Submitted: 06 July, 2023 Accepted: 04 September, 2023 Published: 15 December, 2023 DOI:10.22514/ejgo.2023.103

ORIGINAL RESEARCH

European Journal of Gynaecological Oncology

Based on the surveillance, epidemiology, and end results programme, to develop and validate nomograms for predicting overall survival and cancer-specific survival in geriatric patients with vulvar squamous cell carcinoma

Yuqi Qiu[1], Sufei Wang[1], Jing Yang[1], Yong Chen[1], Hua Wei[2,*]

[1]Department of Obstetrics and Gynecology, The First Affiliated Hospital of Yangtze University, 434000 Jingzhou, Hubei, China
[2]Department of Obstetrics and Gynecology, The First Clinical Medicine College of Yangtze University, 434000 Jingzhou, Hubei, China

***Correspondence**
weihua_tg75@163.com
(Hua Wei)

Abstract

This study aimed to develop and validate nomograms for improving overall survival (OS) and cancer-specific survival (CSS) predictions in elderly patients diagnosed with vulvar squamous cell carcinoma (VSCC). Data from the Surveillance, Epidemiology, and End Results (SEER) database were retrieved to gather information on VSCC patients aged 60 years and older. Univariate and multivariate Cox regression analyses were conducted to identify independent risk factors. Based on these factors, nomograms were constructed to predict patients' OS and CSS. Model accuracy and discriminative power were assessed using the concordance index (C-index), area under the receiver operating characteristic curve (AUC), and calibration curves. Decision curve analysis (DCA) was also employed to assess the clinical significance of the proposed nomograms in comparison to the TNM (Tumor Node Metastasis) and AJCC (American Joint Committee on Cancer) staging systems. Between 2000 and 2019, a total of 2736 elderly VSCC patients met the inclusion criteria and were randomly divided into two groups: a training set (N = 1927) and a validation set (N = 809). Independent risk factors for predicting OS included age, grade, summary stage, T stage, N stage, primary site surgery, chemotherapy, regional node status and tumor size. For predicting CSS, independent risk factors were age, summary stage, AJCC stage, T stage, N stage, primary site surgery, chemotherapy, regional node status and tumor size. The C-index for OS in the training and validation sets was 0.724 (95% CI: 0.710–0.738) and 0.73 (95% CI: 0.708–0.752), respectively. In contrast, for CSS prediction, the C-index was 0.758 (95% CI: 0.740–0.776) in the training set and 0.774 (95% CI: 0.749–0.799) in the validation set. The proposed nomograms for predicting OS and CSS in VSCC patients aged 60 and older demonstrate promising potential as reliable tools that clinicians can consider to make more informed therapeutic decisions.

Keywords

Nomogram; Geriatric; Vulvar squamous cell carcinoma cancer; OS; CSS; SEER

1. Introduction

Vulvar cancer ranks as the fifth most prevalent gynecological cancer in the United States, accounting for approximately three to five percent of all gynecological malignancies [1]. Globally, the prevalence rate ranges between one to two cases per one hundred thousand individuals annually [2, 3]. Typically, vulvar cancer primarily affects postmenopausal women, with a median age at diagnosis of 68 [4, 5]. In 2022, the American Cancer Society estimated around 6330 new cases of vulvar cancer, resulting in nearly 1560 fatalities [6], and it is anticipated that by 2040, the global incidence of vulvar cancer will rise to approximately 73,467 cases with 2602 associated deaths [7]. Squamous cell carcinomas constitute over 90% of vulvar malignancies, followed by melanoma and other histological subtypes such as verrucous carcinoma, basal cell carcinoma and adenocarcinomas [8]. Notably, itching is one of the most prevalent symptoms of vulvar cancer, although less common symptoms may include bleeding, dysuria, secretions and pain. Due to the non-specific nature of these symptoms, many patients experience delayed diagnosis, often mistaken for inflammatory conditions [9]. Vulvar quadratus cell carcinoma can be categorized into two distinct types: the first arises from the progression of HPV (Human Papilloma Virus)-related high-grade squamous intraepithelial lesions (H-SIL), while the second originates independently

from HPV as differentiated vulvar intraepithelial neoplasia (dVIN) [10]. Treatment strategies encompass surgery combined with radiotherapy for locally advanced tumors, while palliative and symptomatic care is appropriate for cases with extensive metastasis [11]. Tumor stage significantly impacts the prognosis of vulvar cancer, with advanced-stage cases associated with poor outcomes, while early-stage cases exhibit high survival rates [12]. The prognosis of gynecological tumors is frequently determined using the International Federation of Gynaecology and Obstetrics (FIGO) staging system [13]. Numerous tumor characteristics, including size, depth of invasion, local extension, nodal status and regional and distant spread, are evaluated for their correlation with overall survival (OS) [14]. However, an increasing number of research based on the SEER database suggests that patient-related factors, such as age, race, marital status, pathological grade, utilization of radiotherapy, chemotherapy and surgical interventions, exert significant influence on prognosis [15–19]. The SEER program in the United States (US) operates as a population-based tumor registry, covering approximately 35% of the current US population and capturing 97% of reported cancer cases in the registry areas [20]. Notably, for staging purposes, vulvar cancer can be evaluated using both the AJCC and FIGO staging methods, in accordance with the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines, which provide a comprehensive schema for converting between AJCC TNM staging and FIGO staging [12].

Nomograms serve as a visual clinical prediction model, offering a robust foundation for clinical decision-making. It offers several advantages over conventional prediction models. First, nomograms represent a simplified and straightforward tool to predict clinical outcomes, making them more user-friendly in clinical decision-making compared to intricate statistical models. Second, nomograms have the unique ability to predict individual patient clinical outcomes based on specific characteristics, thereby facilitating personalized treatment decision-making [21], such that their efficiency in clinical decision-making has been shown to surpass that of the traditional TNM and AJCC staging systems [22, 23].

The median age of vulvar cancer diagnosis tends to be relatively high, mainly because older women are more susceptible to underlying health conditions that can eventually lead to cancer-related deaths unrelated to vulvar cancer itself. However, in our review of relevant literature regarding non-specific causes of death in vulvar cancer [16, 18, 24], we found a lack of nomogram-based predictions specifically designed for non-specific mortality in elderly women with VSCC. Therefore, the primary goal of this research was to identify independent prognostic factors for elderly VSCC patients using the SEER database and to develop and validate prediction models for predicting their cancer-specific survival (CSS) and OS for establishing a solid foundation for clinical diagnosis and treatment practices and offering a valuable reference for healthcare professionals.

2. Patients and methods

2.1 Data source and variables

Our data were obtained from the National Cancer Institute. The data of patients included in this study were retrieved from the SEER Research Plus Data (collected from 17 registries as of November 2021) and encompassed the following clinicopathological variables for all geriatric patients diagnosed with VSCC between 2000 and 2019: age, race, histological tumor grade, Summary stage, AJCC stage, T stage, N stage, M stage, primary site surgery, radiation treatment, chemotherapy, regional nodes status and tumor size. The SEER database also provides crucial patient follow-up information, including survival status, cause-specific mortality and survival duration. The inclusion criteria for this study were: (1) patients aged 60 years or older; (2) confirmed pathological diagnosis of VSCC; (3) multiple primary fields indicating a single primary or the first of two or more primaries; (4) Oncology, 3rd Edition (ICD-O-3) codes corresponding to C51.0, C51.1, C51.2, C51.8 or C51.9; and (5) ICD-O-3 histology codes 8070/3, 8071/3, 8072/3, 8073/3, 8074/3, 8075/3, 8076/3 or 8077/3. The exclusion criteria were: (1) unclear Summary stage; (2) undefined or blank AJCC stage; (3) ambiguous TNM stage; (4) absence of pathological specimens in cases of primary site surgery; (5) indeterminate lymph node statuses; (6) unspecified tumor size; (7) missing data on grade and race; and (8) a survival duration of 0 months. Fig. 1 provides a visual representation of the inclusion and exclusion criteria applied to select patients for this study.

Age at diagnosis was categorized into three groups: 60–69, 70–79 and $\geq$80 years. Race was categorized into White, Black and other racial groups. Tumor histology was classified into four grades: high differentiation (grade I), moderate differentiation (grade II), low differentiation (grade III), and undifferentiated (grade IV). Summary stage was categorized as localized, regional, or distant. Regional nodal statuses were classified as unresected, negative or positive. In the SEER database, tumor size was represented by codes ranging from 001 to 988. Among the 2736 eligible patients, 37 patients had a tumor size with a diameter less than 1 cm, 11 patients had a tumor size and diameter less than 2 cm, 16 patients had a tumor size and diameter less than 3 cm, 4 patients had a tumor size and diameter less than 4 cm, and 4 patients had a tumor size and diameter less than 5 cm. Corresponding codes for these cases were 990, 991, 992, 993, 994 and 995. To convert this continuous variable into a categorical one using appropriate cut-off values, determined from the X-tile software of Yale University (version 3.6.1, New Haven, CT, USA) [25]. In this study, for tumor size, we selected data with codes 001–988, and the optimal cut-off values were determined as $<$46 mm and $\geq$46 mm for OS, and $<$48 mm and $\geq$48 mm for CSS. For data analysis purposes, we rounded the cut-off values for OS and CSS to $<$50 mm and $\geq$50 mm (Fig. 2).

It is important to note that due to the de-identified nature of the patient data in the SEER database, our study did not require ethical approval or patient consent as the data is publicly accessible.

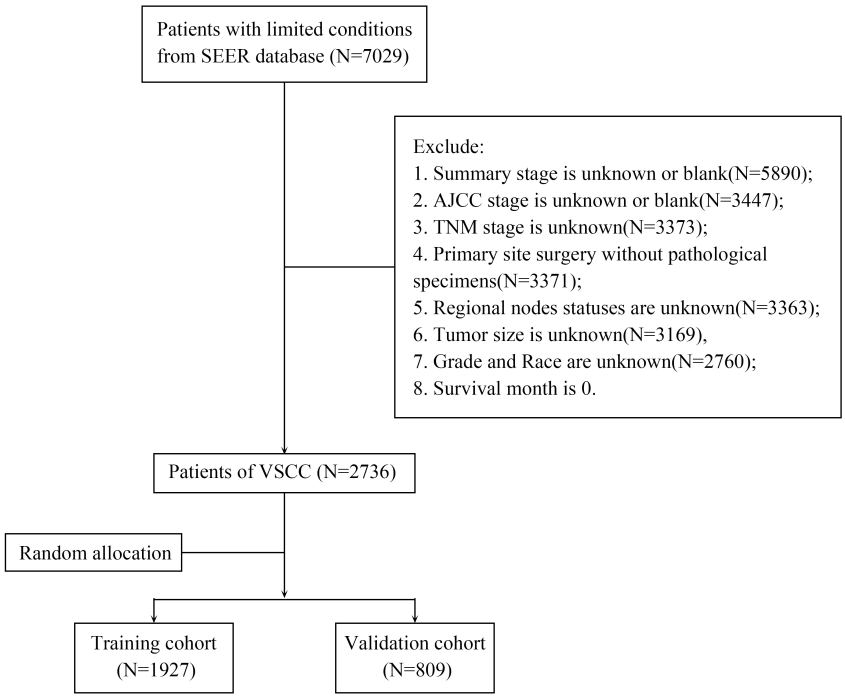

FIGURE 1. Flowchart showing the selection and exclusion of geriatric people with VSCC. SEER: Surveillance, Epidemiology and End Results; VSCC: vulvar squamous cell carcinoma; AJCC: American Joint Committee on Cancer; TNM: Tumor Node Metastasis.

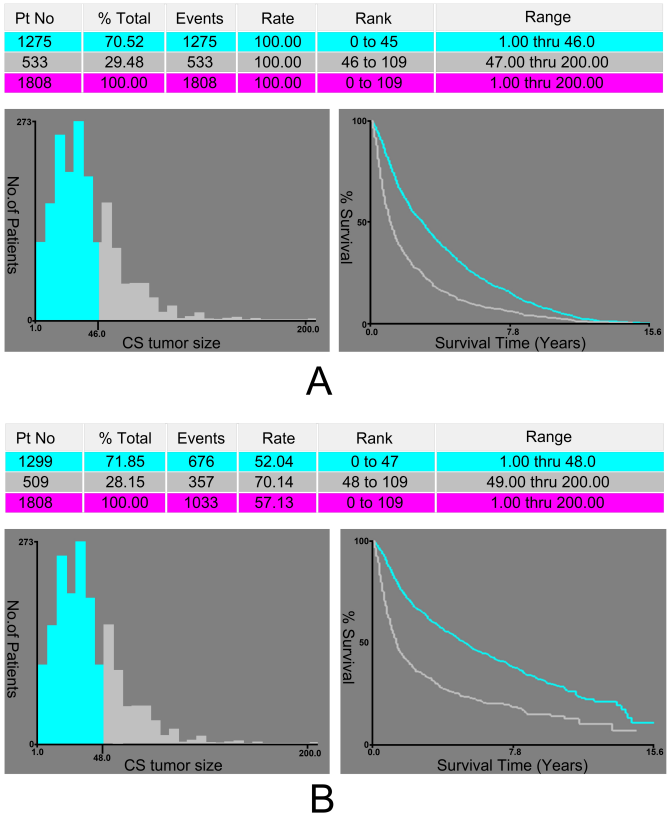

FIGURE 2. Optimal cut-off values for tumor size in OS and CSS, determined using X-tile. (A) Optimal cut-off values for tumor size in OS: 1–46 mm and 47–200 mm. (B) Optimal cut-off values for tumor size in CSS: 1–48 mm and 49–200 mm. CSS: cancer-specific survival.

2.2 Development and validation of the nomograms

To develop and internally validate the nomogram, we randomly divided the patient cohort into two sets of data through random selection: a training set (comprising 70% of the data) and a validation set (comprising the remaining 30%). For multivariate Cox regression analysis, we included variables with $p < 0.05$ from the univariate Cox regression analysis, which were then analyzed utilizing various regression methods, including forced, forward, backward, and stepwise regression techniques. Nomograms for the prediction of both CSS and OS at 1, 3 and 5 years were established using the Akaike information criterion (AIC) to select the optimal model with the minimum AIC score. The nomograms' accuracy was assessed through calibration curves generated from 500 bootstrap samples. To evaluate the models' performance, we employed the consistency index (C-index) and the area under the receiver operating characteristic curve (AUC) for determining their accuracy and discrimination capabilities.

2.3 Clinical application

We assessed the clinical value of the nomograms in predicting CSS and OS at 1, 3 and 5 years in comparison to the TNM and AJCC staging systems using decision analysis curves (DCA) and calculated the risk score for each patient using the nomograms. Based on the cut-off value determined from the receiver operating characteristic curve (ROC), patients were categorized into high-risk and low-risk groups. To analyze the differences in survival outcomes between these high-risk and low-risk groups, the Log-rank test was performed, and we generated Kaplan-Meier (K-M) survival curves.

2.4 Statistical analysis

We compared all clinicopathological variables between the training and validation sets using the chi-square test. For variable selection in the multivariate Cox regression analysis, we applied various regression methods, including forced, forward, backward, and stepwise regression, incorporating variables with $p < 0.05$ from the univariate Cox regression analysis. To predict CSS and OS for vulvar squamous cancer patients aged 60 years and older, we developed two nomograms based on the AIC, selecting the optimal models for 1, 3 and 5 years. We assessed differences in patient survival using the log-rank test and presented Kaplan-Meier (K-M) survival curves. Clinicopathological feature analysis was performed using IBM SPSS statistical software version 26.0 (SPSS, Inc., Chicago, IL, USA), and all other statistical analyses were conducted with R version 4.1.2 (http://www.r-project.org). Statistical significance was determined using two-sided tests, with p-values less than 0.05 considered statistically significant.

3. Result

3.1 Clinicopathological characteristics

Of the total 2736 patients included in this trial, 1927 (70%) were assigned to the training set and 809 (30%) to the validation set. The results showed that age, race, Summary stage, AJCC stage, primary site surgery, radiation, chemotherapy, pathological grade, regional node classifications, tumor size, T stage, N stage and M stage were comparable in both the training and validation sets, with all the corresponding chi-square test showing $p > 0.01$ (Table 1).

3.2 Cox univariate and multivariate analysis

In the training cohort, Cox univariate analysis identified that age, Summary stage, AJCC stage, primary site surgery, radiation, chemotherapy, pathological grade, regional node statuses, tumor size, T stage, N stage and M stage were significant factors affecting both patient OS and CSS. In the subsequent multivariate analysis, based on the AIC principle, we used the backward method to establish models, which revealed that for patient OS (Table 2), the independent prognostic factors were age, pathological grade, Summary stage, T stage, N stage, primary site surgery, chemotherapy, regional node statuses and tumor size. Similarly, for patient CSS (Table 3), the independent prognostic factors were age, Summary stage, AJCC stage, T stage, N stage, primary site surgery, chemotherapy, regional node statuses and tumor size.

3.3 Establishment and validation of OS and CSS nomograms

Based on our multivariable Cox regression models, we have constructed nomograms for predicting the OS and CSS probabilities at 1 year, 3 years and 5 years for geriatric VSCC patients (Fig. 3), which highlight that age, N stage and T stage are the most influential factors for predicting OS, while for CSS, the most significant predictors are AJCC stage, primary site surgery, and age. Notably, the impact of tumor size on OS and regional lymph node status on CSS is relatively modest.

The C-index for predicting OS in the training set was 0.724 (95% CI: 0.710–0.738), and in the validation set, it was 0.73 (95% CI: 0.708–0.752). For predicting CSS, the C-index in the training set was 0.758 (95% CI: 0.740–0.776), and in the validation set, it reached 0.774 (95% CI: 0.749–0.799). Next, we assessed the calibration of the nomograms by comparing actual and predicted estimates and conducting 500 bootstrap iterations. The calibration graphs in Fig. 4 demonstrate a strong alignment between predicted and actual survival rates for both OS and CSS. Regarding the AUC, for OS in the training set, the AUCs at 1, 3 and 5 years were 0.798, 0.774 and 0.763, respectively, and in the validation set for OS, the AUCs were 0.827, 0.811 and 0.787 at 1, 3 and 5 years. For CSS in the training set, the AUCs were 0.852, 0.803 and 0.789 at 1, 3 and 5 years, respectively. In the validation cohort, the AUCs were 0.848, 0.841 and 0.813. Collectively, these findings highlight the high discriminatory performance of the nomograms (Fig. 5).

3.4 Clinical use

Our DCA plots demonstrate that our nomograms outperform the TNM and AJCC stage systems in terms of predicting 1, 3 and 5-year OS and CSS for VSCC patients (Fig. 6), emphasizing the practical utility of our nomograms in potentially guiding clinical decision-making for VSCC patients. Using

TABLE 1. Baseline age and clinical characteristics of vulvar squamous cell cancer patients from the SEER database.

Variables	Total (N = 2736) (%)	Training cohort (N = 1927) (%)	Validation cohort (N = 809) (%)	*p*-value
Age at diagnosis (yr)				
60∼69	869 (31.8)	613 (31.8)	256 (31.6)	
70∼79	865 (31.6)	637 (33.1)	228 (28.2)	0.016
≥80	1002 (36.6)	677 (35.1)	325 (40.2)	
Race				
White	2505 (91.6)	1763 (91.5)	742 (91.7)	
Black	130 (4.8)	95 (4.9)	35 (4.3)	0.720
Others	101 (3.7)	69 (3.6)	32 (4.0)	
Summary stage				
Localized	1438 (52.6)	1021 (53.0)	417 (51.5)	
Regional	1169 (42.7)	818 (42.4)	351 (43.4)	0.724
Distant	129 (4.7)	88 (4.6)	41 (5.1)	
AJCC stage				
I	827 (30.2)	584 (30.3)	243 (30.0)	
II	878 (32.1)	621 (32.2)	257 (31.8)	0.966
III	719 (26.3)	506 (26.3)	213 (26.3)	
IV	312 (11.4)	216 (11.2)	96 (11.9)	
T stage				
T1	940 (34.4)	662 (34.4)	278 (34.4)	
T2	1336 (48.8)	937 (48.6)	399 (49.3)	0.972
T3	395 (14.4)	282 (14.6)	113 (14.0)	
T4	65 (2.4)	46 (2.4)	19 (2.3)	
N stage				
N0	1956 (71.5)	1377 (71.5)	579 (71.6)	
N1	561 (20.5)	396 (20.6)	165 (20.4)	0.996
N2	219 (8.0)	154 (8.0)	65 (8.0)	
M stage				
M0	2656 (97.1)	1871 (97.1)	785 (97.0)	0.932
M1	80 (2.9)	56 (2.9)	24 (3.0)	
Primary site surgery				
No	316 (11.5)	221 (11.5)	95 (11.7)	0.838
Yes	2420 (88.5)	1706 (88.5)	714 (88.3)	
Radiation				
No/Unknown	1832 (67.0)	1284 (66.6)	548 (67.7)	0.575
Yes	904 (33.0)	643 (33.4)	261 (32.3)	
Chemotherapy				
No/Unknown	2318 (84.7)	1623 (84.2)	695 (85.9)	0.264
Yes	418 (15.3)	304 (15.8)	114 (14.1)	
Regional nodes positive				
No resection	1040 (38.0)	731 (37.9)	309 (38.2)	
Negative	1065 (38.9)	758 (39.3)	307 (37.9)	0.739
Positive	631 (23.1)	438 (22.7)	193 (23.9)	
Tumor size (cm)				
<5	2106 (77.0)	1499 (77.8)	607 (75.0)	0.118
≥5	630 (23.0)	428 (22.2)	202 (25.0)	
Grade				
I	833 (30.4)	596 (30.9)	237 (29.3)	
II	1356 (49.6)	943 (48.9)	413 (51.1)	0.287
III	519 (19.0)	372 (19.3)	147 (18.2)	
IV	28 (1.0)	16 (0.8)	12 (1.5)	

AJCC: American Joint Committee on Cancer.

TABLE 2. Univariate and multivariate analyses of OS for patients in the training cohort.

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age at diagnosis (yr)				
60∼69	Reference		Reference	
70∼79	1.72 (1.48–2.00)	<0.001	1.72 (1.47–2.00)	<0.001
≥80	3.06 (2.65–3.53)	<0.001	3.05 (2.62–3.55)	<0.001
Race				
White	Reference			
Black	0.99 (0.77–1.28)	0.968		
Others	0.90 (0.66–1.21)	0.474		
Summary stage				
Localized	Reference		Reference	
Regional	1.79 (1.60–2.01)	<0.001	1.02 (0.86–1.21)	0.812
Distant	4.44 (3.50–5.63)	<0.001	2.16 (1.49–3.13)	<0.001
AJCC stage				
I	Reference			
II	1.70 (1.46–1.97)	<0.001		
III	2.48 (2.13–2.89)	<0.001		
IV	4.42 (3.67–5.33)	<0.001		
T stage				
T1	Reference		Reference	
T2	1.93 (1.69–2.20)	<0.001	1.73 (1.50–2.00)	<0.001
T3	2.77 (2.34–3.28)	<0.001	1.80 (1.43–2.27)	<0.001
T4	4.64 (3.35–6.42)	<0.001	1.75 (1.10–2.77)	0.017
N stage				
N0	Reference		Reference	
N1	1.82 (1.60–2.08)	<0.001	1.30 (0.98–1.71)	0.064
N2	2.95 (2.45–3.56)	<0.001	2.06 (1.53–2.77)	<0.001
M stage				
M0	Reference			
M1	4.15 (3.12–5.51)	<0.001		
Primary site surgery				
No	Reference		Reference	
Yes	0.36 (0.30–0.42)	<0.001	0.53 (0.44–0.65)	<0.001
Radiation				
No/Unknown	Reference			
Yes	1.82 (1.63–2.04)	<0.001		
Chemotherapy				
No/Unknown	Reference		Reference	
Yes	1.51 (1.30–1.74)	<0.001	0.72 (0.60–0.86)	<0.001
Regional nodes positive				
No resection	Reference		Reference	
Negative	0.55 (0.48–0.63)	<0.001	0.68 (0.59–0.86)	<0.001
Positive	1.27 (1.11–1.45)	0.001	1.04 (0.79–1.37)	0.780
Tumor size (cm)				
<5	Reference		Reference	
≥5	1.93 (1.71–2.19)	<0.001	1.18 (1.02–1.36)	0.023
Grade				
I	Reference		Reference	
II	1.30 (1.15–1.49)	<0.001	1.07 (0.93–1.23)	0.320
III	1.70 (1.45–1.99)	<0.001	1.22 (1.03–1.44)	0.020
IV	0.70 (0.33–1.48)	0.354	0.51 (0.24–1.08)	0.080

HR: Hazard Ratio; CI: confidence interval; AJCC: American Joint Committee on Cancer.

TABLE 3. Univariate and multivariate analyses of CSS for patients in the training cohort.

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age at diagnosis (yr)				
60∼69	Reference		Reference	
70∼79	1.41 (1.67–1.71)	<0.001	1.40 (1.15–1.70)	<0.001
≥80	2.16 (1.80–2.60)	<0.001	2.24 (1.84–2.72)	<0.001
Race				
White	Reference			
Black	0.83 (0.58–1.20)	0.320		
Others	0.97 (0.66–1.43)	0.883		
Summary stage				
Localized	Reference		Reference	
Regional	2.48 (2.12–2.90)	<0.001	0.86 (0.63–1.18)	0.356
Distant	8.49 (6.53–11.05)	<0.001	2.16 (1.23–3.79)	0.007
AJCC stage				
I	Reference		Reference	
II	1.85 (1.47–2.33)	<0.001	0.83 (0.54–1.29)	0.414
III	3.85 (3.09–4.78)	<0.001	1.53 (0.86–2.74)	0.151
IV	8.46 (6.64–10.77)	<0.001	1.87 (0.86–4.07)	0.113
T stage				
T1	Reference		Reference	
T2	2.36 (1.96–2.85)	<0.001	2.13 (1.46–3.11)	<0.001
T3	4.04 (3.23–5.06)	<0.001	1.73 (1.11–2.71)	0.016
T4	7.68 (5.26–11.21)	<0.001	1.30 (0.70–2.41)	0.408
N stage				
N0	Reference		Reference	
N1	2.72 (2.31–3.21)	<0.001	1.31 (0.92–1.86)	0.131
N2	4.89 (3.95–6.06)	<0.001	1.867 (1.06–3.28)	0.030
M stage				
M0	Reference			
M1	6.64 (4.96–8.90)	<0.001		
Primary site surgery				
No	Reference		Reference	
Yes	0.27 (0.22–0.32)	<0.001	0.42 (0.32–0.54)	<0.001
Radiation				
No/Unknown	Reference			
Yes	2.60 (2.25–3.01)	<0.001		
Chemotherapy				
No/Unknown	Reference		Reference	
Yes	2.09 (1.76–2.48)	<0.001	0.72 (0.58–0.90)	0.004
Regional nodes positive				
No resection	Reference		Reference	
Negative	0.48 (0.40–0.58)	<0.001	0.76 (0.61–0.95)	0.015
Positive	1.68 (1.42–1.99)	<0.001	1.15 (0.83–1.60)	0.402
Tumor size (cm)				
<5	Reference		Reference	
≥5	2.49 (2.13–2.90)	<0.001	1.26 (1.05–1.51)	0.012
Grade				
I	Reference			
II	1.34 (1.13–1.61)	0.001		
III	1.97 (1.60–2.42)	<0.001		
IV	0.77 (0.29–2.08)	0.609		

HR: Hazard Ratio; CI: confidence interval; AJCC: American Joint Committee on Cancer.

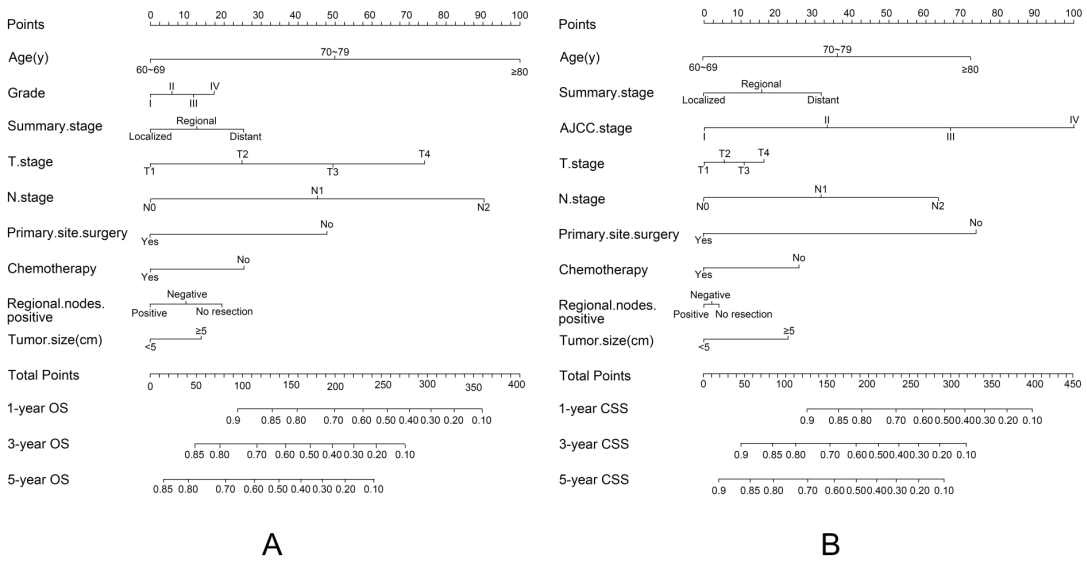

FIGURE 3. The nomograms for predicting the 1-, 3- and 5-year OS and CSS of geriatric patients with VSCC. The nomogram for (A) OS and (B) CSS. OS: overall survival; CSS: cancer-specific survival; AJCC: American Joint Committee on Cancer.

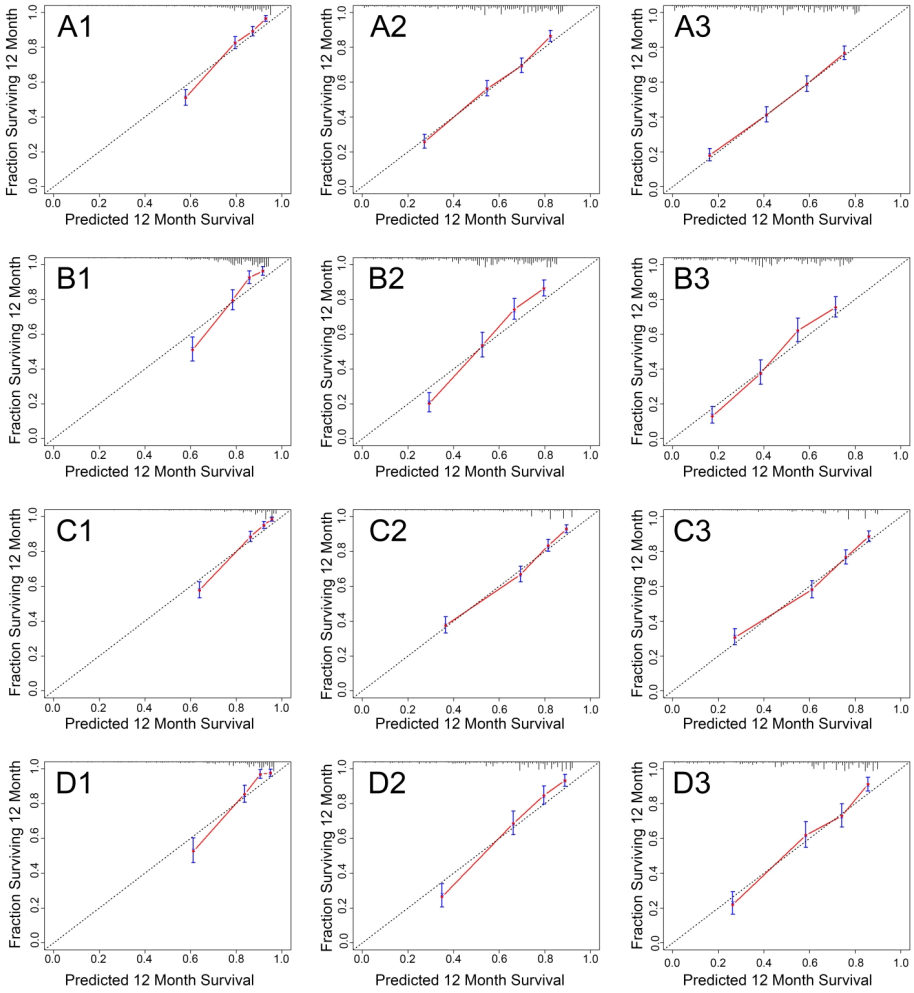

FIGURE 4. Calibration curve for the nomograms for predicting the 1-, 3- and 5-year OS and CSS of geriatric patients with VSCC in the (A1–3) training set (OS), (B1–3) validation set (OS), (C1–3) training set (CSS) and (D1–3) validation set (CSS). The horizontal axis of the nomogram represents the predicted value, while the vertical axis represents the observed value.

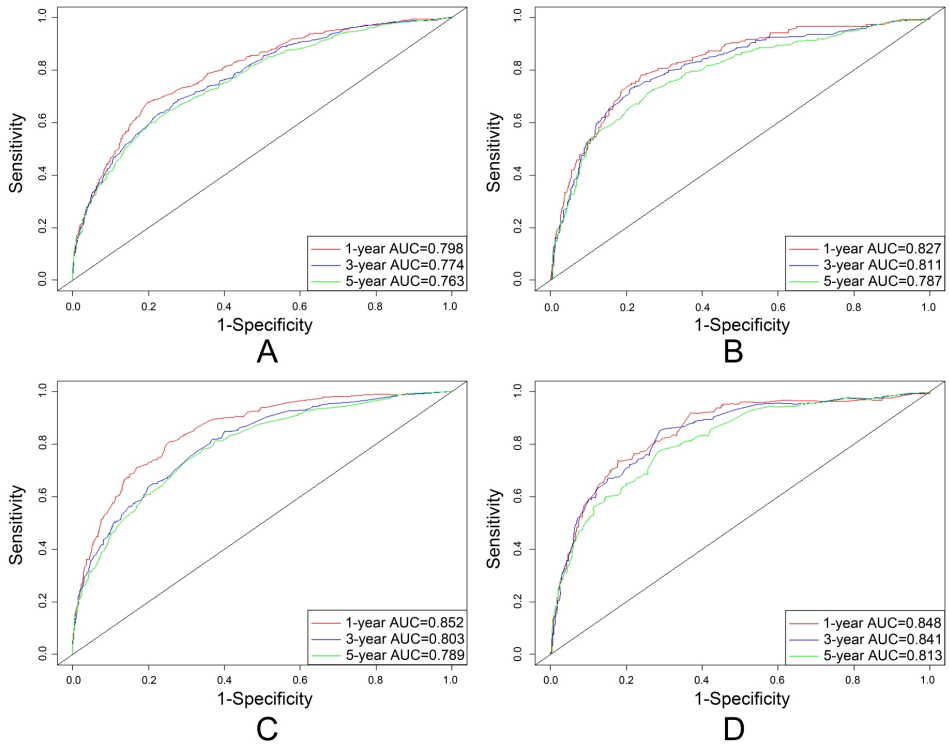

FIGURE 5. AUC for predicting the 1-, 3- and 5-year OS and CSS in geriatric patients with VSCC. (A) The AUC for the 1-, 3- and 5-year OS in the training set was 0.798, 0.774 and 0.763. (B) The AUC for OS in the validation set was 0.827, 0.811 and 0.787. (C) The AUC at 1-, 3- and 5-year for CSS in the training set was 0.852, 0.803 and 0.789. (D) The AUC at 1-, 3- and 5-year for CSS in the validation set was 0.848, 0.841 and 0.813. AUC: area under the receiver operating characteristic curve.

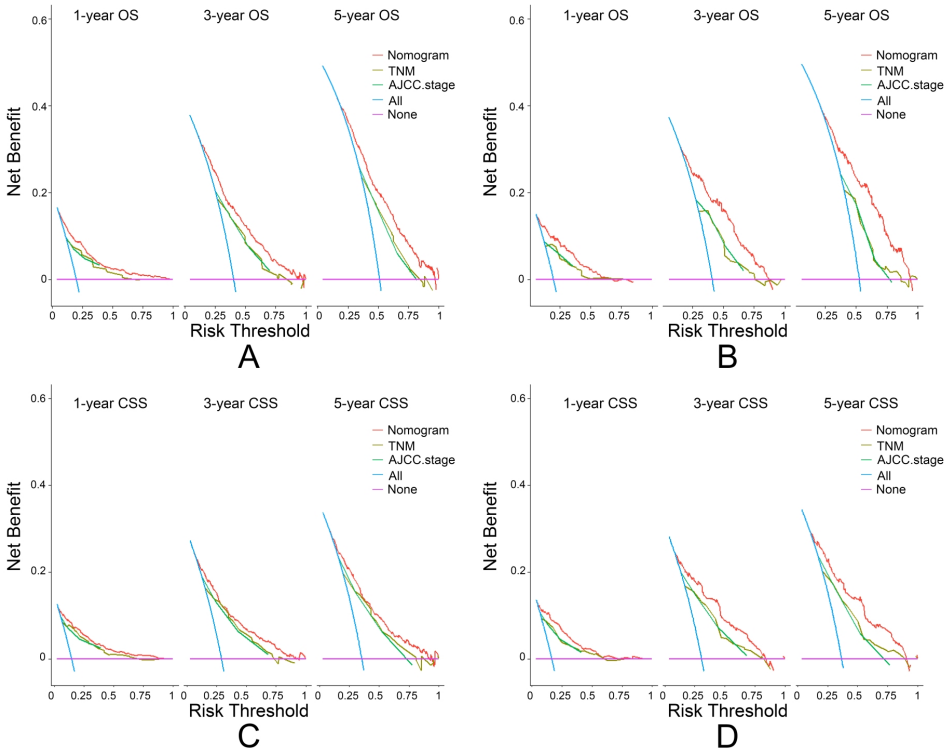

FIGURE 6. DCA of the nomograms used to predict OS and CSS. (A,B) In contrast to the AJCC and TNM stages, the 1-, 3- and 5-year OS of the nomogram demonstrated the best application potential in both the training and validation sets. (C) In training sets, the CSS nomogram at 1, 3 and 5 years showed greater application potential advantages over the other two systems. (D) In the validation set, the CSS nomogram at 1-, 3- and 5-year showed greater clinical promise than the AJCC and TNM systems. OS: overall survival; CSS: cancer-specific survival; TNM: Tumor Node Metastasis; AJCC: American Joint Committee on Cancer.

the ROC curve, we determined each patient's risk value and identified the optimal cut-off value based on the nomograms. For predicting OS, patients were stratified into a high-risk group (total score ≥139.648) and a low-risk group (total score <139.648). Similarly, for predicting CSS, patients were categorized into a high-risk group (total score ≥139.198) and a low-risk group (total score <139.198). Fig. 7 illustrates that the K-M survival curves showing significantly lower OS and CSS rates for high-risk patients compared to low-risk patients in both the training and validation sets. In the high-risk group, the 1, 3 and 5-year OS rates were 67.21%, 41.35% and 41.35%, respectively. Comparatively, the low-risk group exhibited significantly higher 1, 3 and 5-year OS rates of 92.8%, 77.9% and 67.7%, respectively, and for the high-risk group, the 1, 3 and 5-year CSS rates were 70.7%, 50.4% and 42.2%, while the low-risk group demonstrated significantly better CSS rates of 96.8%, 86.7% and 81.4% at the same time intervals.

4. Discussion

4.1 Summary of main results

Using data from the population-based SEER database, this study developed nomograms for predicting both OS and CSS of geriatric patients diagnosed with VSCC, which incorporate multiple independent prognostic variables, including age, grade, Summary stage, T stage, N stage, primary site surgery, chemotherapy, regional nodes status and tumor size for OS prediction. For CSS prediction, the nomograms comprised age, Summary stage, AJCC stage, T stage, N stage, primary site surgery, chemotherapy, regional nodes status and tumor size as the relevant prognostic factors.

4.2 Findings in relation to published literature

The nomogram developed by Weili Zhou *et al.* [16] demonstrated robust predictive accuracy in training, validation and the overall dataset, with c-statistics of 0.80, 0.83 and 0.81, respectively. The variables utilized in the prediction models for both OS and CSS were consistent. It is also worth noting that, in their study, there was no comparison made between the nomogram and the traditional FIGO stage using DCA curves. Comparatively, in this present study, we conducted DCA and found that the nomograms significantly outperformed the TNM and AJCC stage systems. Importantly, due to the absence of FIGO staging in the SEER database, clinicians usually rely on the TNM and AJCC staging as approximations. A retrospective study by Julia *et al.* [26] reported uncertainty in the relationship between age and the OS rate of VSCC patients. In contrast, our study highlights age as a significant factor affecting both the overall mortality rate and non-specific cancer survival in geriatric patients with

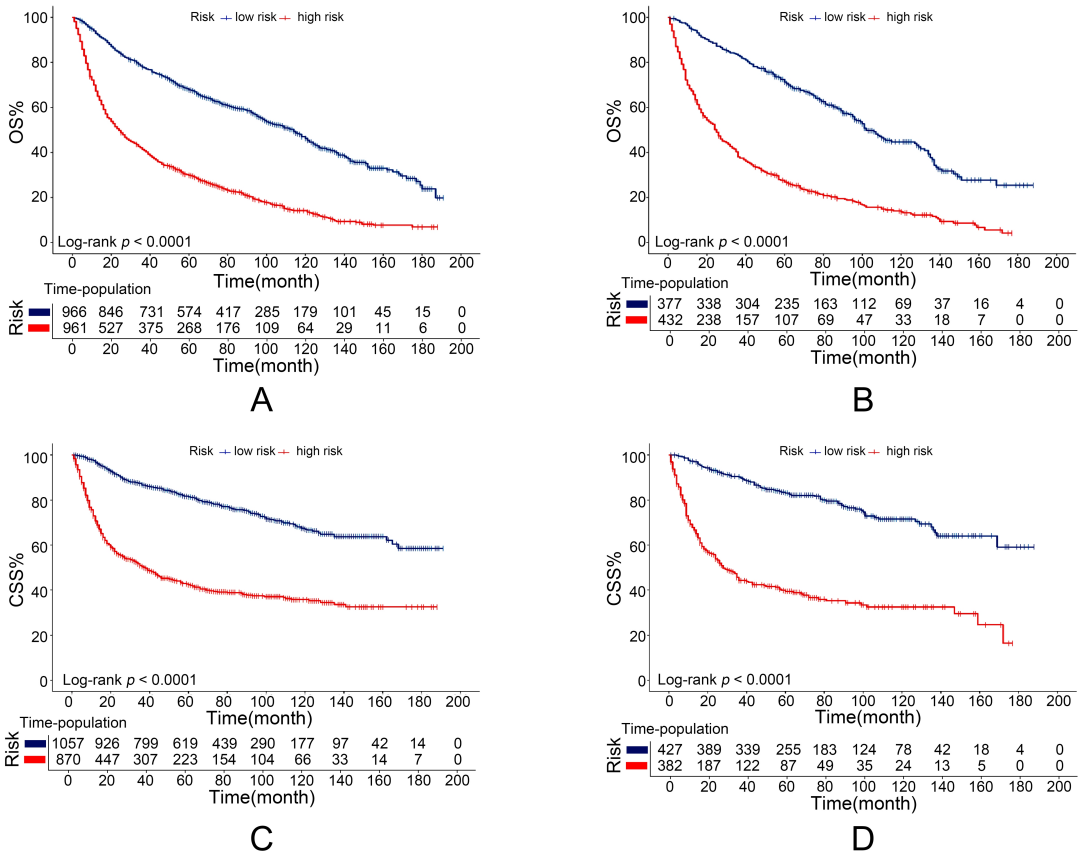

FIGURE 7. Kaplan-Meier curves of patients in the low-risk and high-risk groups. The K-M curve revealed that the OS rate of patients in the high-risk group was significantly lower than that of patients in the low-risk group in both the training and test sets (A) and validation set (B). The K-M curve revealed that the CSS rate of the high-risk group was much lower than that of the low-risk group in both the training set (C) and validation (D) set. OS: overall survival; CSS: cancer-specific survival.

VSCC. Specifically, older patients exhibited poorer survival rates, consistent with prior research [16, 19, 27, 28]. Our study also confirms that both TNM and AJCC stages are significant predictors for OS and cancer-specific CSS in VSCC patients, aligning with their established roles in predicting patient survival [15]. Surgery has traditionally been considered the primary treatment for vulvar cancer [29]. However, it may not be suitable for patients with stage IV tumors involving bone, fixed lymph nodes, or distant metastasis [30]. The constructed nomograms reaffirm that primary site surgery remains a robust predictor of both OS and CSS, even among geriatric patients, which is in line with prior research [15, 16]. Notably, our study found that non-resected and negative local lymph nodes were associated with higher risk compared to positive lymph nodes, which contradicts some prior studies [17]. However, it is important to acknowledge that this conclusion is based solely on statistical analysis of SEER database data, and further research is warranted to confirm these findings. Regarding chemotherapy, our results are consistent with the idea that it can significantly improve OS in vulvar cancer patients [31]. However, a study by Scampa *et al*. [32] reported that the OS of patients benefiting from chemotherapy was statistically lower than those who did not benefit, possibly because chemotherapy is primarily administered to patients with advanced diseases, leading to shorter survival time.

4.3 Strengths and weaknesses

We developed nomograms to predict the OS and CSS of geriatric patients with VSCC using clinical data from the SEER database. However, these nomograms also have some limitations. Firstly, our study is confined to VSCC patients aged 60 years and older, restricting its applicability to a broader age spectrum. Secondly, we excluded VSCC cases with multiple primary malignancies or those not categorized as primary, potentially impacting the generalizability of our findings. Thirdly, the retrospective nature of SEER data introduces inherent selection bias and lacks detailed clinical information, such as tumor invasion depth and specific treatment data. Fourthly, accurate records of human papillomavirus (HPV) status related to VSCC are unavailable. Lastly, as the proposed nomograms were based on patients from the US, this raises uncertainty about the generalizability of our results to other populations with different ethnic and socioeconomic characteristics. Despite these limitations, our nomograms provide valuable survival predictions for geriatric VSCC patients, with the need for future research to address these constraints and validate the nomograms in diverse patient cohorts.

4.4 Consequences for future methodology and study

The proposed nomograms can assist physicians in tailoring treatments for individual patients and predicting their prognosis. In the future, we plan to further validate the accuracy of this prediction model through additional investigations conducted at our institution to promote its clinical adoption. Additionally, we intend to explore vulvar lichen sclerosus, which is considered a chronic inflammatory disease associated with genetic immunity and is more prevalent in postmenopausal women.

5. Conclusions

We investigated the factors that affect the OS and CSS of geriatric patients with VSCC, based on which we developed nomograms that demonstrated promising accuracy and reliability following internal validation, possessing the potential to enhance the clinical decision-making of doctors and patients.

AVAILABILITY OF DATA AND MATERIALS

The authors declare that all data supporting the findings of this study are available within the paper and any raw data can be obtained from the corresponding author upon request.

AUTHOR CONTRIBUTIONS

YQQ and HW—designed the study and carried them out; prepare the manuscript for publication and reviewed the draft of the manuscript. YQQ, SFW, JY and YC—supervised the data collection, analyzed the data, interpreted the data. All authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This article does not contain any studies with human participants or animals performed by any of the authors. Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

ACKNOWLEDGMENT

Not applicable.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA: A Cancer Journal for Clinicians. 2022; 72: 7–33.

[2] Garganese G, Inzani F, Fragomeni SM, Mantovani G, Della Corte L, Piermattei A, *et al*. The vulvar immunohistochemical panel (VIP) project: molecular profiles of vulvar squamous cell carcinoma. Cancers. 2021; 13: 6373.

[3] Mancini S, Bucchi L, Baldacchini F, Giuliani O, Ravaioli A, Vattiato R, *et al*. Incidence trends of vulvar squamous cell carcinoma in Italy from 1990 to 2015. Gynecologic Oncology. 2020; 157: 656–663.

[4] Chow L, Tsui BQ, Bahrami S, Masamed R, Memarzadeh S, Raman SS, *et al*. Gynecologic tumor board: a radiologist's guide to vulvar and vaginal malignancies. Abdominal Radiology. 2021; 46: 5669–5686.

[5] Merlo S. Modern treatment of vulvar cancer. Radiology and Oncology. 2020; 54: 371–376.

[6] Virarkar M, Vulasala SS, Daoud T, Javadi S, Lall C, Bhosale P. Vulvar cancer: 2021 Revised FIGO staging system and the role of imaging. Cancers. 2022; 14: 2264.

[7] Shin DW, Bae J, Ha J, Lee WM, Jung K. Trends in incidence and survival of patients with vulvar cancer in an Asian country: analysis of the Korean Central cancer registry 1999–2018. Gynecologic Oncology. 2022; 164: 386–392.

[8] Verri D, Moro F, Fragomeni SM, Zaçe D, Bove S, Pozzati F, *et al*. The role of ultrasound in the evaluation of inguinal lymph nodes in patients with vulvar cancer: a systematic review and meta-analysis. Cancers. 2022; 14: 3082.

[9] Khullar K, Patrich T, Jabbour SK, Hathout L. Adjuvant radiation in early stage vulvar cancer: a review of indications and optimal dose. Applied Radiation Oncology. 2022; 11: 14–20.

[10] Santoro A, Angelico G, Travaglino A, Inzani F, Arciuolo D, Valente M, *et al*. Prognostic role of perineural invasion in vulvar squamous cell carcinoma: a systematic review and meta-analysis. European Journal of Surgical Oncology. 2022; 48: 2354–2359.

[11] Weinberg D, Gomez-Martinez RA. Vulvar cancer. Obstetrics and Gynecology Clinics of North America. 2019; 46: 125–135.

[12] Matsuo K, Klar M, Nishio S, Mikami M, Roman LD, Wright JD. Validation of the 2021 FIGO staging schema for advanced vulvar cancer. International Journal of Gynecologic Cancer. 2022; 32: 474–479.

[13] Olawaiye AB, Cuello MA, Rogers LJ. Cancer of the vulva: 2021 update. International Journal of Gynecology & Obstetrics. 2021; 155: 7–18.

[14] Olawaiye AB, Cotler J, Cuello MA, Bhatla N, Okamoto A, Wilailak S, *et al*. FIGO staging for carcinoma of the vulva: 2021 revision. International Journal of Gynecology & Obstetrics. 2021; 155: 43–47.

[15] Mao Y, He M, Tang Z, Chen M, Wu L, Liang T, *et al*. Prognostic nomograms to predict overall survival and cause specific death in vulvar squamous cell carcinoma. International Journal of Gynecologic Cancer. 2022; 32: 706–715.

[16] Zhou W, Yue Y. Developing and validating novel nomograms for predicting the overall survival and cancer-specific survival of patients with primary vulvar squamous cell cancer. Frontiers in Medicine. 2021; 8: 777605.

[17] Lei L, Tan L, Zhao X, Zeng F, Xu D. 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. Annals of Translational Medicine. 2020; 8: 1382–1382.

[18] Liu J, Wang M. Development and validation of nomograms predicting cancer-specific survival of vulvar cancer patients: based on the surveillance, epidemiology, and end results program. International Journal of Gynecology & Obstetrics. 2022; 156: 529–538.

[19] Scampa M, Kalbermatten DF, Oranges CM. Squamous cell carcinoma of the vulva: a survival and epidemiologic study with focus on surgery and radiotherapy. Journal of Clinical Medicine. 2022; 11: 1025.

[20] Zippin C, Lum D, Hankey BF. Completeness of hospital cancer case reporting from the SEER program of the national cancer institute. Cancer. 1995; 76: 2343–2350.

[21] Wang X, Lu J, Song Z, Zhou Y, Liu T, Zhang D. From past to future: bibliometric analysis of global research productivity on nomogram (2000–2021). Frontiers in Public Health. 2022; 10: 997713.

[22] Zheng W, Zhu W, Yu S, Li K, Ding Y, Wu Q, *et al*. Development and validation of a nomogram to predict overall survival for patients with metastatic renal cell carcinoma. BMC Cancer. 2020; 20: 1066.

[23] Zhang Z, Zhanghuang C, Wang J, Tian X, Wu X, Li M, *et al*. Development and validation of nomograms to predict cancer-specific survival and overall survival in elderly patients with prostate cancer: a population-based study. Frontiers in Oncology. 2022; 12: 918780.

[24] Micheletti L, Borella F, Preti M, Frau V, Cosma S, Privitera S, *et al*. Perineural invasion in vulvar squamous-cell carcinoma is an independent risk factor for cancer-specific survival, but not for locoregional recurrence: results from a single tertiary referral center. Cancers. 2021; 14: 124.

[25] Camp RL, Dolled-Filhart M, Rimm DL. X-tile: a new bio-informatics tool for biomarker assessment and outcome-based cut-point optimization. Clinical Cancer Research. 2004; 10: 7252–7259.

[26] Julia CJ, Hoang L. A review of prognostic factors in squamous cell carcinoma of the vulva: evidence from the last decade. Seminars in Diagnostic Pathology. 2021; 38: 37–49.

[27] Prieske K, Woelber L, Muallem MZ, Eulenburg C, Jueckstock JK, Hilpert F, *et al*. Age, treatment and prognosis of patients with squamous cell vulvar cancer (VSCC)—analysis of the AGO-CaRE-1 study. Gynecologic Oncology. 2021; 161: 442–448.

[28] Hellman K, Holmberg E, Bjurberg M, Borgfeldt C, Dahm-Kähler P, Flöter Rådestad A, *et al*. Primary treatment and relative survival by stage and age in vulvar squamous cell carcinoma: a population-based SweGCG study. Gynecologic Oncology. 2020; 159: 663–671.

[29] Pedrão PG, Guimarães YM, Godoy LR, Possati-Resende JC, Bovo AC, Andrade CEMC, *et al*. Management of early-stage vulvar cancer. Cancers. 2022; 14: 4184.

[30] Rogers LJ. Management of advanced squamous cell carcinoma of the vulva. Cancers. 2021; 14: 167.

[31] Mokhtech M, Gao SJ, Kassick M, Menderes G, Damast S. Declining use of inguinofemoral lymphadenectomy in the treatment of clinically negative, pathologic node positive vulvar cancer. Gynecologic Oncology. 2022; 166: 61–68.

[32] Scampa M, Kalbermatten DF, Oranges CM. Squamous cell carcinoma of the vulva: a survival and epidemiologic study with focus on surgery and radiotherapy. Journal of Clinical Medicine. 2022; 11: 1025.

How to cite this article: Yuqi Qiu, Sufei Wang, Jing Yang, Yong Chen, Hua Wei. Based on the surveillance, epidemiology, and end results programme, to develop and validate nomograms for predicting overall survival and cancer-specific survival in geriatric patients with vulvar squamous cell carcinoma. European Journal of Gynaecological Oncology. 2023; 44(6): 86-97. doi: 10.22514/ejgo.2023.103.