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Analysis of Homogeneous and Heterogeneous Factors for Bone Metastasis in Esophageal Cancer

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Background: Esophageal cancer is a common cancer worldwide. We performed the present study to assess the homogeneous and heterogeneous risk and prognostic factors of bone metastasis (BM) in esophageal cancer patients using data extracted from the Surveillance, Epidemiology, and End Results (SEER) database.

Material/Methods: Data from patients with esophageal cancer in the SEER database from 2010 to 2016 were extracted to reveal the risk factors for BM through univariable and multivariable logistic regression. Cox hazard regression analysis was used to evaluate the prognostic factors in esophageal cancer patients with BM from 2010 to 2015.

Results: A total of 2075 (8.0%) patients with initial bone metastasis were diagnosed from among 25 955 patients with esophageal cancer from 2010 to 2016. Male sex, T4 stage, brain metastasis, and liver metastasis were common risk factors for the occurrence and prognosis of BM. Patients with age younger than 67 years, grade III, higher N stage (N1, N2, and N3), histological subtype of esophageal adenocarcinoma or others, and lung metastasis were also more likely to experience bone metastasis, while unmarried patients were associated with shorter survival.

Conclusions: The prevalence of initial bone metastasis was approximately 8.0% in esophageal cancer patients. More attention should be paid to patients with revealed risk and prognostic factors because these factors can guide individualize bone metastasis screening and treatment of esophageal cancer patients.

MeSH Keywords: Esophageal Neoplasms • Neoplasm Metastasis • Risk Factors • SEER Program

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Background

Esophageal cancer is a common cancer worldwide. GLOBOCAN 2018 reported the global incidence of esophageal cancer was 3.2% among 35 major cancers. Esophageal cancer, ranking as the ninth most common cancer, resulted in around 5.3% of all cancer-related deaths [1]. Patients at the advanced stage, especially those with distant metastases, showed a significantly shorter survival [2]. Thus, longer survival can be expected in patients who are diagnosed in the early stage.

Bone is a common organ for distant metastasis [3,4]. In patients with esophageal cancer, bone metastasis (BM) was reported as the third common metastatic site [5,6]. Larger-scale esophageal cancer screening in some countries is delayed, and the relatively low incidence and high cost of screening make it difficult to satisfactorily identify BM in patients with esophageal cancer. Immunocytochemical analysis [7] and RT-PCR [8] of bone marrow were previously studied to precisely detect metastasis and to predict the survival of patients. 18F-FDG PET(/CT) imaging [9] and bone scan [10] were also commonly performed for patients with high risk of BM. However, these examinations are invasive and expensive, resulting in higher incidence of iatrogenic injury and increased economic burden. Thus, identification and analyses of risk factors are needed to improve BM screening for patients with esophageal cancer [11].

Compared with early-stage cancer patients, the survival of patients with distant metastases is poor. A previous study investigated the association of various metastatic patterns with survival, and found worse survival in patients with BM than in patients with liver metastasis [12]. Therefore, it is important to study the prognostic factors for BM patients with esophageal cancer. A previous study reported younger age, poor differentiation, adenoma type, and more distant metastatic sites were significantly correlated with worse prognosis [5]. However, these aforementioned studies merely focused on metastases to multiple sites without specially investigating the predictive factors for the prognosis of BM patients with esophageal cancer.

Using data extracting from the Surveillance, Epidemiology, and End Results (SEER) database, we studied the risk and prognostic factors for esophageal cancer patients with initial BM. Common and specific factors for BM occurrence and survival were identified to improve clinical screening and management.

Material and Methods

Data source and cohort selection

All information used in the present study was derived from the SEER database (*https://seer.cancer.gov/data/*), which covers approximately 30% of the population in the USA from 18 registration centers. Due to missing information on metastasis before 2010, we selected patients diagnosed with esophageal cancer between 2010 and 2016 to analyze BM risk factors. Prognostic factors were investigated in a cohort of patients diagnosed from 2010 to 2015 with a follow-up at least for 1 year. Patients were excluded if they were diagnosed via death certificate or at autopsy in this study. Figure 1 shows the flowchart of inclusion and exclusion of patients.

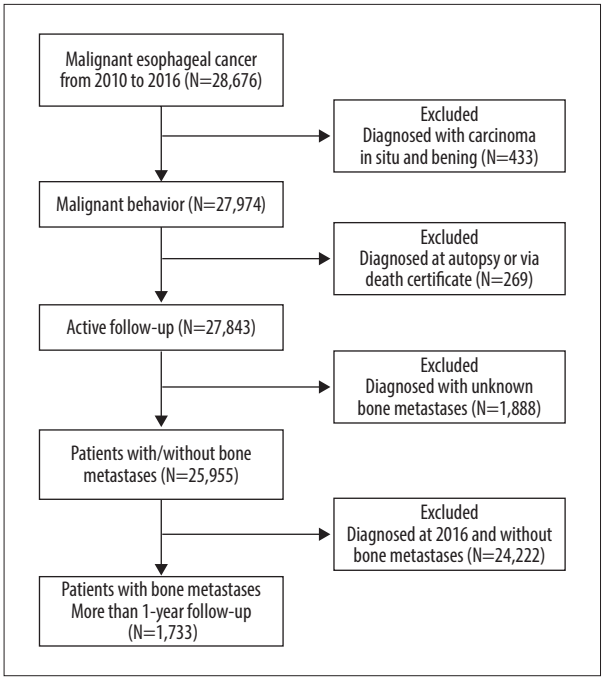

Figure 1. Flowchart of the esophageal cancer patient selection.

The SEER database is an open public database, and informed patient consent is not required for extraction of data. The present study complied with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Statistical analysis

BM risk factors were studied through univariable and multivariable logistic regression analyses, including the following variables: sex (Male *vs.* Female); age of diagnosis (<67 years and ≥67 years); race [white, black, Asian or Pacific Islander (API), and American Indian/Alaska Native (AI)]; insurance status (uninsured and insured); marital status (unmarried and married); site of primary tumor (upper third including the cervical esophagus, middle third including the thoracic esophagus, and lower third including the abdominal esophagus and overlapping lesion); histological types (esophageal adenocarcinoma [EAC], esophageal squamous cell carcinoma [ESCC] and others); tumor grade (I, II, III, and IV); T stage (T1, T2, T3, and T4); stage of lymph nodes (N0, N1, N2, and N3); other distant metastatic sites including

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lung (yes or no), liver (yes or no), and brain (yes or no); and surgical treatment for the primary cancer (yes or no).

The median overall survival (OS) for patients in each category was calculated. Survival duration was obtained by the Kaplan-Meier method, and the log-rank test was used to evaluate difference among curves. Univariable and multivariable Cox hazard regression were performed based on the revealed factors to evaluate the independent factors for prognosis.

Data extraction was performed using the SEER*Stat Software version 8.3.5, and SPSS 23.0 (IBM Corporation, Armonk, NY, USA) was used to conduct all statistical analyses. MedCalc 15.2.2 was used to generate survival curves. Two-sided *p*-values <0.05 were considered to be statistically significant.

Results

Patient characteristics

According to the defined inclusion and exclusion criteria, a total of 25 955 patients with esophageal cancer were initially identified from 2010 to 2016, among whom 2075 (8.0%) cases were initially diagnosed with BM. Compared with females, older patients, and other races, more patients with BM were male (N=1,788, 86.2%), younger than 67 years old (N=1178, 56.8%), and white race (N=1778, 85.7%). Regarding the tumor sites, the majority of cancers (58.9%) were located in the lower third of the esophagus. Compared with EAC, the main histological subtype was ESCC (N=1414, 68.1%). According to the AJCC, most patients were diagnosed at grade III (N=1020, 49.2%) and N1 (N=1039, 50.1%). Other distant metastases included 832 patients with liver metastases, 558 with lung metastases, and 146 with brain metastases. Details are shown in Table 1.

Risk factors for BM

Univariable regression identified less BM occurrence in female patients (OR=0.56, 95% CI: 0.49–0.64), older patients (≥67 years *vs.* <67 years) (OR=0.66, 95% CI: 0.60–0.72), API race (*vs.* white; OR=0.75, 95% CI: 0.59–0.95), and T2 (*vs.* T1; OR=0.51, 95% CI: 0.39–0.65) and T3 (*vs.* T1; OR=0.76, 95% CI: 0.66–0.89). In contrast, risk of BM was higher in patients of AI race (*vs.* white; OR=1.74, 95% CI: 1.13–2.86), middle third (*vs.* upper third; OR=1.70, 95% CI: 1.35–2.16), lower third (*vs.*upper third; OR=1.69, 95% CI: 1.35–2.10), overlapping lesion (*vs.* upper third; OR=2.68, 95% CI: 2.03–3.54), higher tumor grade (II, III and IV *vs.* grade I), higher T stage (T2–T4 *vs.* T1) and N3 stage (*vs.* N0), EAC subtype (*vs.* ESCC; OR=1.53, 95% CI: 1.38–1.70), and patients with metastasis to liver (OR=4.62, 95% CI: 4.20–5.09), lung (OR=4.51, 95% CI: 4.05–5.03), and brain (OR=5.90, 95% CI: 4.82–7.22).

Multivariable analysis further confirmed BM was negatively associated with female sex (OR=0.74, 95% CI: 0.59–0.94), older age (OR=0.81, 95% CI: 0.69–0.95), and higher T stage. More BM was positively associated with grade III (OR=1.66, 95% CI: 1.10–2.50), histological EAC subtype (OR=1.66, 95% CI: 1.30–2.11), higher N stage (N1–N3), and metastasis to liver, lung, and brain. Race, insurance, marital status, and primary site were not independent factors for BM occurrence. More details were provided in Table 1.

Survival estimation and prognostic factors identification in esophageal cancer patients with BM

A total of 1733 esophageal cancer patients with BM, diagnosed from 2010 to 2015, were extracted to estimate the survival and identify the prognostic factors. Among these patients, only 25 patients received surgical treatment of the primary site (Table 2). The median OS for all the patients with esophageal cancer was 11 (95% CI: 10.7–11.3) months, and it was decreased to 4 (95% CI 3.7–4.3) months in patients with BM. Kaplan-Meier analysis was performed among esophageal cancer patients diagnosed with initial BM (Figure 2A, overall), stratified by sex (Figure 2B), age (Figure 2C), race (Figure 2D), insurance recode (Figure 2E), marital status (Figure 2F), primary site (Figure 2G), grade (Figure 2H), histopathologic groups (Figure 2I), T stage (Figure 2J), N stage (Figure 2K), brain metastasis (Figure 2L), liver metastasis (Figure 2M), lung metastasis (Figure 2N), and surgical treatments of the primary site (Figure 2O).

Univariable Cox regression analysis suggested improved survival in married patients (HR=0.71, 95% CI: 0.64–0.78), those with insurance (HR=0.62, 95% CI: 0.49–0.78), tumor in the lower third sites (HR=0.78, 95% CI: 0.61–0.99), histological subtype of EAC (HR=0.82, 95% CI: 0.74–0.93), T2 stage (HR=0.59, 95% CI: 0.44–0.79), T3 stage (HR=0.76, 95% CI: 0.65–0.89), and patients after surgery for the primary site (HR=0.56, 95% CI: 0.36–0.86). Patients older than 67 years (HR=1.11, 95% CI: 1.01–1.22), black race (HR=1.22, 95% CI: 1.04–1.44), and with distant metastases to liver (HR=1.22, 95% CI: 1.11–1.35), lung (HR=1.23, 95% CI: 1.10–1.37) and brain (HR=1.37, 95% CI: 1.14–1.66) showed worse OS. Multivariable Cox analysis only confirmed the female, being married, and T2 stage as the protective factors for patients with BM, while T4 stage, brain metastases, and liver metastases were risk factors. More details were given in Table 2.

Therefore, the homogeneous risk factors for the occurrence and prognosis of BM in esophageal cancer were male, T4 stage, liver metastasis, and brain metastasis. Patients younger than 67 years, grade III, N1–N3, histological subtype of EAC or others, and lung metastases were more likely to have BM occurrence, while unmarried patients were associated with worse survival (Figure 3).

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Table 1. Logistic regression for characteristics to develop initial BM in patients with primary esophageal cancer (diagnosed 2010–2016).

Subject characteristics	No. of esophageal cancer patients					Univariable		Multivariable	
	BM	Entire cohort	%	χ^2	*P*-value	OR [95% CI]	*P*-value	OR [95% CI]	*P*-value
Sex				79.113	<0.001				
Male	1788	20 367	8.78			1.00 (Reference)		1.00 (Reference)	
Female	287	5588	5.14			0.56 (0.49–0.64)	<0.001	0.74 (0.59–0.94)	0.012
Age				82.546	<0.001				
<67	1178	12 256	9.61			1.00 (Reference)		1.00 (Reference)	
≥67	897	13 699	6.55			0.66 (0.60–0.72)	<0.001	0.81 (0.69–0.95)	0.010
Race				18.696	0.001				
White	1778	21 889	8.12			1.00 (Reference)		1.00 (Reference)	
Black	198	2605	7.60			0.93 (0.80–1.08)	0.355	1.21 (0.90–1.62)	0.215
AI	24	180	13.33			1.74 (1.13–2.68)	0.012	0.93 (0.39–2.26)	0.878
API	74	1196	6.19			0.75 (0.59–0.95)	0.017	1.00 (0.67–1.50)	0.996
Unknown	1	85	1.18			NA	NA	NA	NA
Insurance recode				6.946	0.031				
Uninsured	80	760	10.53			1.00 (Reference)		1.00 (Reference)	
Insured	1944	24 520	7.93			0.73 (0.58–0.93)	0.010	1.25 (0.79–1.98)	0.349
Unknown	51	675	7.56			NA	NA	NA	NA
Marital status				4.784	0.091				
Unmarried	854	10 550	8.09			1.00 (Reference)		NA	NA
Married	1,126	13,941	8.08			1.00 (0.91–1.09)	0.959	NA	NA
Unknown	95	1464	6.49			NA	NA	NA	NA
Primary site				82.019	<0.001				
Upper third	91	1922	4.73			1.00 (Reference)		1.00 (Reference)	
Middle third	379	4854	7.81			1.70 (1.35–2.16)	<0.001	1.28 (0.86–1.90)	0.228
Lower third	1223	15 821	7.73			1.69 (1.35–2.10)	<0.001	0.84 (0.56–1.26)	0.407
Overlapping lesion	133	1132	11.75			2.68 (2.03–3.54)	<0.001	0.98 (0.59–1.63)	0.946
Unknown	249	2226	11.19			NA	NA	NA	NA
Grade				129.251	<0.001				
Grade I	48	1255	3.82			1.00 (Reference)	1.00	1.00 (Reference)	1.00
Grade II	502	8461	5.93			1.59 (1.17–2.15)	0.003	1.08 (0.71–1.64)	0.711
Grade III	1020	10 396	9.81			2.74 (2.04–3.68)	<0.001	1.66 (1.10–2.50)	0.015
Grade IV	33	335	9.85			2.75 (1.73–4.36)	<0.001	1.55 (0.73–3.31)	0.255
Unknown	472	5508	8.57			NA	NA	NA	NA

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Table 1 continued. Logistic regression for characteristics to develop initial BM in patients with primary esophageal cancer (diagnosed 2010–2016).

Subject characteristics	No. of esophageal cancer patients					Univariable		Multivariable	
	BM	Entire cohort	%	χ^2	*P*-value	OR [95% CI]	*P*-value	OR [95% CI]	*P*-value
Histology				87.047	<0.001				
ESCC	494	8366	5.90			1.00 (Reference)		1.00 (Reference)	
EAC	1414	16 108	8.78			1.53 (1.38–1.70)	<0.001	1.66 (1.30–2.11)	<0.001
Others	55	425	12.94			2.37 (1.76–3.19)	<0.001	1.99 (1.06–3.71)	0.031
Unknown	112	1056	10.61			NA	NA	NA	NA
T stage				822.064	<0.001				
T1	369	6525	5.66			1.00 (Reference)		1.00 (Reference)	
T2	73	2477	2.95			0.51 (0.39–0.65)	<0.001	0.58 (0.42–0.79)	0.001
T3	355	8099	4.38			0.76 (0.66–0.89)	<0.001	0.65 (0.53–0.81)	<0.001
T4	325	2803	11.59			2.19 (1.87–2.56)	<0.001	1.24 (1.00–1.55)	0.053
Unknown	953	6051	15.75			NA	NA	NA	NA
N stage				385.480	<0.001				
N0	466	10 596	4.40			1.00 (Reference)		1.00 (Reference)	
N1	1039	9879	10.52			2.55 (2.28–2.86)	<0.001	1.96 (1.60–2.39)	<0.001
N2	169	2,429	6.96			1.63 (1.36–1.95)	<0.001	2.00 (1.51–2.64)	<0.001
N3	125	931	13.43			3.37 (2.73–4.16)	<0.001	2.97 (2.14–4.12)	<0.001
Unknown	276	2120	13.02			NA	NA	NA	NA
Brain metastases				769.394	<0.001				
None	1859	25 373	7.33			1.00 (Reference)		1.00 (Reference)	
Yes	146	459	31.81			5.90 (4.82–7.22)	<0.001	3.21 (2.15–4.79)	<0.001
Unknown	70	123	56.91			NA	NA	NA	NA
Liver metastases				1278.829	<0.001				
None	1191	21 863	5.45			1.00 (Reference)		1.00 (Reference)	
Yes	832	3958	21.02			4.62 (4.20–5.09)	<0.001	3.56 (2.96–4.29)	<0.001
Unknown	52	134	38.81			NA	NA	NA	NA
Lung metastases				1083.907	<0.001				
None	1429	23 254	6.15			1.00 (Reference)		1.00 (Reference)	
Yes	558	2448	22.79			4.51 (4.05–5.03)	<0.001	2.73 (2.21–3.37)	<0.001
Unknown	88	253	34.78			NA	NA	NA	NA

BM – bone metastasis; AI – American Indian/Alaska Native; API – Asian or Pacific Islander; ESCC – esophageal squamous cell carcinoma; EAC – esophageal adenocarcinoma; Met – metastases; OR – odds ratio; CI – confidence interval.

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Table 2. Cox regression for analyzing the mortality among BM patients in primary esophageal cancer (diagnosed 2010–2015).

Subject characteristics	No. of patients with BM			Survival, median (IQR), mo	Univariable		Multivariable	
	Overall	Deceased (rate, %)			HR [95% CI]	*P*-value	HR [95% CI]	*P*-value
Sex								
Male	1488	1439	(96.71)	4 (3.68–4.32)	1.00 (Reference)		1.00 (Reference)	
Female	245	233	(95.10)	4 (3.29–4.71)	0.92 (0.80–1.06)	0.229	0.77 (0.60–0.99)	0.043
Age								
<67	987	951	(96.35)	4 (3.56–4.44)	1.00 (Reference)		1.00 (Reference)	
≥67	746	721	(96.65)	3 (2.63–3.37)	1.11 (1.01–1.22)	0.033	1.18 (0.99–1.40)	0.060
Race								
White	1492	1435	(96.18)	4 (3.68–4.32)	1.00 (Reference)		1.00 (Reference)	
Black	161	161	(100.00)	3 (2.41–3.59)	1.22 (1.04–1.44)	0.017	1.10 (0.79–1.53)	0.575
AI	17	17	(100.00)	3 (0.58–5.42)	1.23 (0.76–1.98)	0.398	0.91 (0.37–2.23)	0.840
API	63	59	(93.65)	3 (1.60–4.40)	1.03 (0.79–1.34)	0.816	0.94 (0.61–1.44)	0.777
Unknown				NA	NA	NA	NA	NA
Insurance recode								
Uninsured	72	72	(100.00)	1 (0.38–1.62)	1.00 (Reference)		1.00 (Reference)	
Insured	1615	1554	(96.22)	4 (3.70–4.30)	0.62 (0.49–0.78)	<0.001	0.65 (0.41–1.04)	0.071
Unknown	46	46	(100.00)	NA	NA	NA	NA	NA
Marital status								
Unmarried	704	689	(97.87)	3 (2.68–3.32)	1.00 (Reference)		1.00 (Reference)	
Married	947	903	(95.35)	5 (4.57–5.43)	0.71 (0.64–0.78)	<0.001	0.79 (0.66–0.94)	0.009
Unknown	82	80	(97.56)	NA	NA	NA	NA	NA
Primary site								
Upper third	74	73	(98.65)	3 (1.60–4.40)	1.00 (Reference)		1.00 (Reference)	
Middle third	325	315	(96.92)	4 (3.36–4.64)	0.87 (0.67–1.12)	0.274	0.76 (0.50–1.15)	0.193
Lower third	1009	973	(96.43)	4 (3.53–4.47)	0.78 (0.61–0.99)	0.039	0.85 (0.56–1.29)	0.441
Overlapping lesion	107	102	(95.33)	2 (1.03–2.97)	1.02 (0.75–1.38)	0.903	1.10 (0.64–1.88)	0.731
Unknown	218	209	(95.87)	NA	NA	NA	NA	NA
Grade								
Grade I	42	38	(90.48)	6 (2.82–9.18)	1.00 (Reference)		1.00 (Reference)	
Grade II	415	399	(96.14)	5 (4.29–5.71)	1.30 (0.93–1.82)	0.120	0.96 (0.61–1.49)	0.849
Grade III	854	826	(96.72)	3 (2.59–3.41)	1.61 (1.16–2.23)	0.004	1.14 (0.73–1.76)	0.565
Grade IV	27	27	(100.00)	4 (1.96–6.04)	1.40 (0.85–2.31)	0.184	1.98 (0.92–4.29)	0.082
Unknown	395	382	(96.71)	NA	NA	NA	NA	NA
Histology								
ESCC	409	396	(96.82)	3 (2.52–3.48)	1.00 (Reference)		1.00 (Reference)	
EAC	1179	1132	(96.01)	4 (3.58–4.42)	0.82 (0.74–0.93)	0.001	0.79 (0.61–1.01)	0.061
Others	45	45	(100.00)	2 (0.54–3.46)	0.99 (0.73–1.34)	0.934	0.66 (0.36–1.22)	0.181
Unknown	100	99	(99.00)	NA	NA	NA	NA	NA

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Table 2 continued. Cox regression for analyzing the mortality among BM patients in primary esophageal cancer (diagnosed 2010–2015).

Subject characteristics	No. of patients with BM		Survival, median (IQR), mo	Univariable		Multivariable	
	Overall	Deceased (rate, %)		HR [95% CI]	*P*-value	HR [95% CI]	*P*-value
T stage							
T1	349	337 (96.56)	4 (3.44–4.56)	1.00 (Reference)		1.00 (Reference)	
T2	58	52 (89.66)	7 (4.51–9.49)	0.59 (0.44–0.79)	<0.001	0.52 (0.35–0.76)	0.001
T3	294	279 (94.90)	6 (5.10–6.90)	0.76 (0.65–0.89)	0.001	0.82 (0.66–1.01)	0.060
T4	275	269 (97.82)	3 (2.39–3.61)	1.15 (0.98–1.35)	0.085	1.27 (1.01–1.59)	0.039
Unknown	757	735 (97.09)	NA	NA	NA	NA	NA
N stage							
N0	391	380 (97.19)	3 (2.40–3.60)	1.00 (Reference)		1.00 (Reference)	
N1	913	881 (96.50)	4 (3.54–4.46)	0.93 (0.83–1.05)	0.242	0.93 (0.75–1.14)	0.475
N2	123	118 (95.93)	5 (3.88–6.12)	0.83 (0.68–1.03)	0.085	1.08 (0.79–1.47)	0.641
N3	89	80 (89.89)	3 (1.32–4.68)	0.90 (0.71–1.15)	0.399	1.16 (0.82–1.66)	0.404
Unknown	217	213 (98.16)	NA	NA	NA	NA	NA
Brain metastases							
None	1550	1495 (96.45)	4 (3.68–4.32)	1.00 (Reference)		1.00 (Reference)	
Yes	122	118 (96.72)	3 (2.26–3.74)	1.37 (1.14–1.66)	0.001	1.76 (1.24–2.51)	0.002
Unknown	61	59 (96.72)	NA	NA	NA	NA	NA
Liver metastases							
None	1011	971 (96.04)	4 (3.55–4.45)	1.00 (Reference)		1.00 (Reference)	
Yes	672	652 (97.02)	3 (2.59–3.41)	1.22 (1.11–1.35)	<0.001	1.24 (1.04–1.48)	0.015
Unknown	50	49 (98.00)	NA	NA	NA	NA	NA
Lung metastases							
None	1187	1141 (96.12)	4 (3.60–4.40)	1.00 (Reference)		1.00 (Reference)	
Yes	465	451 (96.99)	3 (2.56–3.44)	1.23 (1.10–1.37)	<0.001	1.16 (0.95–1.42)	0.140
Unknown	81	80 (98.77)	NA	NA	NA	NA	NA
Surg (prim)							
None	1706	1649 (96.66)	4 (3.70–4.30)	1.00 (Reference)		1.00 (Reference)	
Yes	25	21 (84.00)	8 (3.10–12.90)	0.56 (0.36–0.86)	0.009	0.57 (0.31–1.08)	0.084
Unknown	2	2 (100.00)	NA	NA	NA	NA	NA

BM – bone metastasis; AI – American Indian/Alaska Native; API – Asian or Pacific Islander; ESCC – esophageal squamous cell carcinoma; EAC – esophageal adenocarcinoma; Met – metastases; Surg (prim) – surgical treatment of primary site; HR – hazard ratio; CI – confidence interval.

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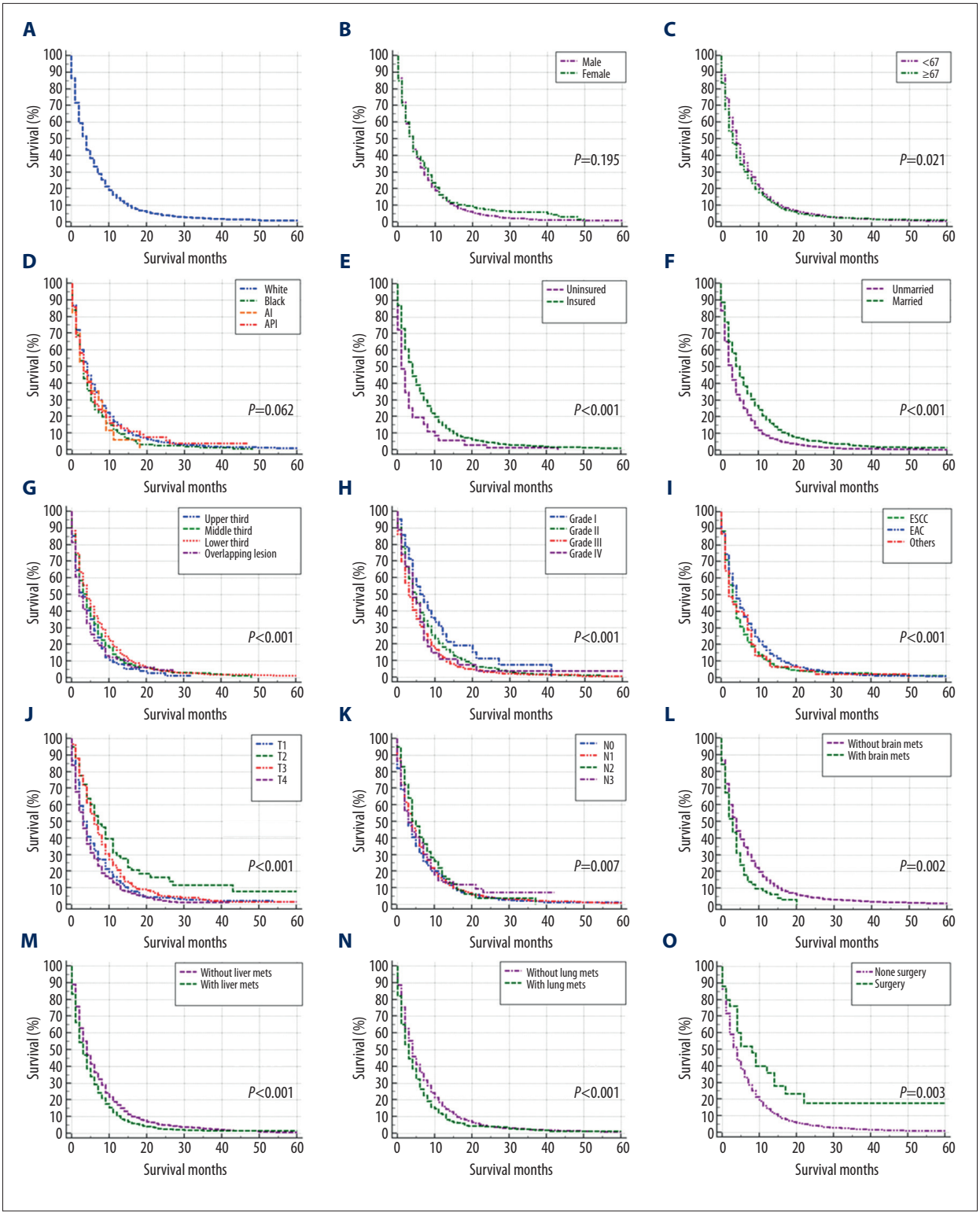

Figure 2. Kaplan-Meier analysis of overall survival for esophageal cancer patients with initial BM. (**A**) Overall; (**B**) sex; (**C**) age; (**D**) race; (**E**) insurance recode; (**F**) marital status; (**G**) primary site; (**H**) grade; (**I**) histopathologic groups; (**J**) T stage; (**K**) N stage; (**L**) brain metastasis; (**M**) liver metastasis; (**N**) lung metastasis; (**O**) surgical treatments on the primary site.

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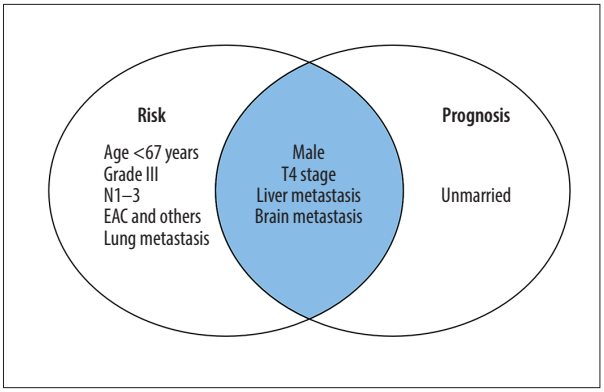

Figure 3. The identification of risk and prognostic factors of BM in esophageal cancer.

Discussion

In the present study, large-population-based research was conducted to thoroughly study the risk and prognostic factors for initial BM in esophageal cancer. Results suggested 8.0% of patients with esophageal cancer were diagnosed with initial BM. Limited by the weakness of BM precise detection in the early stage without significant symptoms, the actual BM incidence in esophageal cancer patients may be underestimated.

Investigating the risk factors was important for identifying patients at high risk for distant metastases [13,14] Results in our study revealed that patients with age younger than 67 years, male sex, T4 stage grade III, N1-3, histological subtype of EAC or others, and metastasis to liver, lung, and brain were more likely to have BM. These revealed risk factors can guide the identification of esophageal cancer patients with high risk of developing BM. A previous study showed that a missed preoperative bone scan was independently associated with poor survival [10]. Thus, bone scans should be recommended for patients with high risk of metastasis. Furthermore, the revealed risk factors could be used to establish an initial BM prediction system in esophageal cancer.

Early diagnosis and timely treatment are crucial to improve the survival of cancer patients. Distant metastases, including liver, lung, and bone, in the advanced stages significantly reduces life expectancy [15]. Thus, identification of predictive prognostic factors is important in clinical cancer management. Previous studies described patterns of distant metastases in esophageal cancer and reported worse survival in male patients [16], unmarried patients [17], black patients and racial difference for surgery [18]. In this study, we further confirmed the females, married patients, and T2 stage are protective factor for BM, while T4 stage, brain metastases, and liver metastases as the risk factors for BM. Surgery was only performed in 25 patients in the cohort, making it difficult to evaluate the real effect of surgery on survival. All these aforementioned prognostic factors can be applied to tailor the individualized treatment regimen and improve patient survival.

EAC and ESCC were the 2 major types of esophageal cancer. Previous studies showed different risk factors and incidence patterns [19], metastatic patterns, and higher male-to-female ratio for BM incidence in different types [20]. In our study, we found more BM occurrence in EAC, but a trend of better survival, although the difference was not statistically significant. Regarding the different origination, main causes, and location for ESCC and EAC [20,21], further research is needed to compare metastatic behavior and survival between these 2 types of esophageal cancer.

Bone is one of the most common metastatic sites for a number of solid tumors. A series of resident cells in bone form the complex tissue and participate in bone functions. Osteoblasts and osteoclasts play major roles in bone remodeling [22]. To meet the various needs of the host, bone physiology can be regulated through osteoblasts and osteoclasts [23]. However, solid tumors can disrupt the delicate balance of bone physiology and result in an environment that promotes metastasis [24]. Recent studies reported the diverse homogeneous and heterogeneous associated factors in cancers correlated with bone metastasis [3,4,13,14]. Few studies have assessed the correlation between bone homeostasis and esophageal cancer, and further research is needed to identify the underlying mechanism.

Currently, there has been no clear screening guide for BM in cancers. For the diagnosis of BM, based on different imaging systems, 5 main imaging strategies are accepted: PET-CT, bone scintigraphy, MRI, CT, and X-ray. In a recent study on prostate cancer patients with BM, PET-CT was proved to have the highest per-patient sensitivity and specificity in detecting BM [25]. Bone scintigraphy has the advantage of being considerably cheaper than PET-CT. A recent study suggested bone scintigraphy combined with parallelepiped classification method could play an important role in the detection of BM, allowing for an easier but correct interpretation of the images [26]. MRI, CT, and X-ray can be applied for the detection of the specific metastatic site. Undoubtedly, with the development of BM diagnostic research, a detailed BM screening guide will be needed.

Based on the largest cohort from the SEER database, we identified homogeneous and heterogeneous factors for initial BM in esophageal cancer patients. Our study has certain limitations that should be mentioned to better interpret the findings. Many important factors, such as region, environment, and genetic characteristics, were not available in the SEER database. Only patients with synchronous diagnosis of cancer and BM are available in the SEER database, making it impossible to evaluate the effect of interval from initial cancer to BM development on survival. Detail types of BM cannot be assessed,

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resulting in bias in survival evaluation. More information on treatment, including chemotherapy, radiotherapy, and surgery, are needed to evaluate their effects on patient survival.

Conclusions

Using the data from the SEER database, we found that the incidence of initial BM in esophageal cancer patients was approximately 8.0%. A series of risk factors for occurrence of BM were found, in which BM was negatively associated with female sex, older age, and higher T stage. More BM was positively associated with grade III, histological EAC subtype, higher N stage, and metastasis to liver, lung, and brain. We also found prognostic factors for BM patient survival in esophageal cancer. Female sex, being married, and T2 stage were the protective factors for survival of BM patients, while T4 stage, brain metastases, and liver metastases were risk factors. Individual assessment and prediction can be performed based on these independent factors, especially the homogeneous factors.

Conflicts of interest

None.

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