of the training cohort (a, b, c) and validation cohort (d, e, f) for 3-, 5-, and 8-years OS probability.

4. Discussion

The FIGO scoring system established the surgical pathological staging of VC in 1998 and revised it in 1994 and 2009. In this staging, stage 0 was cancelled, and according to the depth of tumor invasion, the size, number and shape of inguinal lymph node metastases and VC were further divided into stages I-IV. However, it cannot be ignored that large numbers of additional risk factors are also prognostic parameters, the predictive prognostic accuracy for these patients who accept surgery may be affected, and the FIGO staging system was not specifically established for predicting the OS of patients with VC [9]. Moreover, the pathological type of tumor is closely related to prognosis and survival, and there is no comprehensive prognostic nomogram for VC based on different pathologies. Therefore, it is necessary to develop a specific clinical prediction nomogram for VC to help clinicians make better decisions. To the best of our knowledge, this is an interesting report describing a large-scale survey of the baseline characteristics, diverse types of histopathology, detailed TNM staging, clinical information and follow-up data of VC.

Vulvar malignancies are rare in clinical practice. Current clinical diagnosis is dependent on biopsy and pathologic evaluation, and the treatment depends on histopathologic diagnosis ranging from wide local excision with or without lymph node biopsy or dissection to radiation therapy with chemotherapy or immunotherapy [3]. In our study, the majority of patients were diagnosed at ≥65 years old; married; white; grade I/II; SCC; and had T1, N0, and M0 staging. In patients, the primary tumor site was the vulva, tumor diameters were <4 cm, and the VC stage was localized, while a current neuroendocrine study of carcinomas of the vulva reported that tumors ranged from 0.7 cm to 6 cm and most commonly involved the labium majus [16]. Meanwhile, the median age at diagnosis was 67 years (range: 19–85+ years), which was older than a previous report and showed that the median age at diagnosis was 56 years with adenoid cystic vulvar carcinoma [17]. Moreover, the median survival time was 41 months (IQR = 7-81 months) in the training cohort and 40 months (IQR = 18-78 months) in the validation cohort, which was shorter than that in a previous study and showed that the mean survival time was 47.8 months for patients with adenoid cystic vulvar carcinoma [17]. In addition, several researchers reported that the 3-year OS rate was 84% in sentinel node-negative patients, and the 5-year OS rate ranged from 17% to 86% depending on the stage of the disease at the time of diagnosis [18,19], while in this study, the 3-, 5-, and 8-year OS rates were 53.75%, 35.79%, and 17.61%, respectively.

Multivariate Cox analysis showed that histological type had the greatest impact on OS followed by age at diagnosis, surgery status, T stage, N stage, M stage, tumor grade, summary stage, chemotherapy status, race, marital status and tumor size. The common histological types of VC include SCC, vulvar intraepithelial neoplasms, malignant melanoma, adenocarcinomas and basal cell carcinomas. SCC was the most commonly diagnosed form of VC in this study (87%), which is consistent with previous reports [20,21], and the type of malignant melanoma was associated with a poorer OS for patients with VC. A previous article showed that melanoma was the second most common cancer affecting the vulva, and staging was based on tumor, node, and metastatic spread, [3] which needs further research. Patients with

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older age, higher tumor grade and larger tumor size had a decreased OS, and malignant melanoma and tumors with diameters >4 cm had the lowest survival rates. Age is known as a risk factor for VC, occurring in women over 70 years old [22]. In the FIGO system, tumor size is not further divided when it reaches >4 cm, while it is a prognostic factor for patients with VC, which is consistent with previous reports [9]. Married patients had poorer OS compared to unmarried patients, while another study demonstrated an increased risk of cancer mortality in widows with SCC VC [7]. Typically, patients with VC are primarily treated with surgery, depending on the pathology and extent of the disease, with the option of adjuvant radiation or chemotherapy [23]. Although radical vulvectomy is effective, it was found to be associated with serious adverse effects, including wound complications and lymphedema [20]. Therefore, it has led to a shift towards more conservative treatment approaches focusing on conservation of the vulva and customized tumor resection based on TNM staging. Immunotherapy has gained an important role in the management of VC, but it was not mentioned in our study due to various limitations in the SEER database. Fig. 3 shows that surgery and chemotherapy can improve OS; therefore, active comprehensive treatment is encouraged for patients with VC. Meanwhile, the mixed histological type is a high-risk factor for survival, and doctors should attach great importance to it.

After establishing the nomogram that considered the identified prognostic factors, we performed a series of evaluations on the novel model, which is essential for any clinical prediction model before it is used in practice. We compared this novel model with the FIGO staging system to determine whether it was better for OS prediction using scientific statistical methods. The C-index is an effective indicator for predicting the model's discrimination ability, while the ROC curve is a relatively intuitive method [24,25]. Notably, Fig. 4 shows that the AUC of the nomogram is superior to that of the FIGO models, which indicates that the nomogram has good overall discrimination. In addition, the NRI focuses on more changes at a certain set of cutoff points, which are often used to evaluate the accuracies of the prediction models, and the IDI can reflect the overall improvement of the model, to an extent, complements the NRI [26,27]. The NRI revealed that the proportions of correct classifications for the 3-, 5-, and 8-year OS probabilities increased by 49.7%, 48.1%, and 52.3%, respectively, in the training cohort and by 30.5%, 29.6%, and 26.5%, respectively, in the validation cohort ($p < 0.05$). In our study, compared with the FIGO model, the mean IDI values with the new model had higher prediction abilities for the 3-, 5-, and 8-year OS probabilities, by 9.8%, 10.9%, and 11.5%, respectively, in the training cohort and by 6.1%, 8.1%, and 8.2%, respectively, in the validation cohort ($p < 0.05$). After the above analysis, we conclude that the nomogram has good discrimination and provides preliminary evidence that the model has the ability to correctly classify the survival probabilities of patients with VC. Then, we verified the calibration degree of the model by drawing a calibration plot. Fig. 5 shows that the calibration curve of the model is very close to the standard line, indicating that the model exhibits good consistency. After good overall performance of the model has been demonstrated, the nomogram can be used to predict the 3-, 5-, and 8-year OS probabilities for patients with VC. Finally, we assessed the clinical effectiveness of the model by DCA, which is being employed by an increasing number of researchers to assess the net benefit to patients receiving clinical treatment. As shown in Fig. 6, the overall net benefit of the new model is higher than that of the FIGO staging system, indicating that the new model can bring more net benefits to patients and help clinicians make better clinical treatment decisions.

Our study also has several limitations. First, this retrospective study has information bias, which may affect the treatment approach, operational performance, and survival outcomes. Second, although the nomogram shows better discrimination and verification capabilities than the FIGO staging system, it still requires further verification in large-scale external queues. Third, prognostic factors related to patients with VC were diverse, and some biological markers, behavioral habits, and economic factors need to be considered.

5. Conclusion

We established and validated a nomogram for individual prediction of the 3-, 5-, and 8-year OS probabilities of patients with VC based on the SEER database. The nomogram embodies demographic, clinicopathological and clinical treatment factors and may be a useful comprehensive prognostic tool to guide the oncological prognosis of patients with VC in clinical practice.

Conflict of interest

The authors declare that they have no conflict of interest.

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Author Contributions

ZHC designed the study；JD collected and analyzed the data; LL conceptualized and supervised the conduct of the study. ML drafted the initial manuscript; ML and JL prepared the manuscript for submission; ZHC and JL are correspondence authors. All authors reviewed and critiqued the manuscript for content.

Data availability statement

The data that support the findings of this study are available at the Surveillance, Epidemiology, and End Results database (https://seer.cancer.gov).

References

[1] Judson PL, Habermann EB, Baxter NN, et al. Trends in the incidence of invasive and in situ vulvar carcinoma. Obstet Gynecol, 2006, 107:1018-1022.
[2] Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin, 2021, 0:1-41.
[3] Michalski BM, Pfeifer JD, Mutch D, et al. Cancer of the Vulva: A Review. Dermatol Surg 2021, 47(2):174-183.
[4] Kang YJ, Smith M, Barlow E, et al. Vulvar cancer in high-income countries: Increasing burden of disease. Int J Cancer, 2017,141(11):2174-2186.
[5] Oonk MHM, Planchamp F, Baldwin P, et, al. European Society of Gynaecological Oncology Guidelines for the Management of Patients With Vulvar Cancer. Int J Gynecol Cancer, 2017, 27(4):832-837.
[6] Hacker NF. Revised FIGO staging for carcinoma of the vulva. Int J Gynaecol Obstet, 2009, 105(2):105-6.
[7] Wu SG, Zhang WW, Li FY, et al. Lymph node ratio has prognostic value related to the number of positive lymph nodes in patients with vulvar cancer. Future Oncol, 2018, 14(23):2343-2351.
[8] Rauh-Hain JA, Clemmer J, Clark RM, et al. Racial disparities and changes in clinical characteristics and survival for vulvar cancer over time. Am J Obstet Gynecol, 2013, 209(5):468?
[9] Lei L, Tan L, Zhao X, et al. 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. Ann Transl Med, 2020,8(21):1382.
[10] Iasonos A, Schrag D, Raj GV, et al. How to build and interpret a nomogram for cancer prognosis. J Clin Oncol, 2008, 26(8):1364-70.
[11] Duggan MA, Anderson WF, Altekruse S, et al. The Surveillance, Epidemiology, and End Results (SEER) Program and Pathology: Toward Strengthening the Critical Relationship. Am J Surg Pathol, 2016,40(12): 94-102.
[12] Zhou H, Zou X, Li H, et al. Construction and validation of a prognostic nomogram for primary vulvar melanoma: a SEER population-based study. Jpn J Clin Oncol, 2020,50(12):1386-1394.
[13] Li C, Yang J, Zheng S, et al. Establishment and Validation of a Nomogram for Tonsil Squamous Cell Carcinoma: A Retrospective Study Based on the SEER Database. Cancer Control. 2020,27(1).
[14] Parikh CR, Devarajan P, Zappitelli M, et, al. Postoperative biomarkers predict acute kidney injury and poor outcomes after pediatric cardiac surgery. J Am Soc Nephrol, 2011,22(9):1737-47.
[15] Steyerberg EW, Vickers AJ, Cook NR, et al. Assessing the performance of prediction models: a framework for traditional and novel measures. Epidemiology, 2010,21(1):128-38.
[16] Chen PP, Ramalingam P, Alvarado-Cabrero I, et al. High-grade Neuroendocrine Carcinomas of the Vulva: A Clinicopathologic Study of 16 Cases. Am J Surg Pathol, 2021,45(3):304-316.
[17] Johnson LR, Nair RP, Sambasivan S. Adenoid cystic carcinoma of vulva-11 Years' single-institution experience. J Obstet Gynecol Ind, 2017,67:196-201.
[18] Opfermann KJ, Wahlquist, AE, Garrett-Mayer E. SEER Data: surveillance, Epidemiology and End Results. Am J Clin Oncol-Canc, 2014,37:112-116.
[19] Froeding LP, Hogdall C, Kristensen, E. Recurrence and survival rates in node negative patients after sentinel node biopsy for early-stage vulva cancer-A nationwide study. Gynecol Oncol, 2020, 156:124-130.
[20] Nishio S, Murotani K, Nakao S. Investigation of clinicopathological features of vulvar cancer in 1068 patients: A Japanese Gynecologic Oncology Group (JGOG) nationwide survey study. Gynecol Oncol, 2020, 159:449-455.

ISSN 2618-1584 Vol. 3, Issue 2: 37-47, DOI: 10.25236/FMSR.2021.030209

[21] Tergas AI, Tseng JH, Bristow RE. Impact of race and ethnicity on treatment and survival of women with vulvar cancer in the United States. Gynecol Oncol,2013,129(1):154-8.
[22] Bray F, Laversanne M, Weiderpass E, et al. Geographic and temporal variations in the incidence of vulvar and vaginal cancers. Int J Cancer,2020,147(10):2764-2771.
[23] Velden J, Fons G, Lawrie TA. Primary groin irradiation versus primary groin surgery for early vulvar cancer. Cochrane Database Syst Rev 5.2011.
[24] Wang Y, Li J, Xia Y, et al. Prognostic nomogram for intrahepatic cholangiocarcinoma after partial hepatectomy. J Clin Oncol,2013, 31(9):1188-95.
[25] Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. Radiology, 1983,148(3):839-843.
[26] Iki M, Fujita Y, Tamaki J, et al. Trabecular bone score may improve FRAX® prediction accuracy for major osteoporotic fractures in elderly Japanese men: the Fujiwara-kyo Osteoporosis Risk in Men (FORMEN) Cohort Study. Osteoporos Int, 2015,26(6):1841-8.
[27] Chambless LE, Cummiskey CP, Cui G. Several methods to assess improvement in risk prediction models: extension to survival analysis. Stat Med, 2011,30:22-38.