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Research Paper

Development and validation of a nomogram for prognosis of bone metastatic disease in patients with esophageal squamous cell carcinoma: A retrospective study in the SEER database and China cohort

Bo Huang [a,b,1], Wei-Dong Wang [a,1], Fang-Cai Wu [c,d,1], Xiao-Mei Wang [e], Bu-Qing Shao [e], Ying-Miao Lin [e], Guo-Xing Zheng [a,b], Gui-Qiang Li [a,b], Can-Tong Liu [d,e], Yi-Wei Xu [d,e,**], Xin-Jia Wang [a,b,d,*]

[a] Department of Orthopedics, the Cancer Hospital of Shantou University Medical College, Shantou 515041 Guangdong, China
[b] Department of Orthopedics, the Second Affiliated Hospital of Shantou University Medical College, Shantou 515000 Guangdong, China
[c] Department of Radiation Oncology, the Cancer Hospital of Shantou University Medical College, Shantou 515041 Guangdong, China
[d] Esophageal Cancer Prevention and Control Research Center, the Cancer Hospital of Shantou University Medical College, Shantou 515041 Guangdong, China
[e] Department of Clinical Laboratory Medicine, the Cancer Hospital of Shantou University Medical College, Shantou 515041 Guangdong, China

HIGHLIGHTS

- Identified independent prognostic factors for esophageal squamous cell carcinoma bone metastasis via SEER database analysis.
- Externally validated the prognostic nomogram in a Chinese real-world cohort, enhancing prediction reliability.

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ABSTRACT

Purpose: Esophageal squamous cell carcinoma (ESCC) is a prevalent malignant tumor worldwide, and individuals with ESCC and bone metastasis (BM) often face a challenging prognosis. Our objective was to identify the risk and prognostic factors associated with BM in patients with ESCC and develop a nomogram for predicting Cancer-Specific Survival (CSS) which following the occurrence of BM.

Methods: We conducted a retrospective analysis of data pertaining to ESCC patients with BM registered in the Surveillance, Epidemiology, and End Results (SEER) database from 2010 to 2015, as well as those treated at a Chinese institution from 2006 to 2020. Significant prognostic factors for CSS were assessed through univariate and multivariate Cox regression analyses. Subsequently, a nomogram was developed utilizing the SEER database and externally validated using real-world evidence from a Chinese cohort.

Results: A total of 266 patients from the SEER database and 168 patients from the Chinese cohort were included in the analysis. In the SEER cohort, multivariate analysis indicated that chemotherapy, radiotherapy, liver metastasis, brain metastasis, and sex were independent prognostic factors for ESCC with BM. The prognostic nomogram demonstrated areas under the ROC curve (AUCs) of 0.823, 0.796, and 0.800, respectively, for predicting 3-, 6-, and 12-month CSS. In the Chinese validation cohort, the nomogram exhibited acceptable discrimination (AUCs: 0.822, 0.763, and 0.727) and calibration ability.

Abbreviations: EC, Esophageal cancer; ESCC, Esophageal squamous cell carcinoma; EAC, Esophageal adenocarcinoma; BM, Bone metastasis; SEER, the Surveillance, Epidemiology, and End Results database; ICD-O-3, International Classification of Diseases for Oncology; CSS, Cancer-Specific Survival; HR, Hazard ratio; CI, Confidence interval; ROC, Receiver operating characteristic; C-index, Concordance index; AUC, the area under the ROC curve; DCA, decision curve analysis; AJCC, American Joint Committee on Cancer; TNM, Tumor-node-metastasis; NCCN, National Comprehensive Cancer Network.

* Corresponding author at: Department of Orthopedics, the Cancer Hospital of Shantou University Medical College, Shantou 515041, Guangdong, China.
** Corresponding authors at: Esophageal Cancer Prevention and Control Research Center, the Cancer Hospital of Shantou University Medical College, Shantou 515041, Guangdong, China.
E-mail addresses: yiwei512@126.com (Y.-W. Xu), xjwang4@stu.edu.cn (X.-J. Wang).
[1] These authors contributed equally to this work and share first authorship.

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Conclusion: The study developed a prognostic nomogram to predict CSS in ESCC patients with BM, which can help clinicians assess survival and make individualized treatment decisions.

1. Introduction

Esophageal cancer (EC) is a common malignancy, ranking 11th in terms of incidence and seventh in mortality worldwide [1]. In 2022, Esophageal cancer accounted for 2.6 % of all new cancer cases [1]. According to Cancer Statistics 2024, the 5-year relative survival rate of Esophageal cancer in the United States remains dismal at 22 % [2]. The main histological subtypes of esophageal carcinoma are esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC). Of these, ESCC dominates the esophageal cancer burden and accounts for 85 % of the newly diagnosed cases in 2020 [3]. The prognosis of ESCC is generally poor, especially when metastasis is present. According to a previous study focusing on esophageal squamous cell carcinoma patients with distant organ metastasis at initial diagnosis, the median survival time was 6 months, with a two-year survival rate of approximately 11.8 % [4]. To address these challenges, treatment paradigms have evolved from traditional modalities (surgery, radiation, chemotherapy) to molecular-targeted therapies and immunotherapies, driven by genomic profiling and biomarker-guided strategies [5].

Bone metastasis (BM) is a frequent occurrence in malignant tumors, including those of the esophagus [6]. In patients with esophageal cancer, bone ranks as the third most common site of metastasis[7]. Compared to other metastatic sites, BM is associated with poorer survival, such as the liver, brain, and lung [6,8]. Once bone metastasis occurs in patients with ESCC, they may experience a range of skeletal-related symptoms that significantly impair their quality of life, including pathological fractures, hypercalcemia, and nerve compression syndromes. For clinicians, the treatment objectives for advanced ESCC are to enhance quality of life, manage complications, and prolong survival time through various treatment modalities. A better understanding of the prognosis may drive more individualized treatment regimens for each patient, as well as more cost-effective allocation of healthcare resources. Currently, the prognostic assessment for cancer patients primarily relies on TNM staging [9]. However, several studies have suggested that the conventional TNM staging system, which predominantly focuses on three pathological indicators while overlooking other important prognostic factors, exhibits limited accuracy in predicting prognosis for cancer patients [10,11]. Various studies have been conducted to develop a comprehensive tool by integrating clinicopathological factors and other prognosis-related indicators to offer precise prognosis prediction for EC patients [12–14]. Prognostic research on cancer subtypes represents a critical pillar of precision medicine, enabling the transition from population-based to individualized therapeutic strategies by decoding disease heterogeneity, thereby improving survival outcomes and quality of life. Current many cancer studies have explored cancer subtypes, exemplified by investigations into the role of Cornichon family AMPA receptor auxiliary protein 4 (CNIH4) in head and neck squamous cell carcinoma [15], as well as the expression of cuproptosis and its potential immune implications in clear cell renal cell carcinoma [16]. Nevertheless, none of them have specifically focused on the unique histological subtype and metastatic site: esophageal squamous cell carcinoma with bone metastasis. Therefore, it is crucial to develop an accurate prognosis prediction for patients with ESCC accompanied by BM.

Nomogram is a tool that can integrate various factors, such as clinical, pathological, demographic, and oncological factors, to predict medical events and has gained popularity in predicting the prognosis of cancer patients [17,18]. Numerous contemporary studies emphasize the development of nomograms for prognostic stratification. For instance, Hengrui Liu et al. constructed a prognostic nomogram based on CNIH4 gene expression and patient age in their 2022 study, and developed a multi-parameter prognostic nomogram integrating clinical factors in their 2021 research [15,19]. When it comes to intuitively estimating the survival rates of cancer patients, nomograms possess an advantage in terms of accuracy compared to the traditional TNM staging system [20]. To date, numerous studies have employed nomograms as a predictive

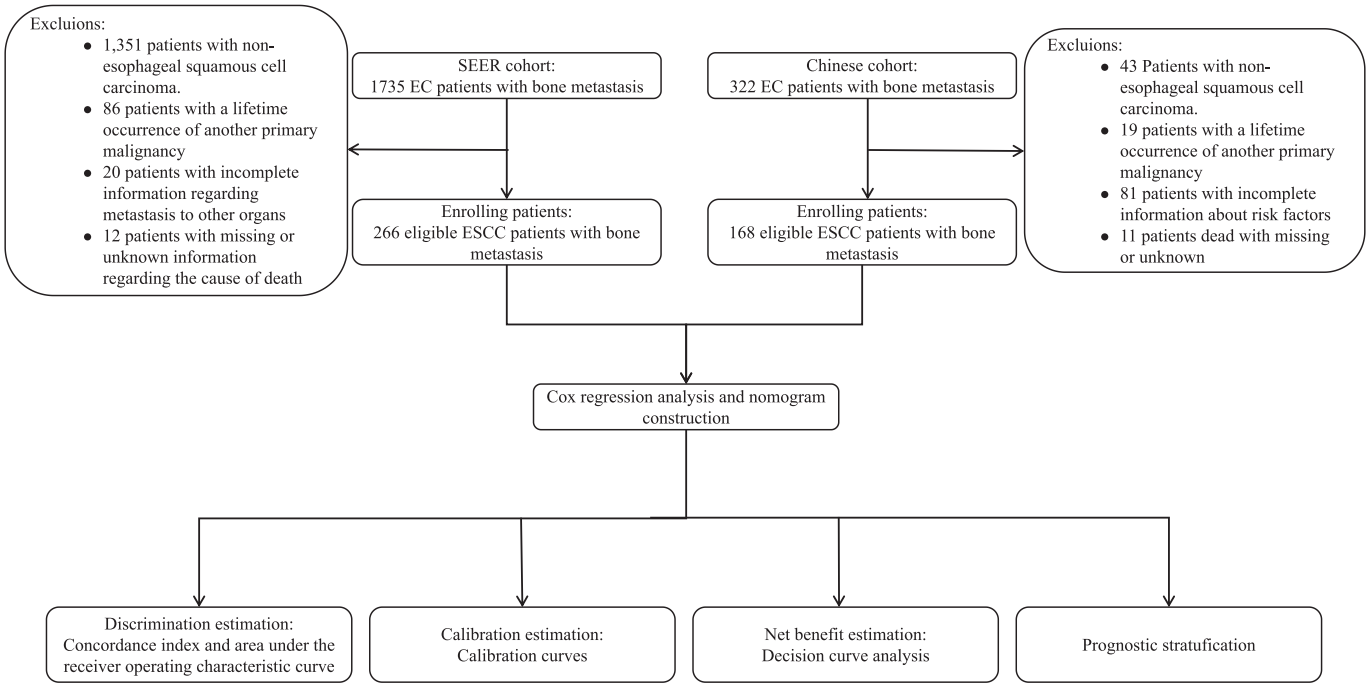

Fig. 1. Flow chart of the study.

tool for assessing the prognosis of cancer patients [21–23]. Recently, Qianhe Ren et al. [24] developed a novel nomogram integrating the Cancer-Associated Fibroblast (CAF)-based risk signature and clinical stage, which exhibited favorable predictability and reliability for ESCC prognosis prediction.

The aim of this study was to identify the clinical characteristics as independent prognostic factors and conduct a prognostic prediction nomogram for bone metastasis in ESCC patients, utilizing data from the Surveillance, Epidemiology, and End Results (SEER) database. Finally, these results were verified in the real-world evidence from a Chinese cohort.

2. Materials and methods

2.1. Patient population

We obtained the data of EC patients with bone metastasis diagnosed between 2010 and 2015 from the SEER database that were released in November 2019 using SEER*Stat 8.3.8. The SEER database is a population-based database sponsored by the National Cancer Institute in the USA that collects cancer incidence and survival data [25]. Available data include patient demographic, clinicopathological, and survival information. We identified 1735 cases of patients diagnosed with EC with bone metastasis based on the International Classification of Diseases for Oncology (ICD-O-3), 3rd edition. Exclusion criteria encompassed patients diagnosed with cancers other than ESCC, individuals with a history of another primary malignancy, patients with incomplete information regarding metastasis to other organs, and patients who died with missing or unknown cause.

Meanwhile, the Chinese cohort consisted of 322 EC patients with bone metastasis treated at Cancer Hospital of Shantou University Medical College from January 2006 to December 2020. Patients met the following inclusion criteria: 1) were diagnosed as primary EC with histopathological analysis; 2) had no other primary tumors; 3) were confirmed with bone metastasis by bone scan and/or CT [26,27]. Moreover, patients with other organ metastases were diagnosed by plain radiographs, CT, and/or MRI. We implemented the following exclusion criteria: patients who were diagnosed with a type of cancer other than ESCC, patients with incomplete information regarding risk factors, and individuals with missing or unknown information regarding the cause of death. Finally, a total of 266 patients from the SEER database and 168 patients from the Chinese cohort met all the eligibility criteria for our study (Fig. 1). In this SEER cohort, we extracted the demographic features: age at diagnosis, sex, and race. The clinical characteristics encompassed the evaluation of bone metastasis status, lung metastasis status, liver metastasis status, brain metastasis status, cause of death, as well as the T-stage and N-stage classifications based on the adjusted criteria of the seventh edition of the American Joint Committee on Cancer (AJCC). In both the SEER and China cohorts, the treatment (radiation therapy, chemotherapy, and surgery) was exclusively targeted at the primary tumor, with no interventions administered to bone metastases.

In this study, the primary endpoint of this study was Cancer-Specific Survival (CSS), which was defined as the classification of death recorded in the SEER database (alive or dead of other cause or cancer-associated death) and calculated from the date of bone metastasis diagnosis to the endpoint event (cancer-related death) or last follow-up. CSS specifically measures the survival rate related to the specific cause of cancer-related death, excluding deaths attributed to other causes.

2.2. Nomogram construction and nomogram evaluation

In the SEER database, we incorporated 12 variables (age, surgery, chemotherapy, radiotherapy, liver metastasis, brain metastasis, lung metastasis, primary site, T stage, N stage, race, and sex) to investigate the relationship between bone metastasis in ESCC patients and cancer-specific survival. Age was transformed from a continuous variable to a categorical variable using X-tile software [28], and was stratified into two groups: <75 years, and ≥ 75 years. We conducted Cox proportional hazards regression analysis to determine the hazard ratio (HR) and 95 % confidence interval (CI) for factors associated with Cancer-Specific Survival. Initially, univariate Cox regression analysis was performed to identify variables with p-values less than 0.05. Subsequently, a multivariate Cox proportional hazards regression analysis was conducted using these significant variables to develop a prognostic predictive model. Based on the Cox regression model, we created a nomogram using the "rms" package in R (https://CRAN.R-project.org/package = rms) to predict the 3-, 6-, and 12-months CSS rates in ESCC patients with bone metastases.

To assess the discriminatory ability of the nomogram, we constructed a receiver operating characteristic (ROC) curve. The effectiveness of the nomogram in predicting CSS was evaluated using the concordance index (C-index) and the area under the ROC curve (AUC). These values range from 0.5 (random prediction) to 1.0 (excellent prediction), with a value greater than 0.7 indicating good performance and moderate predictive capacity [29]. The ROC curve also provides information about accuracy, sensitivity, and specificity [30]. Calibration curves were generated using a bootstrap method with 1000 resamples to compare the agreement between the predicted CSS from the nomogram and the actual CSS. Additionally, a decision curve analysis (DCA) was performed to demonstrate the net benefit of different models [31,32].

Finally, the predicted total points were calculated based on the nomogram, and the patients from SEER database and Chinese cohort were respectively divided into low-risk or high-risk group according to the median value of total points obtained from SEER database (128). Subsequently, Kaplan-Meier survival analysis and the log-rank test were performed to assess the differences in survival outcomes between the two risk groups.

Table1
Patient characteristics of the SEER cohort.

Variables		SEER cohort (n = 266)
		Values (%)
Surgery	YES	4(1.5 %)
Radiotherapy	YES	136(51.13 %)
Chemotherapy	YES	133(50 %)
Liver metastasis	YES	78(29.32 %)
Lung metastasis	YES	96(36.09 %)
Brain metastasis	YES	17(6.39 %)
T-stage	T1	57(21.43 %)
	T2	9(3.38 %)
	T3	37(13.91 %)
	T4	60(22.56 %)
	Tx	102(38.35 %)
N-stage	N0	67(25.19 %)
	N1	134(50.38 %)
	N2	23(8.65 %)
	N3	12(4.51 %)
	Nx	30(11.28 %)
Primary tumor site	Upper third of esophagus	38(14.29 %)
	Middle third of esophagus	102(38.35 %)
	Lower third of esophagus	70(26.32 %)
	Overlapping lesion of esophagus	20(7.52 %)
	NOS	36(13.53 %)
Sex	Male	206(77.44 %)
	Female	60(22.56 %)
Age	≥75 years	31(11.65 %)
	< 75 years	235(88.34 %)
Race	White	146(54.89 %)
	Black	88(33.08 %)
	Other[a]	29(10.9 %)

NOS: not otherwise specified.
Definitive radiotherapy, chemotherapy, and surgery were delivered to the primary tumor.
[a] Including American Indian/AK Native, Asian/Pacific Islander.

Table2
Patient characteristics of the Chinese cohort.

Variables		Chinese cohort (n = 168)
		Values (%)
Surgery	YES	86(51.19 %)
Radiotherapy	YES	104(61.9 %)
Chemotherapy	YES	91(54.17 %)
Liver metastasis	YES	36(21.43 %)
Lung metastasis	YES	48(28.57 %)
Brain metastasis	YES	7(4.17 %)
T-stage	T1	4(2.38 %)
	T2	12(7.14 %)
	T3	52(30.95 %)
	T4	52(30.95 %)
	Unknow	49(29.17 %)
N-stage	N0	28(16.67 %)
	N1	57(33.93 %)
	N2	23(13.69 %)
	N3	12(7.14 %)
	Nx	1(0.6 %)
	Unknow	48(28.57 %)
Primary tumor site	Upper third of esophagus	37(22.02 %)
	Middle third of esophagus	89(52.98 %)
	Lower third of esophagus	36(21.43 %)
	Unknow	7(4.17 %)
Sex	Male	137(81.55 %)
	Female	31(18.45 %)
Age	≥75 years	9(5.3 %)
	< 75 years	159(94.6 %)

Definitive radiotherapy, chemotherapy, and surgery were delivered to the primary tumor.

2.3. Statistical analysis

In this study, all analyses, figures, and tables were conducted using Microsoft Excel (Redmond, WA, USA), X-tile version 3.6.1 (Version 3.6.1, Yale University), and R version 4.1.3 (https://www.r-project.org/). Descriptive statistics were employed to summarize qualitative data as the number of cases (percentage). The chi-square test or Fisher's exact test was used for intergroup comparisons of qualitative data. ROC curves and the corresponding area under the curve (AUC) were generated using the timeROC package in R (https://CRAN.R-project.org/package = timeROC). Decision curve analysis (DCA) was performed using the ggDCA package in R (https://CRAN.R-project.org/package = ggDCA). Kaplan-Meier survival curves were plotted using the survival and survminer packages in R (https://CRAN.R-project.org/package = survival). A p-value of < 0.05 (two-tailed) was considered statistically significant for all analyses.

3. Results

3.1. Baseline characteristics

A total of 266 ESCC patients with bone metastasis from the SEER database were included, comprising 206 (77.44 %) male and 60 (22.56 %) female patients (Table 1). Overall, 168 patients met the eligibility criteria in the Chinese cohort, 137 (81.55 %) were male, and 31 (18.45 %) were female (Table 2).

The median age of patients in the SEER cohort was 62 years (range: 39–90 years), while in the Chinese cohort it was 59 years (range: 38–79 years). Among the survivors, the median cancer-specific survival was 3 months (range: 0–97 months) in the SEER cohort, compared to 5 months (range: 0–129 months) in the Chinese cohort. During the follow-up period, cancer-associated deaths accounted for 98.12 % (261 out of 266) of patients in the SEER cohort, whereas in the Chinese cohort, this proportion was 94.64 % (159 out of 168) of patients.

According to the 7th edition of the AJCC-TNM classification, a greater proportion of patients in the SEER cohort were diagnosed with pathologic Tx cancer, whereas in Chinese cohort, the majority of

Table 3
Univariate and multivariate Cox regression analysis in esophageal squamous cell carcinoma patients with bone metastases in SEER cohort.

Variables	Univariate analysis		Multivariate analysis	
	HR (95 %CI)	P value	HR (95 %CI)	P value
Surgery				
No/Unknown	Ref.			
Yes	0.717 (0.267–1.926)	0.509		
Chemotherapy				
No/Unknown	Ref		Ref	
Yes	0.362 (0.281–0.466)	**< 0.001**	0.339 (0.253–0.453)	**< 0.001**
Radiotherapy				
No/Unknown	Ref		Ref	
Yes	0.621 (0.486–0.793)	**< 0.001**	0.666 (0.508–0.877)	**0.004**
Primary Site				
Upper third esophagus	Ref.			
Middle third esophagus	0.75 (0.514–1.092)	0.134		
Lower third esophagus	0.888 (0.596–1.322)	0.558		
Overlapping lesion	1.216 (0.706–2.096)	0.48		
NOS	1.196 (0.754–1.897)	0.448		
Lung metastasis				
No	Ref.			
Yes	0.950 (0.745–1.236)	0.75		
Liver metastasis				
No	Ref.		Ref.	
Yes	1.59 (1.212–2.086)	**< 0.001**	1.736 (1.301–2.318)	**< 0.001**
Brain metastasis				
No	Ref.		Ref.	
Yes	1.812 (1.099–2.987)	**0.020**	2.031 (1.200–3.438)	**0.008**
T stage				
T1	Ref.			
T2	0.538 (0.264–1.095)	0.087		
T3	0.695 (0.457—1.057)	0.089		
T4	1.255 (0.870–1.811)	0.223		
Tx	1.358 (0.975–1.890)	0.070		
N stage				
N0	Ref.			
N1	0.717 (0.532–0.967)	**0.029**	0.864 (0.632–1.180)	0.358
N2	0.830 (0.516–1.333)	0.44	0.847 (0.525–1.369)	0.499
N3	0.852 (0.459–1.580)	0.61	1.056 (0.568–1.961)	0.864
Nx	0.990 (0.639–1.519)	0.946	1.191 (0.766–1.851)	0.439
Race				
White	Ref.			
Black	0.982 (0.754–1.280)	0.894		
Other	0.818 (0.542–1.234)	0.338		
Age				
≥75 years	Ref.		Ref.	
< 75 years	2.002 (1.366–2.933)	**< 0.001**	1.465 (0.977–2.198)	0.064
Sex				
Female	Ref.		Ref.	
Male	1.353 (1.012–1.809)	**0.045**	1.956 (1.436–2.666)	**< 0.001**

Abbreviations: HR, hazard ratio; CI, confidence interval;
$P < 0.05$ was statistically significant.

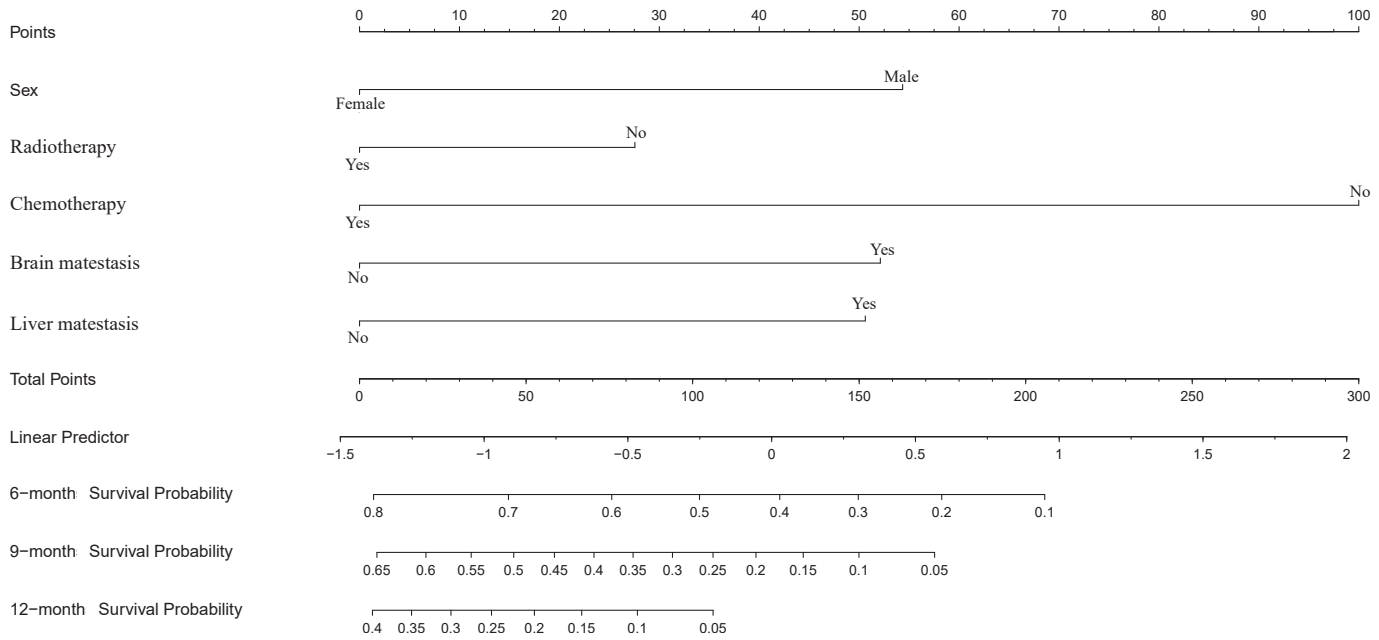

Fig. 2. Nomogram for 3-, 6-, and 12-month CSS prediction of the ESCC patients with bone metastasis. Each prognostic factor was assigned a point on the scale, and the sum of the total points projected on the bottom scale represent the probabilities of 3-, 6-, and 12-month CSS.

patients were diagnosed with T3 and T4 stage tumors. Additionally, the number of patients diagnosed with T1-stage tumors in the SEER database exceeded that in the Chinese cohort (21.43 % vs 2.38 %). The SEER cohort had a higher percentage of patients accompanied by other metastatic organs compared to the Chinese cohort (55.2 % vs 45.2 %). Therein, the results from both cohorts revealed that lung metastasis was the most common metastatic site in ESCC patients with bone metastasis, followed by liver and brain. In terms of treatment, radiotherapy was the primary modality employed for both the SEER and Chinese cohorts. However, with regard to surgical intervention for the primary tumor, the percentage of patients undergoing surgery in the Chinese cohort was significantly higher than that of the SEER cohort(51.2 % vs 1.5 %). (Table 1) (Table 2).

3.2. Cox proportional hazards regression analysis

In the SEER cohort, following univariate Cox regression analysis, 7 variables were found to be significantly associated with CSS, including age (≥75 years and < 75 years), chemotherapy, radiotherapy, liver metastasis, brain metastasis, N stage (N0, N1, N2, N3, Nx and unknow), and sex (Male and Female) (all $p < 0.05$). Subsequently, a prognostic model was developed after adjusting for confounding variables through multivariate Cox regression. This model, as presented in Table 3, identified five variables as independent prognostic factors. These included chemotherapy (HR: 0.339; 95 % CI: 0.253–0.453; $p < 0.001$), radiotherapy (HR: 0.666; 95 % CI: 0.508–0.877; $p = 0.004$), liver metastasis (HR: 1.736; 95 % CI: 1.301–2.318; $p < 0.001$), brain metastasis (HR: 2.031; 95 % CI: 1.200–3.438; $p = 0.008$), and sex (HR: 1.956; 95 % CI: 1.436–2.666; $p < 0.001$).

3.3. Construction of 1-, 3-, and 5-year CSS predicting nomogram

Based on the identified prognostic factors in the SEER cohort, a nomogram, shown in Fig. 2, was developed to predict CSS. In the

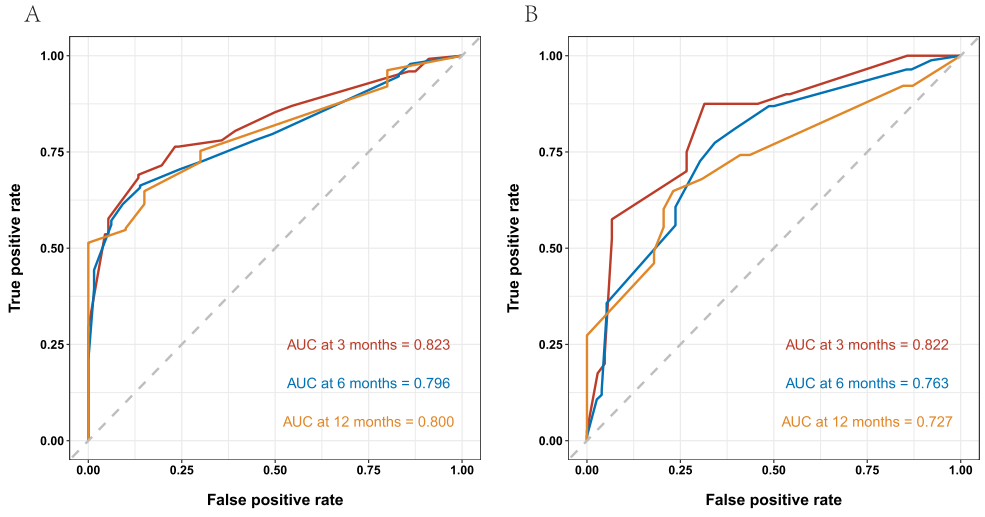

Fig. 3. Receiver operating characteristic (ROC) curves of 3-, 6-, and 12-month in the SEER database(A) and Chinese cohorts (B), respectively. The area under the ROC curve (AUC) was 0.823, 0.796, and 0.800 in the SEER database, and 0.822, 0.763, and 0.727 in the Chinese cohorts, respectively.

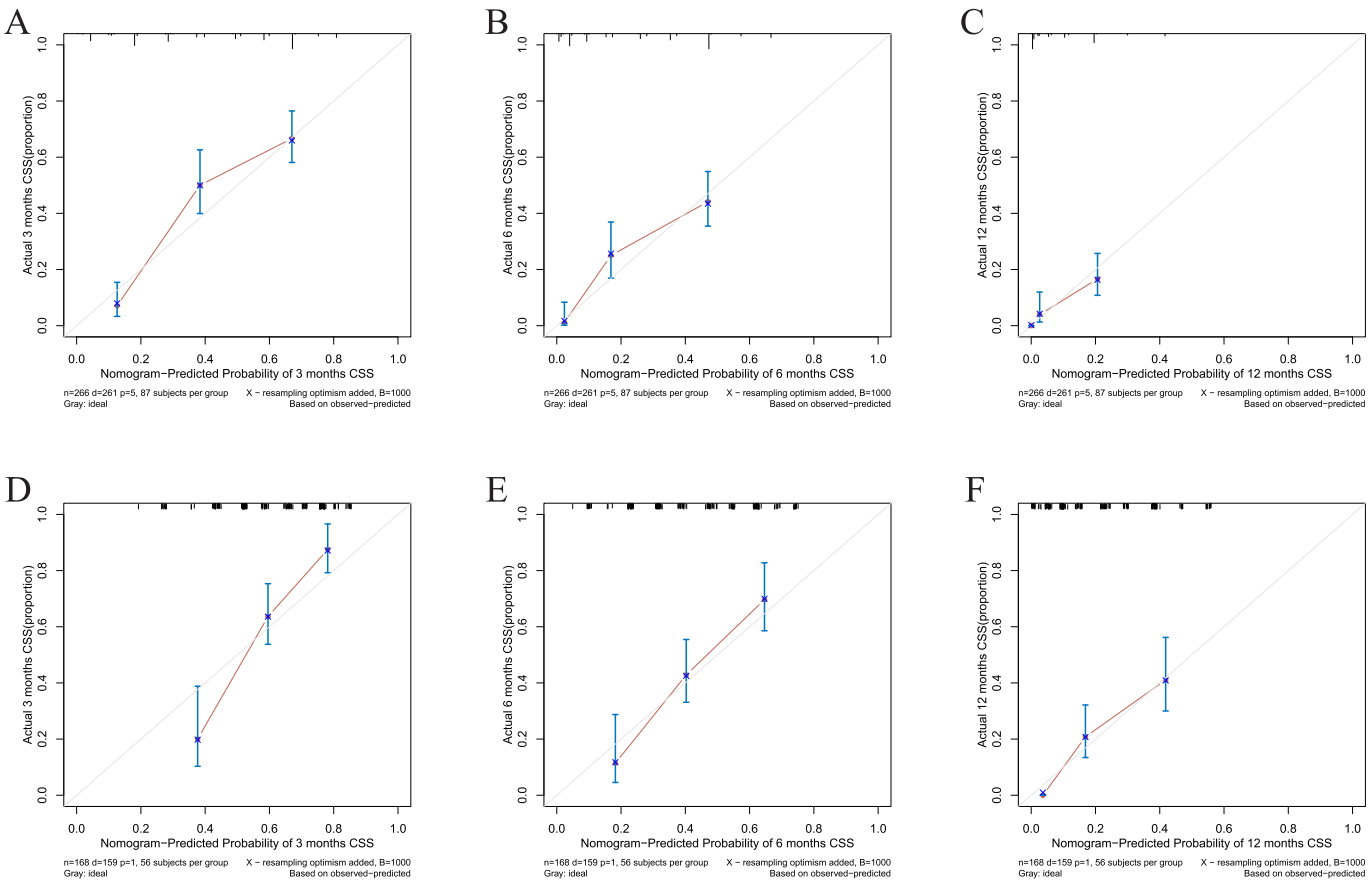

Fig. 4. The calibration curves of the prognostic nomogram for the 3-, 6-, and 12-month CSS prediction of the SEER database (A–C) and Chinese cohort (D–F). The calibration curves suggested that the predictive outcome have good accordance with the actual 3-, 6-, and 12-month CSS in both groups.

prognostic nomogram, each variable was assigned a point scale to quantify its contribution to CSS. A line was then drawn upward to the points axis for each variable to determine the corresponding points. By summing the scores of all variables, an individual total risk score was calculated, allowing for an intuitive estimation of 1-, 3-, or 5-year CSS. The nomogram revealed that chemotherapy exerted the most significant impact on CSS prediction, followed by sex [12].

3.4. Evaluation of the CSS predicting nomogram

In Fig. 3, the nomogram demonstrated an AUC of 0.823, 0.796, and 0.800 for predicting 3-, 6-, and 12-month CSS in the SEER cohort, and 0.822, 0.763, and 0.727 in the Chinese cohort, respectively. Additionally, the C-index of this model was 0.727. Evidently, both the AUC and C-index exceeding 0.7 indicate that our nomogram possessed a moderate predictive efficacy.

As shown in Fig. 4, Calibration curves in both cohorts illustrated strong agreement between the nomogram-predicted CSS and the actual CSS. Moreover, the decision curve analysis curves, shown in Fig. 5, revealed significant clinical utility, demonstrating the model's maximal benefit within a specific range of preference values.

Subsequently, we generated a prognostic score using the Cox model and classified patients in SEER cohort into low-risk and high-risk groups based on the median value of the score. Specifically, patients with a prognostic score below 128 were placed in the low-risk groups, while those with a score of 128 or higher were placed in the high-risk group. Following this, Kaplan-Meier survival analysis and log-rank tests were employed to compare Cancer-Specific Survival between these two groups. Our results revealed that patients in the high-risk group exhibited significantly shorter CSS compared to those in the low-risk group ($p < 0.0001$, Fig. 6). Furthermore, similar analyses were performed in the Chinese cohort, yielding consistent results ($p < 0.0001$, as illustrated in Fig. 7).

4. Discussion

Although Squamous cell carcinoma was the most prevalent subtype among Esophageal cancer patients worldwide, distinct regional differences in incidence were observed between the two primary histological subtypes of esophageal cancer. Specifically, esophageal adenocarcinoma exhibited the highest incidence rates in Northern Europe and North America, while ESCC demonstrated the highest incidence rates in Eastern and South Central Asia and South Africa [3]. To mitigate the potential selection bias arising from histological subtypes between the Chinese single-center data and the SEER database, we excluded patients with adenocarcinoma in our analysis, focusing specifically on evaluating the prognosis of ESCC patients with bone metastasis. Survival analysis encompasses diverse methodological frameworks, with the Kaplan-Meier (KM) method representing a cornerstone technique in clinical outcome studies. However, KM analysis is limited to between-group comparisons of a single variable [33]. Therefore, to evaluate the effects of multiple variables on survival time, alternative methods such as Cox regression or Lasso analysis must be employed [34,35]. In this study, we utilize Cox regression analysis and constructed a prognostic predictive nomogram that incorporates five independent risk factors: sex, radiotherapy, chemotherapy, brain metastasis, and liver metastasis, to help clinicians to preliminarily assess the survival of ESCC patients with bone metastasis. Additionally, we have validated its efficacy by testing it on an external validation cohort, and observed favorable performance results.

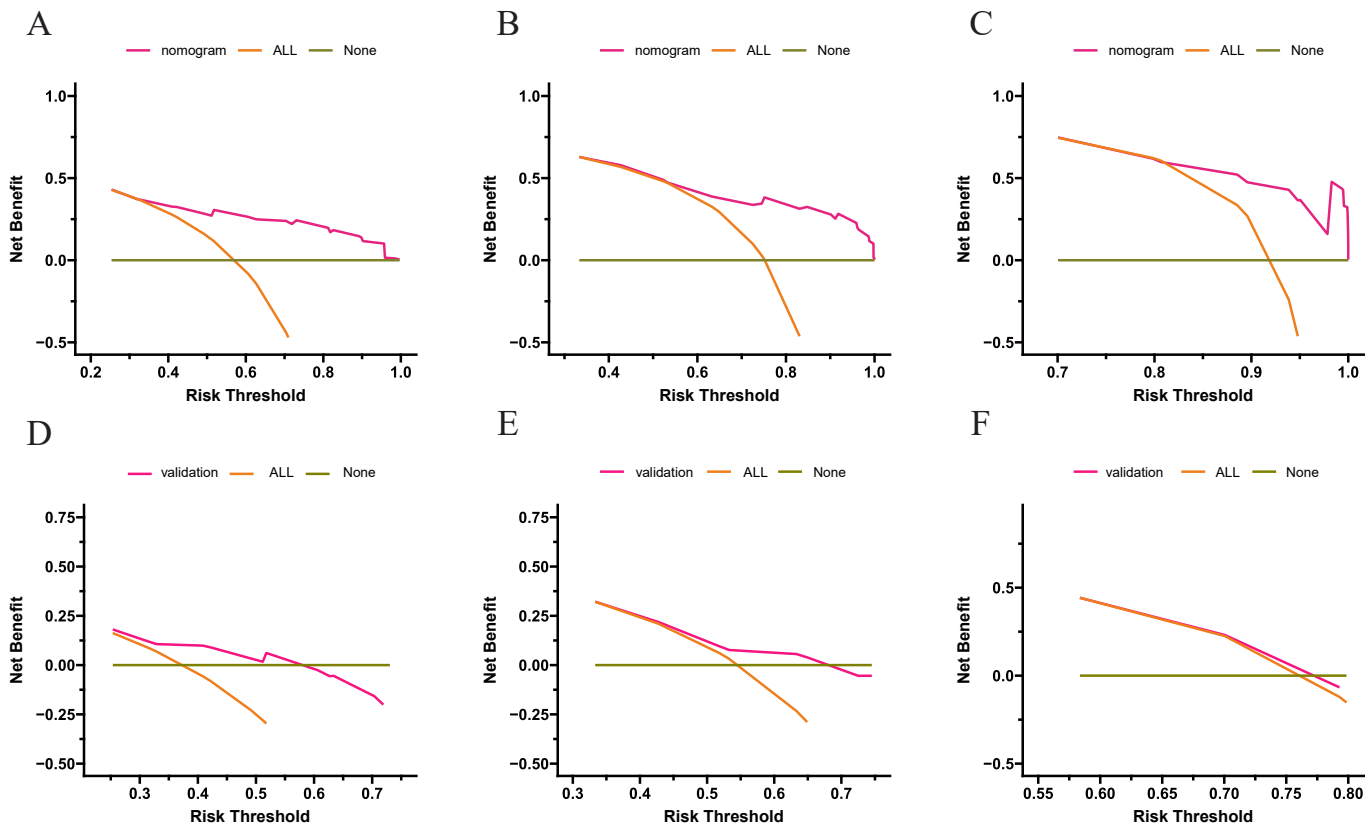

Fig. 5. DCA of the nomogram for the survival prediction of ESCC patients with bone metastasis in the SEER database and Chinese cohort. (A-C) 3-, 6-, and 12-month survival benefit in SEER database; (D-F) 3-, 6-, and 12-month survival benefit in Chinese cohorts. The "ALL", "None" and "Nomogram" lines are represented as "intervention for all" (orange line), "intervention for none" (blackish green line), and "result for the nomogram or validation" (pink line). The "None" and "ALL" lines would show the expected net benefit without and with the intervention development respectively. DCA curves showed that nomogram manifested a higher net clinical benefit than "None" and "All". (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

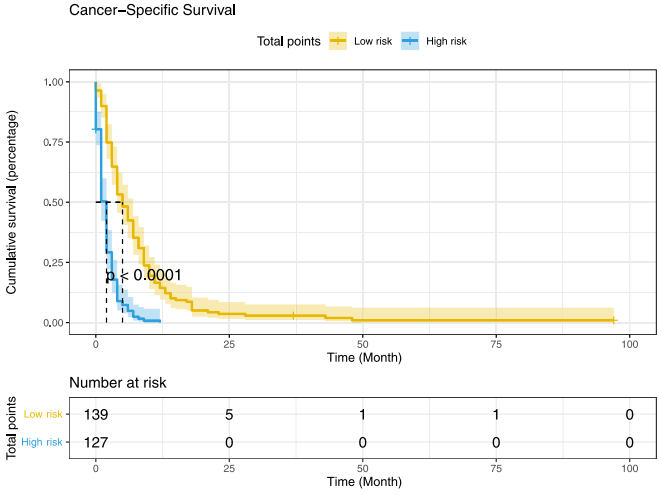

Fig. 6. Kaplan-Meier curve of risk stratification for CSS based on nomogram in SEER database. The low-risk and high-risk meant prognostic scores < 128 and ≥ 128 for CSS, respectively. Log-rank test was applied to estimate the significant difference.

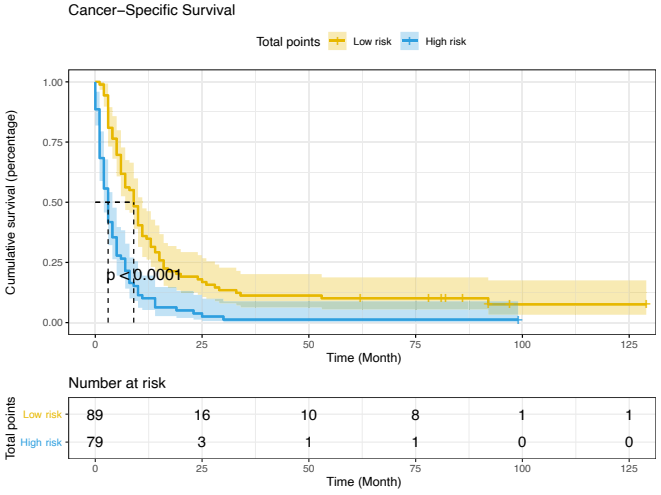

Fig. 7. Kaplan-Meier curve of risk stratification for CSS based on nomogram in Chinese cohort. The low-risk and high-risk meant prognostic scores < 128 and ≥ 128 for CSS, respectively. Log-rank test was applied to estimate the significant difference.

Several differences between the Chinese and SEER cohorts were observed in this study. In the SEER cohort, only 1.5 % of patients underwent primary cancer surgery, while in the Chinese cohort, 51.19 % received surgical treatment. This discrepancy likely stems from differences in disease stage at initial diagnosis and post-therapeutic surveillance. In the Chinese cohort, part of patients were diagnosed with localized, resectable ESCC and underwent curative-intent surgery. Subsequent bone metastases in these patients were detected during the follow-up. Conversely, the SEER database exclusively captures synchronous metastases (present at initial diagnosis) due to its lack of

longitudinal recurrence tracking. Furthermore, this methodological choice aligns with a prior external validation study in colorectal carcinoma patients with lung metastasis, where the validation cohort explicitly included individuals who had undergone primary tumor resection before pulmonary metastasis diagnosis [36]. Interestingly, the number of patients diagnosed with T1-stage tumors in the SEER cohort significantly exceeded that in the Chinese cohort. This finding aligns with a previous study on the prognostic role of the log odds of positive lymph nodes in ESCC patients (22.5 % vs. 8.5 %) [37]. Hence, there may be disparities in T-stage distribution between the two ESCC cohorts of Asian and Caucasian populations, warranting further research.

In our study, radiotherapy and chemotherapy were found to be positively associated with prognosis in ESCC patients with bone metastasis, with chemotherapy having the greatest impact on overall survival prediction. In support of this finding, we identified a relevant study by Jiang et al. [12]. Their nomogram for esophageal cancer patients with bone metastasis similarly highlights chemotherapy as a critical prognostic factor. This alignment underscores the consistent importance of chemotherapy in survival prediction models across different metastatic contexts. This finding aligns with established evidence regarding the prognostic benefits of chemotherapy in metastatic cancer [38,39]. To validate these findings mechanistically, future studies could employ patient-derived xenograft models, which have proven instrumental in recapitulating therapeutic responses [40]. According to the National Comprehensive Cancer Network (NCCN) guidelines chemotherapy is recommended as the first-line treatment for patients with metastatic EC [41]. Qiu et al. discovered that elderly patients who received chemotherapy had improved survival rates compared to those who did not, regardless of whether they underwent surgery or radiation therapy [8]. Radiotherapy is considered effective in relieving pain caused by BM in cancer patients. Previous analyses focusing on the overall population of esophageal cancer patients with bone metastasis indicated that radiotherapy was not an independent prognostic risk factor [12,42]. However, our study focusing on the ESCC patients with bone metastasis revealed a significant and protective association between radiotherapy and prognosis. Additionally, several retrospective and prospective studies have suggested that palliative radiotherapy may improve survival in metastatic EC, consistent with our findings [43,44].

In line with the Chinese cohort, the proportion of female patients in the SEER cohort was higher than that of male patients. Subsequent analysis revealed that males exhibited significantly higher cancer-specific survival rates compared to females. Consequently, gender was identified as a robust and independent prognostic factor. These observations are consistent with previous studies [45–47]. In addition, our study confirmed that brain and liver metastases were also significant prognostic variables in esophageal cancer patients with bone metastasis, while lung metastases did not exhibit the same significance. A retrospective study showed the same result that brain and liver organ metastases were also significant prognostic variables in EC patients with bone metastasis [12].

There were several unavoidable limitations in our study. The SEER database, an open dataset,has inherent limitations [48,49]: (1) absence of comorbidities and germline genetic data, which may confound survival analysis; (2) institutional heterogeneity in tumor staging documentation, potentially introducing reporting biases; (3) lack of post-treatment recurrence records, restricting the training cohort to patients with metastasis at initial diagnosis. Notably, the external validation using the Chinese cohort also has limitations: it included both de novo bone metastases (present at diagnosis) and metachronous bone metastases (developed after initial treatment). This unaddressed temporal heterogeneity may compromise the validity of external validation, as the model's performance could vary between patients with synchronous versus delayed metastatic progression. Additionally, brain metastases are rare occurrences compared to hepatic or pulmonary involvement, and small sample sizes may lead to statistical instability in survival estimates for this subgroup. While external validation with a Chinese cohort supports model generalizability, its predominance of East Asian patients limits extrapolation to other ethnic groups (e.g., European or African ancestries). Therefore, future studies should prioritize multicenter validation of our prognostic nomogram in larger, diverse cohorts to enhance ethnic generalizability and assess model robustness across varied clinical settings. Despite these limitations, our findings play an important role in identifying prognostic factors and predicting survival outcomes in ESCC patients with bone metastasis.

In conclusion, this study successfully developed and validated a prognostic nomogram for predicting cancer-specific survival in ESCC patients with bone metastasis. We identified five clinical features (chemotherapy, radiotherapy, liver metastasis, brain metastasis, and sex) as significant independent risk factors for estimating prognosis in ESCC patients with bone metastasis. Utilizing a Cox regression model, we presented these results visually through a nomogram, providing a straightforward and easily interpretable tool for clinical practitioners. Our nomogram has the potential to aid physicians in evaluating risk factors and predicting the prognosis of ESCC patients with bone metastasis. Additionally, for patients identified as high-risk (with elevated nomogram scores indicating poorer prognoses), clinicians may consider more intensive therapeutic interventions, which may potentially improve their outcomes [50].

5. Institutional review board statement

The research protocol of the Chinese cohort was conducted in the Cancer Hospital of Shantou University Medical College, and this study followed the 2008 Declaration of Helsinki's ethical guidelines and our hospital code of ethics (2022094).

CRediT authorship contribution statement

Bo Huang: Conceptualization, Data curation, Formal analysis, Methodology, Visualization, Writing – original draft. **Wei-Dong Wang:** Conceptualization, Data curation, Formal analysis, Methodology, Visualization, Writing – original draft. **Fang-Cai Wu:** Conceptualization, Data curation, Formal analysis, Methodology, Visualization. **Xiao-Mei Wang:** Investigation. **Bu-Qing Shao:** Investigation. **Ying-Miao Lin:** Investigation. **Guo-Xing Zheng:** Investigation. **Gui-Qiang Li:** Investigation. **Can-Tong Liu:** Software, Investigation. **Yi-Wei Xu:** Funding acquisition, Writing – review & editing. **Xin-Jia Wang:** Funding acquisition, Writing – review & editing.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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