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Models for Predicting Early Death in Patients With Stage IV Esophageal Cancer: A Surveillance, Epidemiology, and End Results–Based Cohort Study

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Abstract

Background: Despite enormous progress in the stage IV esophageal cancer (EC) treatment, some patients experience early death after diagnosis. This study aimed to identify the early death risk factors and construct models for predicting early death in stage IV EC patients.

Methods: Stage IV EC patients diagnosed between 2010 and 2015 in the Surveillance, Epidemiology, and End Results (SEER) database were selected. Early death was defined as death within 3 months of diagnosis, with or without therapy. Early death risk factors were identified using logistic regression analyses and further used to construct predictive models. The concordance index (C-index), calibration curves, and decision curve analyses (DCA) were used to assess model performance.

Results: Out of 4411 patients enrolled, 1779 died within 3 months. Histologic grade, therapy, the status of the bone, liver, brain and lung metastasis, marriage, and insurance were independent factors for early death in stage IV EC patients. Histologic grade and the status of the bone and liver metastases were independent factors for early death in both chemoradiotherapy and untreated groups. Based on these variables, predictive models were constructed. The C-index was .613 (95% confidence interval (CI), [.573–.653]) and .635 (95% CI, [.596–.674]) in the chemoradiotherapy and untreated groups, respectively, while calibration curves and DCA showed moderate performance.

Conclusions: More than 40% of stage IV EC patients suffered from an early death. The models could help clinicians discriminate between low and high risks of early death and strategize individually-tailed therapeutic interventions in stage IV EC patients.

Keywords

stage IV esophageal cancer, early death, risk factors, nomogram, Surveillance, Epidemiology, and End Results database

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Introduction

Esophageal cancer (EC) is one of the top ten frequent malignancies worldwide and ranks as the sixth most common cancer based on mortality in 2020.[1] Eastern Asia contributes to the highest regional EC incidence rates, partly due to the huge burden from China. However, the EC incidence and the associated mortality has been declining from 1998 to 2012 in China, but the corresponding US and UK numbers remained

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stable or increased slightly.[2,3] Approximately 40% of patients have organ metastasis at initial diagnosis, and the 5-year overall survival rate of stage IV EC cases is less than 5%.[4]

Published studies have mainly focused on exploring the risk factors related to overall survival in patients with EC or stage IV cancer. He et al. reported that gender, marital status, occupation, family history of any cancer, tumor topographical site, differentiation status, and pathological stage were related to the survival rate of EC in a large cohort from China.[5] According to the Surveillance, Epidemiology, and End Results (SEER) database, Saad et al. found that factors, including age at diagnosis, race, and differentiation status were associated with patient survival in both stage IV squamous-cell carcinoma and adenocarcinoma EC cases.[6] However, in reality, differences are commonly observed in the overall survival rate among patients with stage IV cancer. Moreover, studies have highlighted that risk factors related to short- and long-time survivals were significantly different.[7,8]

Currently, chemotherapy remains the mainstay treatment for stage IV EC patients.[9] Although the treatment of stage IV EC has been improved in recent years, especially with regard to immunotherapy,[10] a subset of patients suffers from early death after diagnosis. Early death is often defined as an overall survival time of ≤3 months after initial diagnosis. This threshold is considered a decision-making point for stage IV cancer patients for the choice of whether to receive chemotherapy or the best supportive care needs.[11] A deep understanding of the relationship between risk factors and early death may help us explore the causes of early death in high-risk patients and shed light on further investigation in active treatments and supportive therapies. To date, only a few studies have focused on the early death of patients with stage IV EC. Little is known about the early mortality and related factors in such patients. Thus, there is significant need to pursue the risk factors of early death for prognostic assessment and clinical treatment guidance.

Nomograms have been widely used to predict the prognosis and incidence of a disease. Similar models for predicting early death in other metastatic cancers, such as epithelial ovarian cancer[12] and gastric cancer,[8] have been constructed. There is also a lack of a clinically convenient model for predicting early death in stage IV EC patients. In this study, information of patients with stage IV EC patients was retrieved from the SEER database to determine the risk factors for early death after initial diagnosis. Moreover, models for predicting the risk for early mortality have been constructed.

Materials and Methods

Patient Selection

Stage IV EC patients diagnosed between 2010 and 2015 were included in this study using the incidence-SEER 18 Registries Custom Data (with additional treatment fields), which was released in April 2019, based on the November 2018 submission. The "sequence number" in the SEER database specifies the number and sequence of all reportable malignant primary tumors, occurring over the lifetime of a patient. Patients with "sequence number" zero, indicating solely one primary tumor in the patient's lifetime, were only included in this study.

Patients with missing information about race, marital status, insurance, and metastasis sites were excluded. Considering that surgery is controversial in stage IV EC patients,[13,14] patients who underwent surgery were excluded. No institutional review was sought because the SEER database is publicly anonymized.

Variable Collection

The variables consisted of demographic characteristics, including age at diagnosis, race, and sex and clinicopathological characteristics, including primary site, histologic grade, histology, N classification, therapy, metastases of bone, brain, liver, and lungs, marital status, insurance status, cause of death, and survival months. Since the value of T classification was missing in over 20% of individuals, the variable was removed. All malignancies were staged according to the American Joint Committee on Cancer, the seventh edition and adapted to patients in the SEER database with a diagnosis period between 2010 and 2015. As reported in previous studies, the primary sites were classified into the upper third esophagus (including the C15.0 and C15.3), middle third esophagus, (including the C15.1 and C15.4), lower third esophagus (including the C15.2 and C15.5), and others (including C15.8), according to the International Classification of Diseases for Oncology, the Third Edition (ICD-O-3).[15] The histological types were divided into squamous-cell carcinoma (including ICD-O-3 codes 8052, 8070–8072, 8074, and 8083), and adenocarcinoma (including ICD-O-3 codes (8140, 8144, 8210, 8211, 8255, 8260, 8261, 8263, 8480, 8481, 8490, and 8560). According to the ICD-O-2, we classified the histologic grade into G1/2 (well/moderate) and G3/4 (poor/undifferentiated) similar to a previous report.[16] The therapy was divided into 4 groups: none, mono-chemotherapy, mono-radiotherapy, and chemotherapy plus radiotherapy. Death within 3 months after the initial diagnosis with or without therapy was defined as early death based on previous studies.[8,12]

Data Analysis

We signed the SEER research data agreement to access SEER information with the username10067-Nov2018. All clinical data were obtained using the SEER*stat software version 8.3.6. Missing values for histologic grade and N classification were imputed using multiple imputations by SPSS software (Supplementary Table S1). Univariate and multivariate logistic regression analyses were conducted using the SPSS

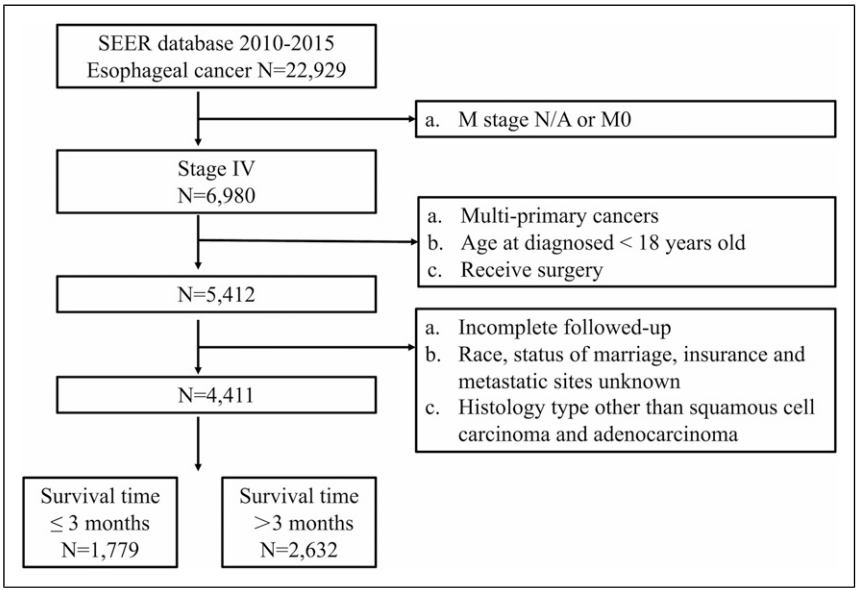

Figure 1. Flowchart for selection of patients.

software. Odds ratio (OR) and 95% confidence interval (CI) were calculated. The chi-square test for trend was performed with the linear-by-linear association method using the SPSS software. Nomogram and forest plot were constructed using the R language (version 3.6.0). The discrimination of the nomogram was assessed using the concordance index (C-index), and calibration curves were plotted to evaluate the calibration degree. Decision curve analysis (DCA) was used to test model's reliability. Statistical significance was set at $P < .05$.

Results

Patient Characteristics

This study enrolled 4411 stage IV EC patients selected from the SEER database between 2010 and 2015. Out of these, 1779 (40.3%) patients survived less than 3 months after diagnosis, which shown in Figure 1. Demographic characteristics revealed that 84.7% were white, 84.4% were male, 47.7% were married, and 74.1% were insured. Regarding tumor characteristics, 61.5% were in the lower esophagus, which was the most common site, 66.8% were poorly differentiated, 68.9% had lymph node invasion, and 72.8% belonged to adenocarcinoma, the main histological type. The main sites of tumor metastases were the liver (54.5%) and lungs (36.0%). More than half of the patients did not receive therapy. Specific clinicopathological features are listed in Table 1.

Risk Factors for Early Death

The results of univariate and multivariate logistic regression analyses for early death in the entire cohort are presented in Table 2. After univariate analysis, all covariates (except sex) were selected for multivariate analysis. Multivariate logistic analysis showed that G3/G4 (OR, 1.63; 95% CI, 1.39–1.91; $P < .001$), bone metastasis (OR, 1.83; 95% CI, 1.53–2.18; $P < .001$), brain metastasis (OR, 1.44; 95% CI, 1.05–1.97; $P = .024$), liver metastasis (OR, 1.69; 95% CI, 1.44–1.98; $P < .001$), lung metastasis (OR, 1.47; 95% CI, 1.25–1.73; $P < .001$), unmarried status (OR, 1.21; 95% CI, 1.04–1.42; $P = .0016$), and uninsured (OR, 1.46; 95% CI, 1.20–1.78; $P < .001$) were independent risk factors for early death in patients with stage IV EC. The risk for early death in patients receiving any treatment was significantly lower than those who did not receive any therapy ($P < .001$). We prepared a forest plot to describe our study visually (Supplementary Figure S1A).

The results of univariate and multivariate logistic regression analyses for early death in patients receiving no therapy are presented in Table 3. After the univariate analysis, 3 variables (histologic grade and status of bone and liver metastases) were selected for the multivariate analysis. Multivariate logistic analysis showed that G3/G4 (OR, 1.60; 95% CI, 1.18–2.17; $P = .003$), bone metastasis (OR, 2.60; 95% CI, 1.65–4.11; $P < .001$), and liver metastasis (OR, 1.91; 95% CI, 1.40–2.59; $P < .001$) were independent risk factors for early death in stage IV EC patients who receiving no therapy. A forest plot is presented in Supplementary Figure S1B.

The results of univariate and multivariate logistic regression analyses for early death in the patients receiving chemotherapy and radiotherapy are presented in Table4. After the univariate analysis, 6 variables (sex, histologic grade, N classification, and status of bone, liver, and lung metastases)

Table 1. Demographic and Clinicopathologic Characteristic of Patients with Stage IV Esophageal Cancer Who Survival Time ≤3 Months.

Characteristic	Survival Time	
	>3 Months	≤3 Months
	2632	1779
Age at diagnosis, years		
Mean (SD)	63.21 (11.09)	65.95 (11.60)
Range	21–92	24–98
Race		
White	2239 (85.1)	1506 (84.7)
Black	238 (9.0)	203 (11.4)
Others	155 (5.9)	70 (3.9)
Sex		
Male/female	2215/417 (84.2/15.8)	1501/278 (84.4/15.6)
Primary site		
Upper esophagus	106 (4.0)	74 (4.2)
Middle esophagus	382 (14.5)	279 (15.7)
Lower esophagus	1772 (67.3)	1094 (61.5)
Others	372 (14.1)	332 (18.7)
Histologic grade		
G1/G2	1096 (41.6)	590 (33.2)
G3/G4	1536 (58.4)	1189 (66.8)
Histology		
SCC/AD	610/2022 (23.2/76.8)	484/1295 (27.2/72.8)
N classification		
N0	634 (24.1)	554 (31.1)
N1	1530 (58.1)	993 (55.8)
N2	302 (11.5)	130 (7.3)
N3	166 (6.3)	102 (5.7)
Therapy		
None	213 (8.1)	946 (53.2)
Mono-radiotherapy	188 (7.1)	301 (16.9)
Mono-chemotherapy	1120 (42.6)	308 (17.3)
Chemoradiotherapy	1111 (42.2)	224 (12.6)
Bone metastasis		
No/yes	2068/564 (78.6/21.4)	1277/502 (71.8/28.2)
Brain metastasis		
No/yes	2491/141 (94.6/5.4)	1655/124 (93.0/7.0)
Liver metastasis		
No/yes	1440/1192 (54.7/45.3)	809/970 (45.5/54.5)
Lung metastasis		
No/yes	1941/691 (73.7/26.3)	1138/641 (64.0/36.0)
Marital status		
Married/unmarried	1602/1030 (60.9/39.1)	848/931 (47.7/52.3)
Insurance status		
Insured/uninsured	2187/445 (83.1/16.9)	1319/460 (74.1/25.9)

Abbreviations: SCC, squamous-cell carcinoma; AC, adenocarcinoma.

were selected for the multivariate analyses. Multivariate logistic analysis showed that G3/G4 (OR, 1.40; 95% CI, 1.03–1.90; P = .034), bone metastasis (OR, 1.41; 95% CI, 1.03–1.92; P = .033), liver metastasis (OR, 1.57; 95% CI, 1.17–2.10; P = .003), and lung metastasis (OR, 1.64; 95% CI, 1.20–2.23; P =.002) were independent risk factors for early death in stage IV EC patients who receiving chemoradiotherapy concurrently. The forest plot is presented in Supplementary Figure S1C.

Construction of Nomogram

Based on the results of multivariate analysis, we constructed 2 nomograms to predict the early death of patients with stage IV

Table 2. Univariate and Multivariate Logistic Regression for Analyzing the Risk Factors for Early Death in the Total Study Population.

Characteristic	Univariate Logistic Regression	Multivariate Logistic Regression		
	P	OR	95% CI	*P*
Age at diagnosis, years	<.001			.092
<50		Ref.		
50–70		1.20	.92–1.58	.187
>70		1.37	1.02–1.85	.037
Race	.001			.111
White		Ref.		
Black		1.00	.76–1.31	.978
Others		.68	.47–.98	.038
Sex	.846			
Male				
Female				
Primary site	<.001			.189
Upper esophagus		Ref.		
Middle esophagus		1.32	.87–2.01	.198
Lower esophagus		1.36	.90–2.05	.141
Others		1.57	1.02–2.41	.039
Histologic grade	<.001			<.001
G1/G2		Ref.		
G3/G4		1.63	1.39–1.91	<.001
Histology	.002			.148
SCC		Ref.		
AD		.85	.69–1.06	.148
N classification	<.001			.722
N0		Ref.		
N1		.96	.81–1.15	.656
N2		.86	.65–1.15	.305
N3		1.05	.74–1.47	.796
Therapy	<.001			<.001
No		Ref.		
Mono-radiotherapy		.35	.27–.44	<.001
Mono-chemotherapy		.06	.05–.08	<.001
Chemoradiotherapy		.05	.04–.06	<.001
Bone metastasis	<.001			<.001
No		Ref.		
Yes		1.83	1.53–2.18	<.001
Brain metastasis	.027			.024
No		Ref.		
Yes		1.44	1.05–1.97	.024
Liver metastasis	<.001			<.001
No		Ref.		
Yes		1.69	1.44–1.98	<.001
Lung metastasis	<.001			<.001
No		Ref.		
Yes		1.47	1.25–1.73	<.001
Marital status	<.001			.016
Married		Ref.		
Unmarried		1.21	1.04–1.42	.016
Insurance status	<.001			<.001
Insured		Ref.		
Uninsured		1.46	1.20–1.78	<.001

Abbreviations: SCC, squamous-cell carcinoma; AC, adenocarcinoma.

Table 3. Univariate and Multivariate Logistic Regression for Analyzing the Risk Factors for Early Death in Patients with Stage IV Esophageal Cancer with No Therapy.

Characteristic	Univariate Logistic Regression	Multivariate Logistic Regression		
	P	OR	95% CI	*P*
Age at diagnosis, years	.791			
<50				
50–70				
>70				
Race	.424			
White				
Black				
Others				
Sex	.686			
Male				
Female				
Primary site	.405			
Upper esophagus				
Middle esophagus				
Lower esophagus				
Others				
Histologic grade	.002			.003
G1/G2		Ref.		
G3/G4		1.60	1.18–2.17	.003
Histology	.296			
SCC				
AD				
N classification	.102			
N0				
N1				
N2				
N3				
Bone metastasis	<.001			<.001
No		Ref.		
Yes		2.60	1.65–4.11	<.001
Brain metastasis	.654			
No				
Yes				
Liver metastasis	<.001			<.001
No		Ref.		
Yes		1.91	1.40–2.59	<.001
Lung metastasis	.438			
No				
Yes				
Marital status	.057			
Married				
Unmarried				
Insurance status	.832			
Insured				
Uninsured				

Abbreviations: SCC, squamous-cell carcinoma; AC, adenocarcinoma.

Table 4. Univariate and Multivariate Logistic Regression for Analyzing the Risk Factors for Early Death in Patients with Stage IV Esophageal Cancer Receiving Chemoradiotherapy Concurrently.

Characteristic	Univariate Logistic Regression	Multivariate Logistic Regression		
	P	OR	95% CI	*P*
Age at diagnosis, years	.224			
<50				
50–70				
>70				
Race	.637			
White				
Black				
Others				
Sex	.049			.083
Male		Ref.		
Female		.67	.43–1.05	.083
Primary site	.081			
Upper esophagus				
Middle esophagus				
Lower esophagus				
Others				
Histologic grade	.040			.034
G1/G2		Ref.		
G3/G4		1.40	1.03–1.90	.034
Histology	.902			
SCC				
AD				
N classification	.034			.073
N0		Ref.		
N1		.92	.65–1.31	.636
N2		.50	.28–.90	.020
N3		.62	.30–1.26	.183
Bone metastasis	.009			.033
No		Ref.		
Yes		1.41	1.03–1.92	.033
Brain metastasis	.176			
No				
Yes				
Liver metastasis	.001			.003
No		Ref.		
Yes		1.57	1.17–2.10	.003
Lung metastasis	.001			.002
No		Ref.		
Yes		1.64	1.20–2.23	.002
Marital status	.138			
Married				
Unmarried				
Insurance status	.060			
Insured				
Uninsured				

Abbreviations: SCC, squamous-cell carcinoma; AC, adenocarcinoma.

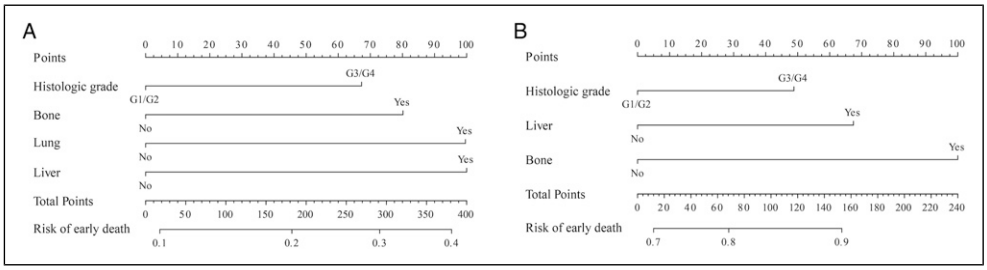

Figure 2. Models to predicting the risk for early death in patients with stage IV esophageal cancer in patients with concurrent chemoradiotherapy (A) and in patients without therapy (B).

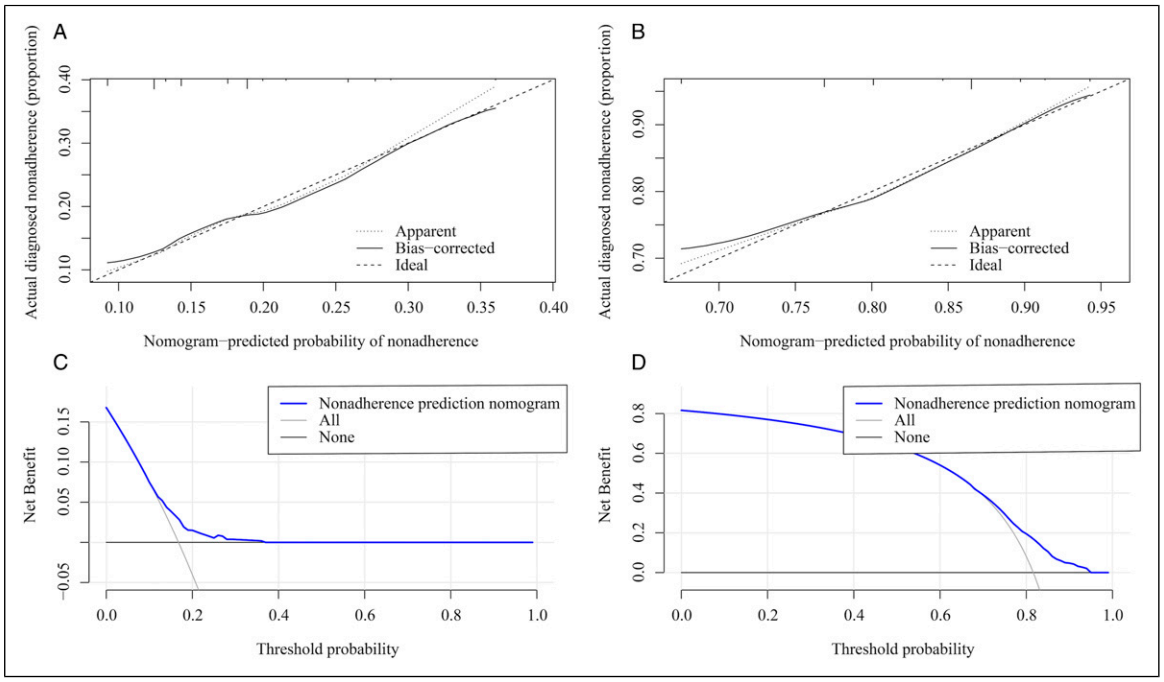

Figure 3. Calibration curves and DCA of models. The calibration curves in patients with concurrent chemoradiotherapy (A) and without therapy (B) and DCA in patients with concurrent chemoradiotherapy (C) and without therapy (D) are presented. Abbreviation: DCA, decision curve analyses.

EC, as shown in Figure 2. The nomogram for patients receiving no therapy reveals that bone metastasis had the strongest effect on the risk for early death, followed by liver metastasis and histologic grade. For patients receiving chemoradiotherapy concurrently, liver metastasis had the strongest effect on the risk for early death, followed by lung and bone metastases and histologic grade. The use of a nomogram involved drawing a vertical line on the horizontal axis marked with "points" at the top of the nomogram, based on the classification of each variable (for example, lung metastasis status was divided into "yes" and "no"). At the point where the vertical line crossed the axis, each variable was assigned a value. The final points were summarized, and the position marked as "total points" on the horizontal axis was obtained. Next, a vertical line drawn from this position to the axis represented the risk for early death. The intersection depicted the risk value for an early death in an individual.

In our study, the C-index of the nomogram in the chemoradiotherapy and untreated groups was .613 (95% CI, .573–.653) and .635 (95% CI, .596–.674), respectively. As shown in Figure 3A and B, the calibration curves of chemoradiotherapy and the untreated set also showed good prediction ability and observation consistency in the risk for early death. In addition, DCA exhibited moderately positive net benefits both in the chemoradiotherapy (range, .11–.36) and untreated groups (range, .70–.94) (Figure 3C and D).

Discussion

Esophageal cancer is a malignancy characterized by high mortality and morbidity. The incidence rate of esophageal adenocarcinoma has steadily increased, and the increase rate in incidence was the highest among all other malignancies in

the USA over the past 25 years.[17] Furthermore, among 41 countries, Southern America was one of the regions with the highest incidence: mortality ratio of EC among females.[18] Thus, EC has become an increasing healthcare burden in the USA. The number of patients in the whole stage IV EC experiencing early death was quite high and remained stable at high levels in recent years (Supplementary Figure S1, P = .150). Similar studies were conducted in other digestive tract cancers revealed that the number of patients with early death in advanced gastric cancer and colorectal cancer was 32.6% and 28.1%, respectively.[19,20] Although significant progress has been made in the treatment of stage IV EC, it is imperative to pay more attention to reduce the incidence of early death among this population.

Most EC patients are in an advanced stage at the time of initial diagnosis due to a lack of specific symptoms at an early stage.[21] In our study, among the 4411 patients with stage IV EC, the early mortality (≤3 months) was 40.4%, according to the SEER database. Eight variables (histologic grade, therapy, status of bone, brain, liver and lung metastases, marriage, and insurance) were identified as independent factors for early death using multivariate logistic analysis in the whole stage IV EC patients. Subsequently, in the subgroup analysis, histologic grade and status of bone and liver metastases were independent factors for early death in both the chemoradiotherapy and untreated groups. In addition, the status of lung metastasis was an independent factor for early death in the chemoradiotherapy group. Lastly, nomograms with moderate discrimination and calibration degrees were constructed to predicting early death.

To date, most researchers have attempted to identify risk factors associated with the overall survival in EC patients.[22,23] To our knowledge, this is the first study to explore the risk factors related to early death in patients with stage IV EC. Previous studies have reported that histologic grade is related to the prognosis, and poorly differentiated tumors usually indicate worse survival in metastatic EC.[24,25] Our study results were consistent with these findings. Similar results have also been observed in other tumor cases.[19,20] The prognosis of the disease at advanced stages is extremely poor. Few studies have explored the impact of metastatic sites on early death. The liver and lungs were the most common site for metastatic organs in patients with stage IV EC experiencing early death. Moreover, stage IV EC patients with synchronous liver or lung metastases also had an increased risk for early death, consistent with the findings of similar studies in advanced epithelial ovarian and endometrial cancer.[12,26] Furthermore, the involvement of lungs affects the respiratory system. Additionally, it has been reported that EC patients with liver metastasis are difficult to treat effectively.[27] Thus, routine imaging examination of the liver should be conducted as recommended by the NCCN guidelines. Marital status is significantly associated with prognosis in various other malignancies. In our study, married patients had a better prognosis than unmarried patients, possibly due to better compliance and less emotional burden in married patients, as noted by Wu et al.[28] The insurance status plays a critical role in access to health care services. Consistent with a previous study,[29] the early mortality risk was found to be higher among uninsured patients in this study, possibly because patients with health insurance would likely to receive early medical intervention. Interestingly, in the subgroup analysis, insurance status was no longer associated with prognosis. Based on our data, we believe that insurance status primarily affects patients receiving monotherapies. If patients receive the appropriate treatment for their EC, insurance might not affect survival, as observed in a study on hepatocellular carcinoma.[30] Additionally, the relationship between risk for early death and age differs with tumor types.[12,19]

Our study found that both chemotherapy and radiotherapy were powerful protective factors for early death, as reported by other researchers.[29,31,32] Moreover, a recent study demonstrated that chemoradiotherapy was superior to radiotherapy alone in elderly EC patients.[33] Hence, there is no doubt that active therapy could prolong the survival of patients. However, in clinical settings, chemotherapy and radiotherapy are usually administered to patients with good performance status (PS); hence, selection bias could exist in this study. Performance status is a well-known strong prognosticator for early death and is an important pillar to decide between systemic therapy and supportive care. However, due to the lack of PS in the SEER database, an inherent limitation to studies using a pre-existing database exists. We were unable to determine whether patient with poor PS could benefit from the systemic therapy. To reduce the effect of PS on our results, we performed subgroup analysis. We postulated that patients receiving chemoradiotherapy usually had good PS, while patients without any treatment were primarily related to their poor PS. Therefore, based on the study findings, we present the following recommendations to reduce the risk for early death. First, early screening of EC is helpful for early detection, and early treatment reduces mortality from the source. Moreover, the imaging assessments of the bone and liver were equally important for patients with EC. Second, active therapy, emotional support from partners, and lifting the financial burden of patients through insurance are critical interventions for patients with stage IV EC. Finally, although PS is very important, it can be reversible with supportive therapy in patients with poor PS. Clinicians should focus on the dynamic changes in PS.

This study has several limitations. This is a retrospective study with an inevitable selection bias, and thus, prospective research is needed for further demonstration. Some known risk factors, such as PS, number of metastatic sites, and family history were not recorded in the SEER database. Furthermore, although the patients included in this study received no surgery, the role of surgery was worth further exploration in stage IV EC, especially in downstaged patients after medical treatment (including neoadjuvant, adjuvant, radical, palliative). Neoadjuvant/adjuvant treatment was important for patients with EC, while the SEER database lacked related information. Lastly, our model need to be verified on external populations. These results may not be applicable to countries other than the United States.

Conclusions

This study explored the risk factors associated with early death in stage IV EC patients, and novel nomograms were constructed based on these factors to help clinicians assess the risk for early death. Early identification of the factors affecting early death would enable clinicians to screen high-risk patients and provide insight into the strategies for the prevention of early death in patients with stage IV EC.

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Declaration of Conflicting Interests

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Abbreviations

EC, esophageal cancer; C-index, concordance index; DCA, decision curve analyses; SEER, Surveillance, Epidemiology, and End Results; PS, performance status.

Ethics Statement

No institutional review was sought because SEER database is a public anonymized database.

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Supplemental Material

Supplemental material for this article is available online.

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