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A Novel Nomogram and Risk Classification System Predicting the Cancer-Specific Survival of Patients with Initially Diagnosed Metastatic Esophageal Cancer: A SEER-Based Study

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ABSTRACT

Background. Metastatic esophageal cancer (mEC) is the end stage of esophageal cancer. We aimed to construct a predictive model predicting the cancer-specific survival (CSS) of mEC patients.

Methods. Data from 1917 patients with initially diagnosed mEC were extracted from the Surveillance, Epidemiology, and End Results database between 2010 and 2015. Patients were randomly divided into the training and validation cohorts (7:3). Cox regression was conducted to select the predictors of CSS. The validation of the nomogram was performed using concordance index (C-index), calibration curves, and decision curve analyses (DCAs).

Results. Cancer-specific death occurred in 1559/1917 (81.3%) cases. Multivariate Cox regression indicated that factors including age, sex, grade at diagnosis, number of metastatic organs at diagnosis, pathological type, local treatment, and chemotherapy were independent predictors of CSS. Based on these factors, a predictive model was built and virtualized by nomogram. The C-index of the nomogram was 0.762. The calibration curves showed good consistency of CSS between the actual observation and the nomogram prediction, and the DCA showed great clinical usefulness of the nomogram. A risk classification system was built that could perfectly classify mEC patients into three risk groups. In the total cohort, the median CSS of patients in the low-, intermediate- and high-risk groups was 11.0 months (95% confidence interval [CI] 10.1–11.9), 8.0 months (95% CI 7.3–8.7), and 2.0 months (95% CI 1.8–2.2), respectively.

Conclusions. We constructed a nomogram and a corresponding risk classification system predicting the CSS of patients with initially diagnosed mEC. These tools can assist in patient counseling and guiding treatment decision making.

Esophageal cancer (EC) accounts for a substantial proportion of gastrointestinal malignancies, with an annual incidence of 16,940 cases in the US and over 450,000 cases worldwide.[1,2] EC ranks as the eighth most common cancer and is the sixth leading cause of cancer-related death.[3] Remarkably, nearly 50% of EC patients present with distant metastasis at the time of initial diagnosis, and, of the remaining patients who have only locoregional disease at the time of diagnosis, 25% eventually develop distant metastases.[4]

Despite the continued research on, and advances in, the treatment strategies for EC, the prognosis of EC is still unsatisfactory. The 5-year overall survival (OS) rates for all EC patients only showed a modest improvement over the past few decades, from 5% to approximately 20%.[5] However, the clinical outcomes of metastatic EC (mEC) patients are still extremely poor, with the median OS being 8–10 months and the 5-year OS rate merely 5%.[6,7] There are several reasons for the poor prognosis of mEC patients, including ineffective screening tools, late diagnosis of most cases, and, most importantly, the lack of an efficient treatment method.[8]

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Of note, substantial heterogeneity exists among patients with mEC in terms of demographic and clinicopathological information, such as age, sex, T and N stages, pathological type, and tumor stage, and the applied therapeutic schemes. Thus, the prognosis of mEC differs substantially across different cases.

A nomogram is a convenient tool to predict and quantify the chance of an individual patient developing a certain clinical event. Nomograms are helpful in clinical decision making and have value in risk stratification, personalized treatment, and clinical trial design. However, almost all of the existing models of EC are based on patients with localized disease, and there is a lack of a predictive model specifically designed for mEC patients.

Therefore, the aim of this study was to construct and validate a novel predictive model for predicting the prognosis of patients with mEC using a cohort from the Surveillance, Epidemiology, and End Results (SEER) database.

MATERIALS AND METHODS

Patients

Data from 1917 patients initially diagnosed with mEC were derived from the SEER program of the National Cancer Institute.[9] The SEER program is a population-based cancer registry system collecting data from 18 registries among 14 states across the US, representing nearly 30% of the US population. The inclusion criteria for data extraction in this study were (1) patients aged 18–100 years and diagnosed with EC between 2010 and 2015; and (2) patients confirmed to have distant metastasis at initial diagnosis. The exclusion criteria included (1) patients with a pathology type other than adenocarcinoma or squamous cell carcinoma; and (2) patients with missing or incomplete data such as survival status and time, age, sex, race, grade, T stage, N stage, primary tumor site, metastatic sites, number of metastatic organs, pathological type, local treatment, and chemotherapy. The demographic and clinicopathological data of all eligible cases were collected and retrospectively analyzed.

Endpoint Definition

EC-specific death was defined as death from EC as the underlying cause according to the SEER database. The endpoint of the current study was cancer-specific survival (CSS), which was the interval between the initial diagnosis of EC and the occurrence of EC-specific death.

Statistical Methods

All of the eligible cases were randomly divided into either the training or validation cohort (the split ratio was 7:3), with the training cohort being used to establish the predictive model and to construct the nomogram and risk classification system. Validation of the model was carried out using the data from the validation cohort.

The nomogram and risk classification systems were built as follows. First, a univariate Cox proportional hazards model was used to check each parameter's power in predicting CSS. Second, factors with a p value < 0.05 in univariate analysis were further analyzed in a multivariate Cox proportional hazards model using a backwards model selection procedure (elimination criterion: $p > 0.10$). Finally, factors that were included in the final model were utilized to build the nomogram and risk classification system.

According to the regression coefficients of each factor in the multivariate analysis, the predictive model was virtualized by the nomogram. The validation of the nomogram was performed using the concordance index (C-index), calibration curves, and decision curve analyses (DCAs). The C-index was used to reflect the predictive accuracy and discrimination ability of each factor and of the nomogram. Calibration curves (500 bootstrap resamples) were generated to test the calibration of the nomogram, and DCAs were performed to assess the clinical usefulness of the novel nomogram. In addition, a risk classification system was established according to the total scores of each patient in the training cohort by using the nomogram to divide all patients into three prognostic groups with a similar number of cases, i.e. the low-, intermediate-, and high-risk groups. Kaplan–Meier curves and the log-rank test were used to illustrate and compare the CSS of patients in the different risk groups.

Data extraction was performed using SEER*Stat software version 8.3.5 (www.seer.cancer.gov/seerstat). Data analyses were performed using R software version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS version 25.0 (IBM Corporation, Armonk, NY, USA). All tests were two-sided. A p value < 0.1 was chosen as the criterion for removing a variable from the multivariate Cox proportional hazards model, and a p-value < 0.05 was considered significant for all other tests.

RESULTS

Patient Characteristics

A total of 1917 eligible patients from 2010 to 2015 were identified from the SEER database. All cases were confirmed to have mEC at the initial diagnosis. The baseline

clinicopathological characteristics and treatment experience of all patients are summarized in Table 1. The median age of all patients was 63 years, the majority of cases were male and had adenocarcinoma ($n = 1625$ [84.8%] and $n = 1438$ [75.0%], respectively), and the median follow-up time was 31 months. All eligible cases were randomly divided into the training (1342, 70%) and validation cohorts (575, 30%). At the end of follow-up, EC-specific death had occurred in 1559/1917 (81.3%), 1087/1342 (81.0%), and 472/575 (82.1%) patients in the total, training, and validation cohorts, respectively. The median CSS was 6.0 months (95% confidence interval [CI] 5.4–6.6), 6.0 months (95% CI 5.1–6.9), and 6.0 months (95% CI 5.5–6.5) in the total, training, and validation cohorts, respectively (log-rank test, training vs. validation cohort: $p = 0.904$). The baseline characteristics were balanced between the training and validation cohorts (Table 1).

Univariate and Multivariate Analyses and Identification of Predictive Factors

The Cox proportional hazards model was performed in the training cohort to investigate each variable's power in predicting the CSS. Univariate analyses indicated that factors such as age, sex, race, grade at diagnosis, metastatic sites at diagnosis, number of metastatic organs at diagnosis, pathological type, radiation therapy (RT), and chemotherapy were associated with patients' prognosis (Table 2a). Among these factors, the number of metastatic organs at diagnosis (C-index = 0.565), RT (C-index = 0.558), and chemotherapy (C-index = 0.666) had superior discrimination power in predicting CSS compared with other factors. Factors with a p value < 0.05 in univariate analyses were further analyzed in the multivariate analyses using a backward model selection procedure (elimination criterion: $p > 0.10$). Finally, factors such as age, sex, grade at diagnosis, number of metastatic organs at diagnosis, pathological type, RT, and chemotherapy were identified as independent predictors of CSS and were included in the predictive model (Table 2b).

Building and Validating the Novel Nomogram

The predictive model was virtually presented in the form of a nomogram (Fig. 1), and was validated using the validation cohort. The C-index of the novel nomogram was 0.762, reflecting the good discrimination ability of the model. The calibration curves also showed good consistency in the probability of 6-, 12-, and 18-month CSS between the actual observation and the nomogram prediction (Fig. 2a–c). In addition, DCA exhibited great positive net benefits in the predictive model among almost all of the threshold probabilities at different time points, indicating the favorable potential clinical effect of the predictive model (Fig. 2d–f).

Risk Classification System

In addition to the nomogram, a risk classification system for CSS was also developed according to the total scores of each patient in the training cohort produced by the nomogram to divide all patients into three prognostic groups, with a similar number of cases per group. Based on the novel classification system, all patients were classified into the low-risk (599/1917, 31.2%; score 0–55.0), intermediate-risk (654/1917, 32.8%; score 55.1–110.0), or high-risk groups (664/1917, 33.1%; score 110.1–237.0) (Fig. 1). The Kaplan–Meier curves showed that CSS in the different groups was accurately differentiated by the risk classification system (Fig. 3). In the total cohort, the median CSS of patients in the low-, intermediate-, and high-risk groups was 11.0 months (95% CI 10.1–11.9), 8.0 months (95% CI 7.3–8.7), and 2.0 months (95% CI 1.8–2.2), respectively.

DISCUSSION

mEC is the end stage of EC and has a poor prognosis. Due to its high heterogeneity and the discrepancy in treatment choices for different patients, the survival outcome of mEC varies from patient to patient. To date, no predictive model is available for predicting the prognosis of patients with mEC. In this study, based on the patients' pretreatment clinicopathological characteristics and treatment regimens, we established and validated a nomogram and a risk classification system predicting the CSS of patients with mEC. The predictive factors included in the predictive model can be conveniently obtained from clinical practices. The validation of the model using different statistical methods demonstrated its great performance.

According to a recent review, there were 23 existing studies in which a nomogram was constructed to predict the prognosis of EC patients;[10] however, the majority of these studies focused on patients with localized EC, and only two studies were conducted in the setting of advanced EC.[11,12] Nonetheless, both studies had only a small sample size and included only a specific group of patients, thus inhibiting their generalization.

A review study also showed that the average C-index of the existing models was 0.75 (ranging from 0.65 to 0.85).[10] The C-index of the novel nomogram in our study was 0.762, which is higher than that of most of the other previous models. Furthermore, in addition to a nomogram, a risk classification, which could satisfactorily separate the

TABLE 1 Baseline clinicopathological characteristics and treatment experience of all patients and those in the training and validation cohort

	All cohorts (N = 1917)	Training cohort (n = 1342)	Validation cohort (n = 575)	p value[a]
Age, years				
Median (IQR)	63 (56–71)	63 (56–71)	64 (57–71)	
≤ 75	1611 (84.0)	1123 (83.7)	488 (84.9)	0.515
> 75	306 (16.0)	219 (16.3)	87 (15.1)	
Sex				
Male	1625 (84.8)	1147 (85.5)	478 (83.1)	0.192
Female	292 (15.2)	195 (14.5)	97 (16.9)	
Race				
White	1625 (84.8)	1139 (84.9)	486 (84.5)	0.844
Other	292 (15.2)	203 (15.1)	89 (15.5)	
Grade				
Well/moderately differentiated	755 (39.4)	537 (40.0)	218 (37.9)	0.388
Poorly differentiated	1162 (60.6)	805 (60.0)	357 (62.1)	
T stage				
T1–2	810 (42.3)	570 (42.5)	240 (41.7)	0.765
T3–4	1107 (57.7)	772 (57.5)	335 (58.3)	
N stage				
N1–2	1543 (80.5)	1080 (80.5)	463 (80.5)	0.982
N3–4	374 (19.5)	262 (19.5)	112 (19.5)	
Primary tumor site				
Upper	89 (4.6)	58 (4.3)	31 (5.4)	0.398
Middle	256 (13.4)	189 (14.1)	67 (11.7)	
Lower	1442 (75.2)	1006 (75.0)	436 (75.8)	
Overlapping	130 (6.8)	89 (6.6)	41 (7.1)	
Metastatic sites				
Distant lymph node(s) only	269 (14.0)	193 (14.4)	76 (13.2)	0.501
With visceral metastasis	1648 (86.0)	1149 (85.6)	499 (86.8)	
Number of metastatic organs				
0	426 (22.2)	296 (22.1)	130 (22.6)	0.583
1	1043 (54.4)	742 (55.3)	301 (52.3)	
2	379 (19.8)	259 (19.3)	120 (20.9)	
≥ 3	69 (3.6)	45 (3.4)	24 (4.2)	
Pathological type				
Adenocarcinoma	1438 (75.0)	1000 (74.5)	438 (76.2)	0.442
Squamous cell carcinoma	479 (25.0)	342 (25.5)	137 (23.8)	
Local treatment				
No local treatment	1091 (56.9)	759 (56.6)	332 (57.7)	0.632
RT	826 (43.1)	583 (43.4)	243 (42.3)	
Chemotherapy				
With	636 (33.2)	439 (32.7)	197 (34.3)	0.509
Without	1281 (66.8)	903 (67.3)	378 (65.7)	

Data are expressed as n (%) unless otherwise specified

RT radiation therapy, *IQR* interquartile range

[a]Chi square test

whole mEC cohort into three distinct prognostic groups and supplement the nomogram, was developed in the present study.

Among the five parameters included in the novel nomogram, the number of visceral metastasis organs had the highest discriminating power. There are very few

TABLE 2 Univariate and multivariate analyses of each factor's ability in predicting CSS

(a) Univariate analyses	HR	95% CI of HR	*p* value	C-index
Age, years				
> 75 versus ≤ 75	1.351	1.152–1.584	0.000	0.528
Sex				
Female versus male	0.832	0.721–0.959	0.011	0.508
Race				
White versus other	1.136	0.965–1.336	0.125	0.510
Grade				
Poorly versus well/moderately differentiated	1.145	1.013–1.293	0.030	0.515
T stage				
T3–4 versus T1–2	0.910	0.807–1.026	0.123	0.523
N stage				
N3–4 versus N1–2	1.003	0.861–1.169	0.968	0.491
Metastatic sites				
With visceral metastasis versus distant lymph node(s) only	1.383	1.163–1.644	0.000	0.530
Tumor site				
Middle versus upper	0.899	0.653–1.238	0.514	0.514
Lower versus upper	0.901	0.678–1.195	0.468	
Overlapping versus upper	1.198	0.841–1.705	0.317	
Number of metastatic organs				
1 versus 0	1.333	1.144–1.552	0.000	0.565
2 versus 0	1.763	1.465–2.121	0.000	
≥ 3 versus 0	2.086	1.478–2.946	0.000	
Pathological type				
Squamous cell carcinoma versus adenocarcinoma	1.147	1.001–1.313	0.048	0.524
Local treatment				
RT vs. no local treatment	0.876	0.825–0.930	0.000	0.558
Chemotherapy				
With versus without	0.319	0.280–0.362	0.000	0.666

(b) Multivariate analyses	HR	95% CI of HR	*p* value
Age, years			
> 75 versus ≤ 75	1.159	0.983–1.367	0.080
Sex			
Female versus male	0.810	0.678–0.967	0.020
Grade			
Poorly versus well/moderately differentiated	1.150	1.017–1.300	0.025
Number of metastatic organs			
1 versus 0	1.245	1.067–1.453	0.005
2 versus 0	1.650	1.368–1.989	0.000
≥ 3 versus 0	2.157	1.523–3.055	0.000
Pathological type			
Squamous cell carcinoma versus adenocarcinoma	1.171	1.018–1.348	0.027
Local treatment			
RT versus no local treatment	0.914	0.860–0.972	0.004
Chemotherapy			
With versus without	0.337	0.295–0.384	0.000

CSS cancer-specific survival, *HR* hazard ratio, *CI* confidence interval, *C-index* concordance index, *RT* radiation therapy

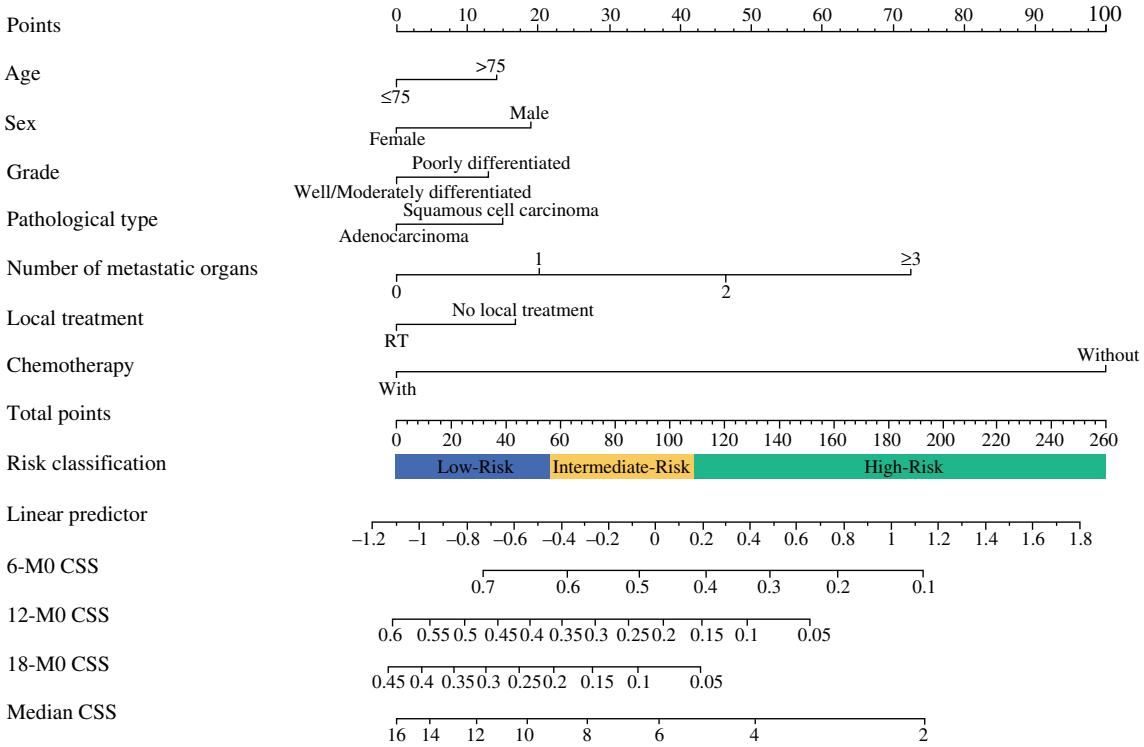

FIG. 1 Nomogram predicting the CSS for patients with initially diagnosed mEC. For every patient, seven lines are drawn upward to determine the points received from the seven predictors in the nomogram. The sum of these points is located on the 'Total Points' axis. In addition, a line is drawn downward to determine the possibility of 6-, 12-, and 18-month CSS, and the median CSS for patients with the same total score. Furthermore, according to the total scores, the risk group that the patient belongs to could be obtained. *MO* month, *CSS* cancer-specific survival, *mEC* metastatic esophageal cancer, *RT* radiation therapy

studies focusing on the number of visceral metastasis organs and patient prognosis in mEC. In 2017, Chen and colleagues found that mEC patients with multiorgan metastasis had a prognosis inferior to that of those with single-organ metastasis.[13] In the same year, Ai et al. also reported a similar finding that the number of metastatic sites was accompanied by poorer OS in mEC patients.[14] In this study, both metastatic sites (distant lymph nodes only vs. those with visceral metastasis) and the number of metastatic organs was a predictor of CSS in univariate analyses, while the predictive ability of the metastatic sites was lost in multivariate analyses, which implied that the number of metastatic sites was the more pivotal prognosticator. In addition, age, sex, grade at diagnosis, and pathological type were identified as prognosticators of mEC, consistent with the findings of previous studies.[6,15–18]

Despite the lack of high-level evidence, National Comprehensive Cancer Network (NCCN) guidelines recommend chemotherapy as the first-line treatment for patients with either adenocarcinoma or squamous cell carcinoma mEC.[19] Notably, according to our nomogram, chemotherapy was the single most powerful prognosticator of CSS, with the highest C-index among all predictive factors. This result enhanced the status of palliative chemotherapy in treating mEC. From the overall perspective, most clinical trials reported that chemotherapy was positively associated with a survival benefit for mEC patients,[20–23] and that it could also improve the quality of life of mEC patients.[24]

However, there are still several issues regarding chemotherapy in mEC that remain to be settled. The most critical issue is that there is no generally accepted standard regimen of chemotherapy for mEC patients. Additionally, whether triplet or doublet chemotherapy should be considered as first-line treatment in mEC patients is still controversial. A recent review study showed that although triplet treatment seemed to have a slightly better survival advantage over doublet therapy in mEC patients, it was accompanied by an increased risk of side effects.[25] In the current study, since the details of chemotherapy for a certain patient could not be acquired from the SEER database, subgroup analyses according to different chemotherapy regimens were not carried out.

In addition to palliative chemotherapy, local treatment also had a role in the management of mEC. The value of RT in mEC was explored in several studies. Definitive RT to the primary lesion has been proven to be associated with

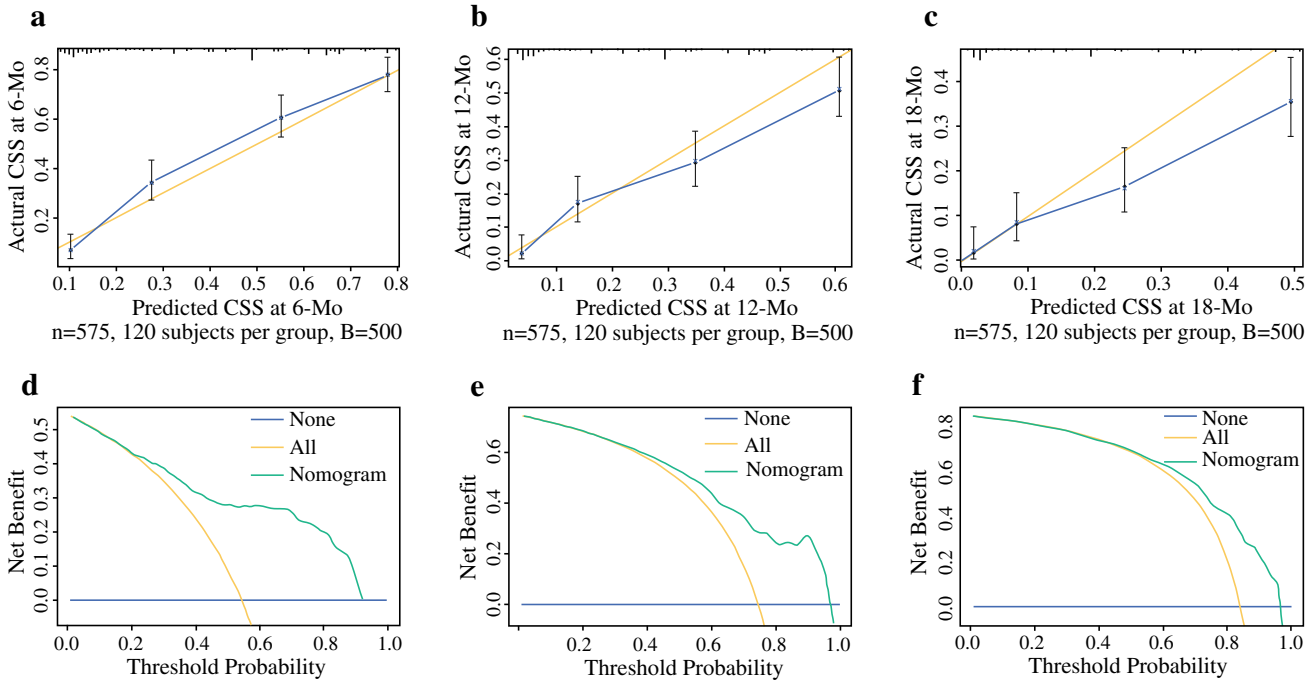

FIG. 2 **a–c** Calibration curves showing the probability of 6-, 12-, and 18-month CSS between the nomogram prediction and the actual observation. Perfect prediction would correspond to a slope of 1 (diagonal 45-degree gray line). **d–f** Decision curves of the nomogram predicting CSS. The *x*-axis represents the threshold probabilities, and the *y*-axis measures the net benefit calculated by adding the true positives and subtracting the false positives. The horizontal line along the *x*-axis assumes that cancer-specific death occurred in no patients, whereas the solid gray line assumes that all patients will have cancer-specific death at a specific threshold probability. The dashed line represents the net benefit of using the nomogram. *CSS* cancer-specific survival, *Mo* month

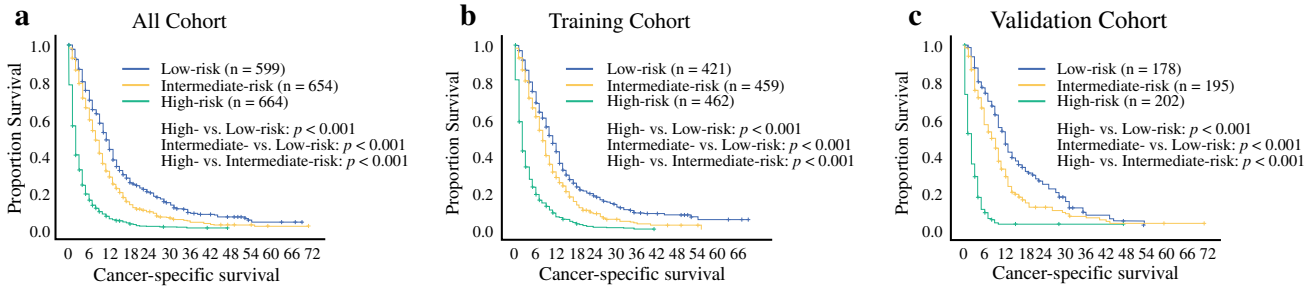

FIG. 3 Kaplan–Meier curves of CSS for patients in the low-, intermediate-, and high-risk groups. *CSS* cancer-specific survival

a longer survival time for mEC patients;[17,18,26] however, the therapeutic efficacy of palliative RT is controversial. Two studies with a relatively small sample size both came to a similar conclusion that palliative chemotherapy combined with palliative RT could significantly extend the OS of mEC patients (18.3 vs. 10.2 months, $p = 0.001$; and 17.3 vs. 8.3 months, $p = 0.006$, respectively).[27,28] However, the results of a different study with a larger sample size indicated that definitive but not palliative RT was associated with improved OS for this group of patients.[26] In addition, De et al. found that RT (including both definitive and palliative treatment) could effectively prolong the OS of mEC patients, while definitive RT showed a survival extension superior to that of palliative RT.[17] The above studies support the idea that for patients with mEC, local control is of great importance in improving patients' prognosis, which is in accordance with what the novel nomogram in this study revealed.

There are several limitations in our study. First, this study was a retrospective analysis with inherent biases. Second, the predictive model was developed based on data obtained from the SEER database, which cannot represent the global population. Third, due to the limitations of the SEER database, the details of the chemotherapy regimens and radiotherapy doses could not be obtained, which hindered further prognostic analyses based on detailed treatment schemes. Finally, although the nomogram and

risk classification were built using a large cohort, and validated in a split subgroup of patients, an external validation of the predictive model is still necessary.

CONCLUSIONS

We built a nomogram and a corresponding risk classification system for predicting the CSS of patients with initially diagnosed mEC using five clinicopathological factors and two treatment-related factors. The validation of the model proved its great performance. Although future external validation is needed, these tools can be useful in assisting patient counseling and guiding treatment decision making in areas such as prognostic evaluation, individualized therapy, and clinical trial design.

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