RESEARCH ARTICLE

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The Prevalence, Risk Factors for Bone Metastases Development and Prognosis in Gastric Cancer Patients: A Population-based Study

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Abstract

Objective: The objective of the present study was to explore the prevalence, risk and prognostic factors for bone metastases (BM) developement in patients with initial gastric cancer (GC). **Methods:** A total of 30,817 patients with GC in the Surveillance, Epidemiology and End Results (SEER) database, diagnosed from 2010 to 2016, were used to investigate the incidence and associated risk factors for BM developments using multivariate logistic regression. Among those, 1397 and 1121 BM patients were selected to identify independent prognostic factors for BM overall survival (OS) and cancer-specific survival (CSS) using multivariate Cox regression respectively. **Result:** A total of 1397 (4.53%) GC patients were diagnosed with BM at initial diagnosis. Younger age (<60 years), white race, cardia cancer, signet ring cell, higher grade, tumor size between 2.1 and 4.0 cm, the presence of regional lymph nodes (RLN) metastases, brain metastases, liver metastases, and lung metastases were positively associated with BM development. Conversely, a lower T stage was negatively associated with BM development compared to the T4 stage. The median survival time for GC patients with BM decreased dramatically to 5 months. The presence of RLN metastases was an independent predictor of worse overall survival and cancer-specific survival. Conversely, T2 stage and chemotherapy were associated with better overall survival and cancer-specific survival. Additionally, patients with cardia cancer had favorable cancer-specific survival. **Conclusion:** The prognosis of gastric cancer patients with BM was dismal. Our findings of several risk factors for BM development and prognostic factors for BM patients could be useful for clinical surveillance and individualized treatment.

Keywords: gastric cancer, bone metastases, prevalence, risk factor, prognostic factor

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Introduction

Gastric cancer (GC) is the fifth most commonly diagnosed cancer worldwide and the third leading cause of cancer-specific deaths. According to GLOBOCAN 2020, over 1,089,103 new cases of GC and an estimated 768,793 deaths were identified [1]. Radical gastrectomy without residual tumor is the primary curative treatment for GC [2]. The increased rate of early diagnosis and aggressive surgical approaches including extensive lymphadenectomy significantly increased the overall survival of GC [3]. However, after curative treatment, locoregional recurrence and distant recurrence still happened [4-7]. More than 60% of GC patients experienced recurrence after curative resection with a range from 18% to 40% of distant recurrence rate [8-11]. The most frequently metastatic sites are the liver, peritoneum, and lung. Bone metastases (BM) are considered infrequent in GC. The prevalence of BM among GC patients was previously reported from 1.7% to 3.8% [10, 12-15]. Bone scintigraphy, plain radiography, positron emission tomography-computed tomography (PET-CT), and magnetic resonance imaging (MRI) were used as the diagnostic imaging methods of diagnosing BM [16]. The prognosis of GC with BM development is dismal [15, 17, 18]. To date, a number of previous studies have reported the prognostic factors of GC with BM development [12, 14, 15, 18]. Nevertheless, risk factors of BM development in GC are still unclear.

The Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute is a comprehensive source of population-based information on cancer incidence and survival in the United States,

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which including 18 registries covering 28% of the U.S. population. The objective of our study was to explore the prevalence, the risk and prognostic factors for BM development in GC patients by retrospectively reviewing data from this large population database.

Materials and Methods

Patient selection

Patients data was extracted from Incidence – SEER 18 Regs Custom Data (with additional treatment fields), Nov 2018 Sub (1975-2016 varying) using SEER*Stat 8.4.0 software (https://seer.cancer.gov/seerstat/). Because the information on bone metastases was only available after 2010, we restricted eligibility to patients who were aged ≥18 years with the initial diagnosis of gastric cancer between 2010 and 2016. The primary site code was limited to Stomach (C16.0-C16.9), and histology code was limited to adenocarcinoma (8140 to 8147, 8210 to 8211, 8220 to 8221, 8255, 8260 to 8263), mucinous adenocarcinoma (8480 and 8481) and signet ring cell carcinoma (8490) according to the International Classification of Diseases for Oncology-3 (ICD-O-3). The exclusion criteria were as follows: diagnosis at autopsy or via death certificate, and lack of records regarding exact survival time; tumor size code 0 cm or no size of focus given and unknown bone metastases. The detailed population selection procedure was described in the flow chart (Figure 1).

After selection, a total of 30,817 eligible patients initially diagnosed as malignant gastric cancer with or without BM from January 1, 2010, to December 31, 2016, who were used for identifying the prevalence, risk and prognostic factors of BM. Of these, 1397 BM patients were retrieved to analyze the prognostic factors of overall survival (OS) for BM in GC. 1121 BM patients were left after excluding 276 patients who were dead from other causes to predict prognostic factors for cancer-specific survival (CSS).

Demographic and clinical characteristics

Patient demographics and clinical characteristic variables were collected, such as sex (female, male), age (≥60 years, <60 years), race (black, white, others), primary site (cardia and non-cardia), histological type, tumor grade (I , II, III, IV), T stage (T1, T2, T3, T4), tumor size (≤2.0 cm, 2.1-4.0 cm, >4.0 cm), the presence or absence of regional lymph nodes (RLN) metastases, brain metastases, liver metastases, lung metastases, radiation, chemotherapy, gastrectomy, and RLN removed. Tumor histological type included adenocarcinoma, mucinous adenocarcinoma, and signet ring cell carcinoma. Lauren's classification was divided into two types: intestinal type and diffuse type. Radiation and chemotherapy were referred to as the treatment for the primary tumor site.

Statistical analysis

Chi-square test was used to evaluate the differences between groups for categorical variables. The risk factors for GC patients with initial BM were analyzed using a multivariate logistic regression model after the characteristic was significant (with $P<0.05$) by univariate logistic regression. The odds ratio (OR) and corresponding 95% confidence interval (CI) were used to show the association between clinical characteristics and BM development. Kaplan-Meier analysis and log-rank tests were utilized to evaluate OS and CSS differences between different groups of BM patients. Multivariate Cox regression model was conducted to determine independent prognostic factors for BM patients. The hazard ratios (HR) and corresponding 95% confidence interval (CI) were

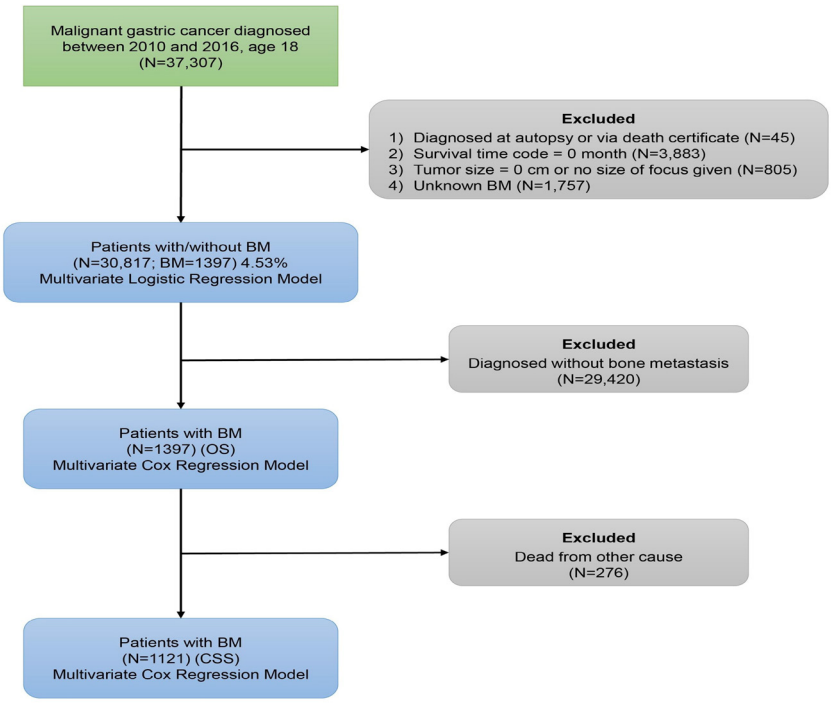

Figure 1. Flow Chart of Inclusion and Exclusion Criteria for Bone Metastases Patients in GC. BM: bone metastasis; OS: overall survival; CSS: cancer-specific survival.

calculated to show the effect of factors on OS and CSS. All statistical analyses and all charts on survival were performed using R language (version 4.0.5). Two-tailed and P-values less than 0.05 were considered statistically significant in all statistical tests.

Results

Prevalence of bone metastases

Based on the inclusion criteria, a total of 30,817 eligible patients were diagnosed with malignant GC. The mean age for those patients was 67.32±13.79 years. Among those, 4.53% (1,397/30,817) of the entire cohort was diagnosed with BM at initial diagnosis and the mean age of BM patients was 62.14±14.06 years. According to the result of Chi-squared test as shown in Table 1, we found that the BM prevalence in younger age (<60 years, P<0.001), white race (P<0.001), cardia cancer (P<0.001), signet ring cell type (P<0.001), diffuse type (P<0.001), grade III (P<0.001), T4 stage (P<0.001), tumor size as 2.1-4.0 cm (P<0.001), the presence of RLN metastases (P<0.001), the presence of brain metastases (P<0.001), the presence of liver metastases (P<0.001), and the presence of lung metastases (P<0.001) were significantly higher than other groups. Furthermore, a higher proportion of patients with BM received chemotherapy compared to those without BM.

Risk factors for developing bone metastases

As demonstrated in Table 2, univariate analysis showed several factors were significantly associated with higher BM risk. These factors were: younger age (<60 years) (OR=1.77, 95% CI: 1.59-1.98, P<0.001), white race (OR=1.59, 95% CI: 1.32-1.92, P<0.001), cardia cancer (OR=1.34, 95% CI: 1.20-1.50, P<0.001), signet ring cell type (OR=1.62, 95% CI: 1.44-1.83, P<0.001), diffuse type (OR=1.45, 95% CI: 1.29-1.63, P<0.001), higher grade (OR=1.35, 95% CI: 1.28-1.41, P<0.001), tumor size as 2.1-4.0 cm (OR=1.67, 95% CI: 1.27-2.20, P<0.001), tumor size >4.0 cm (OR=1.44, 95% CI: 1.11-1.88, P<0.001), the presence of RLN metastases (OR=1.47, 95% CI: 1.30-1.65, P<0.001), the presence of brain metastases (OR=11.01, 95% CI: 8.24-14.72, P<0.001), the presence of liver metastases (OR=3.30, 95% CI: 2.94-3.71, P<0.001), and the presence of lung metastases (OR=7.15, 95% CI: 6.22-8.22, P<0.001). T2 and T3 stage were less likely to have BM than those with T4 stage (OR=0.47, 95% CI=0.34-0.65, P <0.001; OR=0.64, 95% CI=0.52-0.79, P < 0.001; respectively).

Multivariate analyses indicated younger age (<60 years), white race, cardia cancer, signet ring cell type, higher grade, tumor size as 2.1-4.0 cm, the presence of RLN metastases, brain metastases, liver metastases, and lung metastases were positively associated with BM development at initial diagnosis. Lower T stage was negatively associated with BM development at initial diagnosis compared to T4 stage.

Survival time and prognostic factors for BM patients' overall survival (OS) and cancer-specific survival (CSS)

At the end of follow-up, 88.48% (N=1236) of GC patients with initial BM had died. The median overall survival for 1397 BM patients was only 5 months (95% CI: 4.576-5.424 months, Figure 2A), while the median survival of the cohort was 15 months (95% CI: 14.671-15.329, Figure 2B). As shown in Table 3 and Table 4, BM patients with T2 stage, RLN removed and underwent gastrectomy had the longest median survival time (MST) for OS (MST=9 months) and CSS (MST=9 months), while those without chemotherapy treatment showed the shortest MST for OS (MST=2 months) and CSS (MST=2 months). Kaplan-Meier analysis demonstrated the OS and CSS of BM patients with younger age (Figure 3A, 4A), white race (Figure 3B, 4B), cardia cancer (Figure 3C, 4C), lower T stage (Figure 3D, 4D), chemotherapy treatment (Figure 3F, 4F), underwent gastrectomy (Figure 3G, 4G) and RLN removed (Figure 3H, 4H) were better than their counterparts. In contrast, the OS and CSS of patients with RLN metastases were worse than in those without RLN metastases (Figure 3E, 4E). The median OS and CSS of patients receiving chemotherapy treatment were 7 months compared to 2 months without receiving chemotherapy.

Multivariate Cox regression model showed that the presence of RLN metastases independently predicted worse OS and CSS. Conversely, T2 stage was associated with better OS and CSS, while chemotherapy had improved OS and CSS for BM patients. Furthermore, BM patients with cardia cancer also had favorable CSS.

Discussion

The present study utilized the large population provided by the SEER database to investigate the prevalence, risk factors for BM development and prognostic factors for BM patients. Based on our study, we found that 4.53% of GC patients developed BM at initial diagnosis. This result was a little higher than that of previously published studies [10, 12-15]. However, the BM prevalence might be underestimated for unrecording the asymptomatic BM patients. Indeed, recent data indicates that while clinical detection hovers around 4%, autopsy and bone scintigraphy studies reveal a prevalence as high as 13.4–15.9% [19, 20]. Furthermore, BM has been characterized as a late-onset event with a median latency of 16.5 months after radical gastrectomy, suggesting that long-term surveillance is crucial [21].

Previous studies concluded that BM patients had unfavorable prognosis. Our study also proved the dismal prognosis of GC patients with BM (Figure 2A). Thus, determining factors that can identify the clinical characteristics of GC patients who are related to high risk of developing BM is necessary. We identified the clinical characteristics of GC patients who are at high risk of developing BM by using multivariate logistic regression. As shown in our study, we found that younger age (<60 years), white race, signet ring cell type, cardia cancer, diffuse type, higher grade, tumor size as 2.1-4.0 cm, the presence of RLN metastases, brain metastases, liver metastases, and lung metastases increased risk of developing BM.

Signet ring cell type were independent risk factors for BM development, which is an agreement with Kim's study [22]. The association between younger age and

Table 1. Baseline of the Demographic and Related Clinical Characteristics for Patients Diagnosed with Gastric Cancer (diagnosed 2010–2016)

Characteristics	With BM		Without BM		Entire cohort		χ^2	P
	n=1397	4.53%	n=29420	95.47%	N=30817			
Sex							3.3	0.069
Female	463	4.24%	10451	95.76%	10914	35.42%		
Male	934	4.69%	18969	95.31%	19903	64.58%		
Age (67.32±13.79)							106.1	<0.001
≥60	842	3.78%	21444	96.22%	22286	72.32%		
<60	555	6.51%	7976	93.49%	8531	27.68%		
Race							35.5	<0.001
Black	125	3.18%	3803	96.82%	3928	12.75%		
White	1086	4.96%	20802	95.04%	21888	71.03%		
Others	184	3.79%	4670	96.21%	4854	15.75%		
Unknown	2	1.36%	145	98.64%	147	0.47%		
Primary site							28.2	<0.001
Non-cardia	808	4.07%	19062	95.93%	19870	64.48%		
Cardia	589	5.38%	10358	94.62%	10947	35.52%		
Histology							62.6	<0.001
Adenocarcinoma	979	4.05%	23175	95.95%	24154	78.38%		
Mucinous	29	4.84%	570	95.16%	599	1.94%		
Signet ring cell	389	6.41%	5675	93.59%	6064	19.68%		
Lauren's classification							40	<0.001
Intestinal	950	4.10%	22209	95.90%	23159	75.15%		
Diffuse	447	5.84%	7211	94.16%	7658	24.85%		
Grade							178.1	<0.001
I	10	0.76%	1302	99.24%	1312	4.26%		
II	189	2.55%	7216	97.45%	7405	24.03%		
III	867	5.12%	16056	94.88%	16923	54.91%		
IV	12	2.88%	404	97.12%	416	1.35%		
Unknown	319	6.70%	4442	93.30%	4761	15.45%		
T Stage							929.8	<0.001
T1	227	2.96%	7453	97.04%	7680	24.92%		
T2	45	1.61%	2748	98.39%	2793	9.06%		
T3	180	2.20%	7987	97.80%	8167	26.50%		
T4	185	3.39%	5267	96.61%	5452	17.69%		
Unknown	760	11.30%	5965	88.70%	6725	21.83%		
RLN metastases							253.7	<0.001
None	461	3.28%	13611	96.72%	14072	45.66%		
Yes	671	4.73%	13518	95.27%	14189	46.04%		
Unknown	265	10.37%	2291	89.63%	2556	8.30%		
Tumor size							441	<0.001
≤2.0 cm	73	1.81%	3962	98.19%	4035	13.09%		
2.1-4.0 cm	173	2.99%	5620	97.01%	5793	18.80%		
>4.0 cm	229	2.59%	8616	97.41%	8845	28.70%		
Unknown	922	7.59%	11222	92.41%	12144	39.41%		
Brain metastases							1012.8	<0.001
None	1273	4.17%	29235	95.83%	30508	99.00%		
Yes	70	32.41%	146	67.59%	216	0.70%		
Unknown	54	58.06%	39	41.94%	93	0.30%		

Abbreviations: RLN, regional lymph nodes; BM, bone metastases.

Table 1. Continued

Characteristics	With BM		Without BM		Entire cohort		χ^2	P
	n=1397	4.53%	n=29420	95.47%	N=30817			
Liver metastases							547	<0.001
None	903	3.44%	25380	96.56%	26283	85.29%		
Yes	463	10.52%	3939	89.48%	4402	14.28%		
Unknown	31	23.48%	101	76.52%	132	0.43%		
Lung metastases							1191.6	<0.001
None	1029	3.54%	28057	96.46%	29086	94.38%		
Yes	311	20.77%	1186	79.23%	1497	4.86%		
Unknown	57	24.36%	177	75.64%	234	0.76%		
Radiation							19.7	<0.001
No/unknown	917	4.20%	20937	95.80%	21854	70.92%		
Yes	480	5.36%	8483	94.64%	8963	29.08%		
Chemotherapy							54.8	<0.001
No/unknown	464	3.52%	12721	96.48%	13185	42.78%		
Yes	933	5.29%	16699	94.71%	17632	57.22%		
Gastrectomy							963.6	<0.001
None	1353	7.75%	16101	92.25%	17454	56.64%		
Yes	43	0.32%	13229	99.68%	13272	43.07%		
Unknown	1	1.10%	90	98.90%	91	0.29%		
RLN removed							879.8	<0.001
None	1352	7.49%	16702	92.51%	18054	58.58%		
Yes	45	0.35%	12718	99.65%	12763	41.42%		

Abbreviations: RLN, regional lymph nodes; BM, bone metastases.

BM risk is particularly noteworthy. A very recent study on early-onset gastric cancer in 2025 highlighted that BM in younger patients is significantly driven by unique pathological profiles, including immune suppression, inflammatory activation, and coagulopathy [23]. This suggests that the aggressive nature of tumors in younger patients creates a microenvironment favorable for hematogenous dissemination. Lauren diffuse type, tumor T2 stage, proximal tumor, the presence of RLN metastases had reported a higher rate of recurrence compared to their counterparts in patients [24-26]. On the other hand, the proximal (upper one third) was shown as risk factor for the presence of venous invasion [27]. The possible mechanism of hematogenous metastases

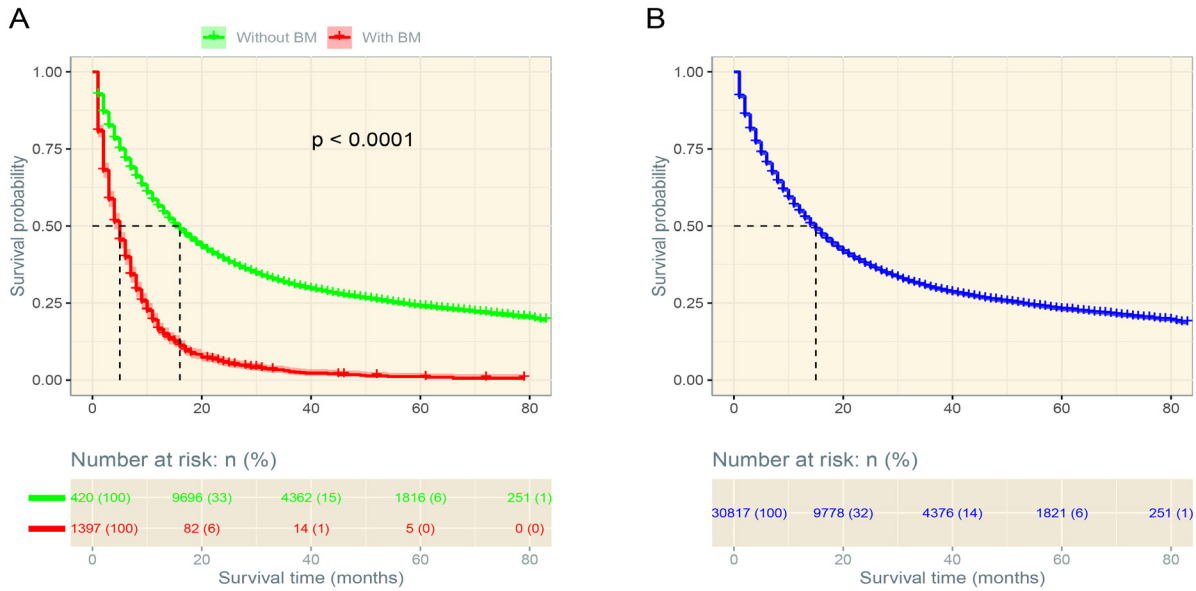

Figure 2. Kaplan–Meier Analysis of Overall Survival among with or without Bone Metastases in Gastric Cancer Patients (A) and the entire cohort (B).

Table 2. Univariate and Multivariate Logistic Regression for Analyzing the Demographic and Related Clinical Characteristics for Bone Metastases in Patients Diagnosed with Gastric Cancer (diagnosed 2010–2016)

Characteristics	With BM	Entire cohort	Prevalence	Univariate analysis		Multivariate analysis	
	n=1397	N=30817	%	OR (95% CI)	P	OR (95% CI)	P
Sex							
Male	934	19903	4.69%	R		NI	
Female	463	10914	4.24%	0.90 (0.80-1.01)	0.069		
Age							
≥60	842	22286	3.78%	R		R	
<60	555	8531	6.51%	1.77 (1.59-1.98)	<0.001	1.51 (1.34-1.70)	<0.001
Race					<0.001		<0.001
Black	125	3928	3.18%	R		R	
White	1086	21888	4.96%	1.59 (1.32-1.92)	<0.001	1.48 (1.21-1.81)	<0.001
Others	184	4854	3.79%	1.20 (0.95-1.51)	0.124	1.37 (1.07-1.74)	0.012
Unknown	2	147	1.36%	NA	NA	NA	NA
Primary site							
Non-cardia	808	19870	4.07%	R		R	
Cardia	589	10947	5.38%	1.34 (1.20-1.50)	<0.001	1.39 (1.22-1.57)	<0.001
Histology					<0.001		0.048
Adenocarcinoma	979	24154	4.05%	R		R	
Mucinous	29	599	4.84%	1.20 (0.82-1.76)	0.336	1.24 (0.82-1.89)	0.307
Signet ring cell	389	6064	6.41%	1.62 (1.44-1.83)	<0.001	1.40 (1.04-1.88)	0.025
Lauren's classification							
Intestinal	950	23159	4.10%	R		R	
Diffuse	447	7658	5.84%	1.45 (1.29-1.63)	<0.001	1.12 (0.84-1.50)	0.428
Grade					<0.001		<0.001
I	10	1312	0.76%	R		R	
II	189	7405	2.55%	3.41 (1.80-6.46)	<0.001	2.423(1.27-4.63)	0.007
III	867	16923	5.12%	7.03 (3.76-13.15)	<0.001	4.62 (2.45-8.73)	<0.001
IV	12	416	2.88%	3.87 (1.66-9.02)	0.002	3.05 (1.28-7.25)	0.012
Unknown	319	4761	6.70%	NA	NA	NA	NA
T Stage					<0.001		<0.001
T1	227	7680	2.96%	0.87 (0.71-1.06)	0.157	1.22 (0.98-1.51)	0.079
T2	45	2793	1.61%	0.47 (0.33-0.65)	<0.001	0.66 (0.47-0.92)	0.015
T3	180	8167	2.20%	0.64 (0.52-0.79)	<0.001	0.76 (0.61-0.95)	0.014
T4	185	5452	3.39%	R		R	
Unknown	760	6725	11.30%	NA	NA	NA	NA
RLN metastases					<0.001		<0.001
None	461	14072	3.28%	R		R	
Yes	671	14189	4.73%	1.47 (1.30-1.65)	<0.01	1.51 (1.31-1.73)	<0.001
Unknown	265	2556	10.37%	NA	NA	NA	NA
Tumor size					<0.001		<0.001
≤2.0 cm	73	4035	1.81%	R		R	
2.1-4.0 cm	173	5793	2.99%	1.67 (1.27-2.20)	<0.001	1.38 (1.04-1.84)	0.028
>4.0 cm	229	8845	2.59%	1.44 (1.11-1.88)	0.007	1.01 (0.76-1.34)	0.936
Unknown	922	12144	7.59%	NA	NA	NA	NA
Brain metastases					<0.001		<0.001
None	1273	30508	4.17%	R		R	
Yes	70	216	32.41%	11.01 (8.24-14.72)	<0.001	4.42 (3.19-6.12)	<0.001
Unknown	54	93	58.06%	NA	NA	NA	NA

Abbreviations: RLN, regional lymph nodes; BM, bone metastases; OR, odds ratio; CI, confidence interval; R, reference; NA, not applicable; NI, not included

Table 2. Continued

Characteristics	With BM	Entire cohort	Prevalence	Univariate analysis		Multivariate analysis	
	n=1397	N=30817	%	OR (95% CI)	P	OR (95% CI)	P
Liver metastases					<0.001		<0.001
None	903	26283	3.44%	R		R	
Yes	463	4402	10.52%	3.30 (2.94-3.71)	<0.001	1.62 (1.41-1.87)	<0.001
Unknown	31	132	23.48%	NA	NA	NA	NA
Lung metastases					<0.001		<0.001
None	1029	29086	3.54%	R		R	
Yes	311	1497	20.77%	7.15 (6.22-8.22)	<0.001	3.66 (3.13-4.29)	<0.001
Unknown	57	234	24.36%	NA	NA	NA	NA

Abbreviations: RLN, regional lymph nodes; BM, bone metastases; OR, odds ratio; CI, confidence interval; R, reference; NA, not applicable; NI, not included

of GC was suggested that gastric cancer cells might invade through portal vein or lymphatic channels into the systemic circulation [28]. This reason may also illustrate why BM development was associated with the presence of RLN, brain, liver, lung metastases and cardia cancer. Moreover, the bone microenvironment itself, involving interactions between RANKL, PTHrP, and tumor cells, plays a critical role in facilitating these metastases [29]. In contrast, lower T stage was negatively associated with BM at initial diagnosis compared to T4 stage. Bone scintigraphy showed its high sensitivity to detect BM [16, 17, 20]. Accordingly, screening examinations such as bone scintigraphy, PET-CT could be recommended for GC patients with the above-mentioned factors.

Our findings regarding the risk factors for BM development have practical implications for clinical surveillance. The strong association between advanced T-stage, RLN involvement, and the occurrence of BM suggests that clinicians should maintain a high index of suspicion for skeletal involvement in these subgroups. Specifically, for patients presenting with T4 stage or extensive RLN metastases at initial diagnosis, proactive skeletal screening such as bone scintigraphy or targeted imaging could lead to earlier detection of BM, potentially before the onset of debilitating skeletal-related events.

The median survival of GC patients with BM was reported previously to be approximately 3-4 months [14, 17, 30]. In the present study, the median survival of the entire cohort was 15 months. Once GC patients were diagnosed with BM development, the median survival dramatically decreased to 5 months. It is noteworthy that BM patients who received chemotherapy treatment can be prolonged from 2 months to 7 months of MST. Although the National Comprehensive Cancer Network (NCCN) guidelines recommend individualized systemic chemotherapy based on HER2 status and specific agents like trastuzumab or ramucirumab, our study reflects a broad clinical benefit across the population. Given the nature of the SEER database, this observed improvement in MST from 2 to 7 months represents the collective

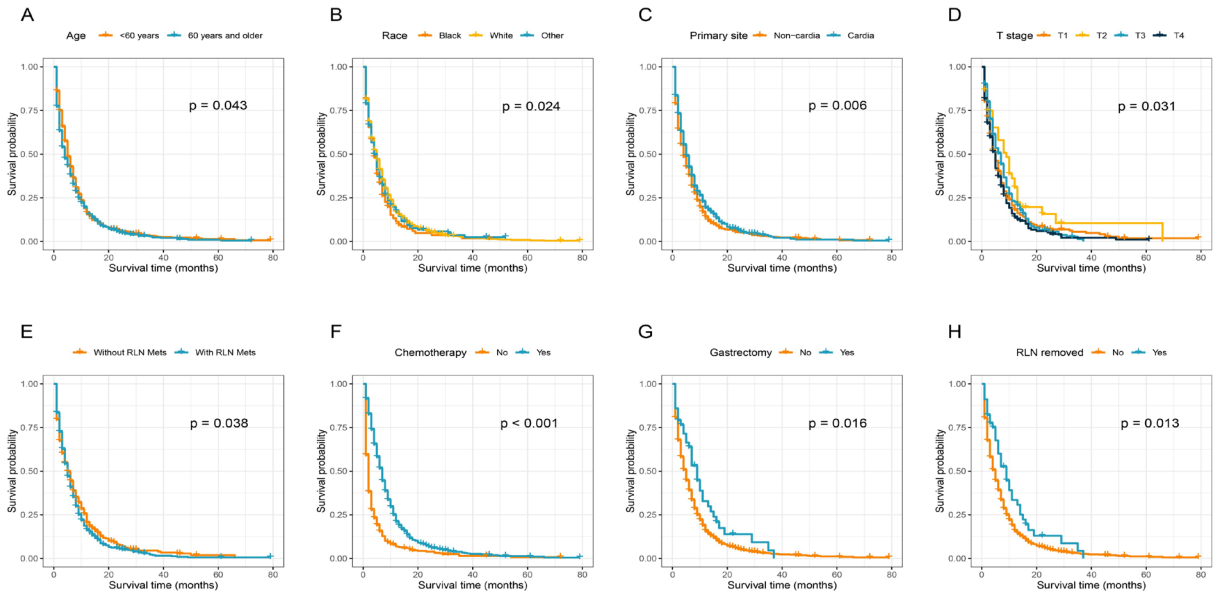

Figure 3. Kaplan–Meier Analysis of OS among BM Patients in GC Stratified by Age (A), race (B), tumor site (C), T stage (D), the presence of RLN mets (E), chemotherapy (F), gastrectomy (G), RLN removed (H). OS: overall survival; BM: bone metastases; GC: gastric cancer; RLN: regional lymph nodes; mets: metastases.

Table 3. Univariate Log-Rank and Multivariate Cox Regression for Analyzing the Overall Survival among Gastric Cancer Patients with Bone Metastases (diagnosed 2010–2016)

Characteristics	Number of GC patients with BM (2010-2016)					Multivariate analysis	
	Overall (OS)	Deceased (OS)		Median survival time	P	HR (95%CI)	P
	n=1397	n=1236	(rate, %)	(95% CI, month)			
Sex						NI	
Female	463	401	86.61%	4 (3.357-4.643)	0.643		
Male	934	835	89.40%	5 (4.493-5.507)			
Age					0.043		
≥60	842	752	89.31%	4 (3.490-4.510)		R	
<60	555	484	87.21%	5 (4.421-5.579)		0.98 (0.87-1.11)	0.779
Race					0.024		
Black	125	114	91.20%	4 (3.000-5.000)		R	
White	1086	963	88.67%	5 (4.000-NA)		0.94 (0.77-1.15)	0.531
Others	184	159	86.41%	4 (3.000-5.000)		0.96 (0.75-1.22)	0.729
Unknown	2	0	0.00%	NA		NA	NA
Primary site					0.006		
Non-cardia	808	712	88.12%	4 (3.457-4.543)		R	
Cardia	589	524	88.96%	5 (4.363-5.637)		0.91 (0.80-1.02)	0.109
Histology					0.182	NI	
Adenocarcinoma	979	866	88.46%	5 (4.512-5.488)			
Mucinous	29	24	82.76%	8 (3.130-12.870)			
Signet ring cell	389	346	88.95%	5 (4.167-5.833)			
Lauren's classification					0.579	NI	
Intestinal	950	841	88.53%	5 (4.495-5.505)			
Diffuse	447	395	88.37%	5 (4.220-5.780)			
Grade					0.195	NI	
I	10	9	90.00%	4 (2.418-5.582)			
II	189	168	88.89%	5 (3.830-6.170)			
III	867	771	88.93%	5 (4.421-5.579)			
IV	12	9	75.00%	6 (0.309-11.691)			
Unknown	319	279	87.46%	NA			
T Stage					0.003		
T1	227	208	91.63%	5 (4.071-5.929)		0.88 (0.72-1.09)	0.248
T2	45	36	80.00%	9 (5.877-12.123)		0.61 (0.42-0.88)	0.007
T3	180	159	88.33%	7 (5.674-8.326)		0.79 (0.63-0.98)	0.035
T4	185	162	87.57%	5 (4.177-5.823)		R	
Unknown	760	671	88.29%	4 (3.486-4.514)		NA	NA
RLN metastases					<0.001		<0.001
None	461	395	85.68%	5 (4.121-5.879)		R	
Yes	671	602	89.72%	5 (4.475-5.525)		1.30 (1.13-1.49)	<0.001
Unknown	265	239	90.19%	NA		NA	NA
Tumor size					0.831	NI	
≤2.0 cm	73	60	82.19%	6 (2.624-9.376)			
2.1-4.0 cm	173	151	87.28%	5 (3.891-6.109)			
>4.0 cm	229	209	91.27%	5 (3.940-6.060)			
Unknown	922	816	88.50%	NA			
Brain metastases					0.299	NI	
None	1273	1120	87.98%	5 (4.547-5.453)			
Yes	70	64	91.43%	3 (2.404-3.596)			
Unknown	54	52	96.30%	NA			

Abbreviations: RLN, regional lymph nodes; BM, bone metastases; OR, odds ratio; CI, confidence interval; R, reference; NA, not applicable; NI, not included.

Table 3. Continued

Characteristics	Number of GC patients with BM (2010-2016)				Multivariate analysis	
	Overall (OS) n=1397	Deceased (OS) n=1236	(rate, %)	Median survival time (95% CI, month)	P	HR (95%CI)	P
Liver metastases					0.957	NI	
None	903	798	88.37%	5 (4.476-5.524)			
Yes	463	410	88.55%	4 (3.293-4.707)			
Unknown	31	28	90.32%	NA			
Lung metastases					0.569	NI	
None	1029	904	87.85%	5 (4.492-5.508)			
Yes	311	278	89.39%	4 (3.231-4.769)			
Unknown	57	54	94.74%	NA			
Radiation					0.935	NI	
No/unknown	917	813	88.66%	5 (4.434-5.566)			
Yes	480	423	88.13%	5 (4.402-5.598)			
Chemotherapy					<0.001		
No/unknown	464	428	92.24%	2 (1.789-2.211)		R	
Yes	933	808	86.60%	7 (6.518-7.482)		0.44 (0.39-0.50)	<0.001
Gastrectomy					0.026		
None	1353	1200	88.69%	5 (4.598-5.402)		R	
Yes	43	35	81.40%	9 (6.524-11.476)		0.77 (0.39-1.52)	0.447
Unknown	1	1	100.00%	NA		NA	NA
RLN removed					0.013		
None	1352	1199	88.68%	5 (4.598-5.402)		R	
Yes	45	37	82.22%	9 (6.012-11.988)		0.73 (0.38-1.42)	0.359

Abbreviations: RLN, regional lymph nodes; BM, bone metastases; OR, odds ratio; CI, confidence interval; R, reference; NA, not applicable; NI, not included.

efficacy of various systemic interventions available during the study period. This is in accordance with previous studies, GC patients with BM who had received chemotherapy had a significantly longer MST than those

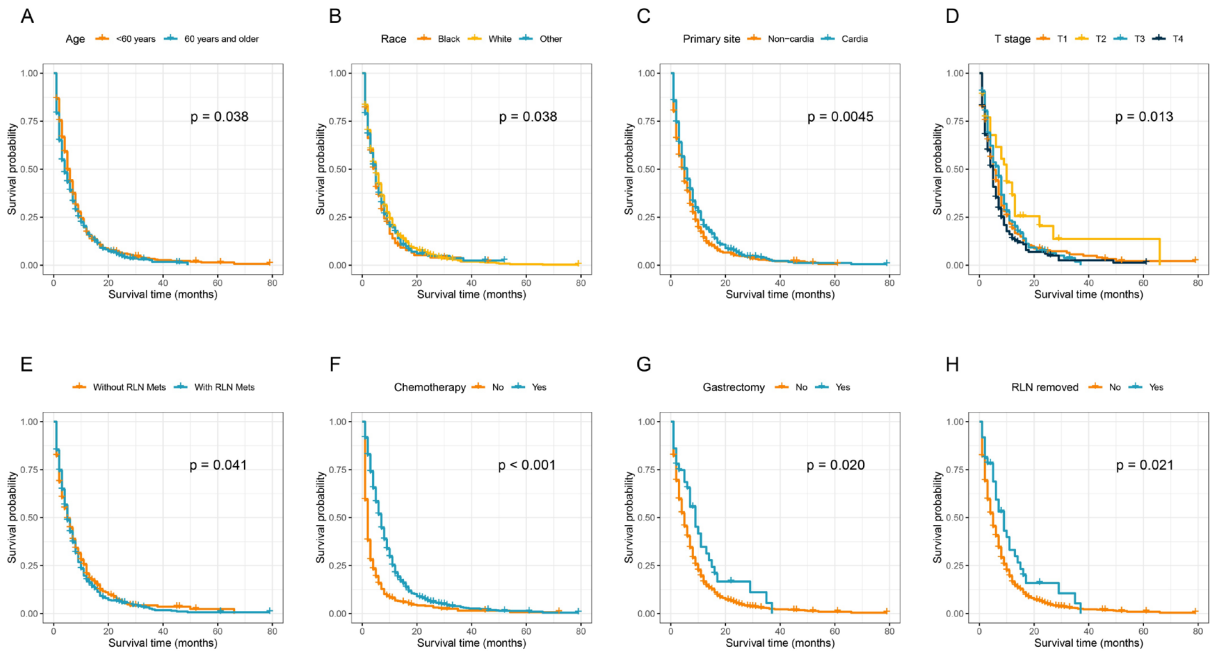

Figure 4. Kaplan–Meier Analysis of CSS among BM Patients in GC Stratified by age (A), race (B), tumor site (C), T stage (D), the presence of RLN mets (E), chemotherapy (F), gastrectomy (G), RLN removed (H). CSS: cancer-specific survival; BM: bone metastases; GC: gastric cancer; RLN: regional lymph nodes; mets; metastases.

Table 4. Univariate Log-Rank and Multivariate Cox Regression for Analyzing the Cancer-Specific Survival among Gastric Cancer Patients with Bone Metastases (Diagnosed 2010–2016)

Characteristics	Number of GC patients with bone metastases (2010-2016)					Multivariate analysis	
	Overall (CSS) n=1121	Deceased (CSS) n=989	(rate, %)	Median survival time (95% CI, month)	P	HR (95%CI)	P
Sex					0.732	NI	
Female	362	309	85.36%	5 (4.337-5.663)			
Male	759	680	89.59%	5 (4.416-5.584)			
Age					0.038		
≥60	614	548	89.25%	4 (3.443-4.557)		R	
<60	507	441	86.98%	5 (4.4165-5.584)		0.95 (0.83-1.08)	0.42
Race					0.034		
Black	104	94	90.38%	NA		R	
White	850	753	88.59%	NA		0.97 (0.78-1.21)	0.807
Others	165	142	86.06%	NA		1.01 (0.78-1.31)	0.944
Unknown	2	0	0.00%	NA		NA	NA
Primary site					0.004		
Non-cardia	645	565	87.60%	5 (4.442-5.558)		R	
Cardia	476	424	89.08%	6 (5.2316.769)		0.86 (0.75-0.98)	0.025
Histology					0.413	NI	
Adenocarcinoma	770	682	88.57%	5 (4.421-5.579)			
Mucinous	25	20	80.00%	8 (3.570-12.430)			
Signet ring cell	326	287	88.04%	5 (4.128-5.872)			
Lauren's classification					0.552	NI	
Intestinal	754	669	88.73%	5 (4.421-5.579)			
Diffuse	367	320	87.19%	5 (4.189-5.811)			
Grade					0.249	NI	
I	9	8	88.89%	4 (2.442-5.558)			
II	149	132	88.59%	5 (3.741-6.259)			
III	696	615	88.36%	5 (4.375-5.625)			
IV	9	7	77.78%	4 (1.381-6.619)			
Unknown	258	227	87.98%	NA			
T Stage					0.001		0.049
T1	182	167	91.76%	5 (3.788-6.212)		0.84 (0.66-1.06)	0.14
T2	36	27	75.00%	10 (7.255-12.745)		0.55 (0.36-0.83)	0.005
T3	147	128	87.07%	7 (5.703-8.297)		0.80 (0.63-1.02)	0.072
T4	158	137	86.71%	5 (4.160-5.840)		R	
Unknown	598	530	88.63%	NA		NA	NA
RLN metastases					<0.001		0.004
None	359	307	85.52%	5 (4.001-5.999)		R	
Yes	556	496	89.21%	5 (4.393-5.607)		1.25 (1.07-1.45)	0.005
Unknown	206	186	90.29%	NA		NA	NA
Tumor size					0.549	NI	
≤2.0 cm	58	47	81.03%	6 (2.179-9.821)			
2.1-4.0 cm	137	119	86.86%	5 (3.789-6.211)			
>4.0 cm	188	169	89.89%	6 (4.789-7.211)			
Unknown	738	654	88.62%	NA			
Brain metastases					0.254	NI	
None	1019	894	87.73%	5 (4.506-5.494)			
Yes	60	55	91.67%	3 (2.414-3.586)			
Unknown	42	40	95.24%	NA			

Abbreviations: RLN, regional lymph nodes; BM, bone metastases; CSS, cancer-specific survival; HR, hazard ratio; CI, confidence interval; R, reference; NA, not applicable; NI, not included.

Table 4. Continued

Characteristics	Number of GC patients with bone metastases (2010-2016)					Multivariate analysis	
	Overall (CSS) n=1121	Deceased (CSS) n=989	(rate, %)	Median survival time (95% CI, month)	P	HR (95%CI)	P
Liver metastases					0.849	NI	
None	711	624	87.76%	5 (4.413-5.587)			
Yes	383	341	89.03%	5 (4.281-5.719)			
Unknown	27	24	88.89%	NA			
Lung metastases					0.448	NI	
None	833	732	87.88%	5 (4.458-5.542)			
Yes	242	214	88.43%	4 (3.209-4.791)			
Unknown	46	43	93.48%	NA			
Radiation					0.901	NI	
No/unknown	736	650	88.32%	5 (4.409-5.591)			
Yes	385	339	88.05%	5 (4.310-5.690)			
Chemotherapy					<0.001		
No/unknown	322	302	93.79%	2 (1.753-2.247)		R	
Yes	799	687	85.98%	7 (6.457-7.525)		0.41 (0.36-0.48)	<0.001
Gastrectomy					0.02		
None	1085	960	88.48%	5 (4.529-5.471)		R	
Yes	36	29	80.56%	9 (5.242-12.758)		0.71 (0.31-1.60)	0.409
RLN removed					0.021		
None	1084	959	88.47%	5 (4.522-5.478)		R	
Yes	37	30	81.08%	9 (5.835-12.165)		0.71 (0.34-1.70)	0.503

Abbreviations: RLN, regional lymph nodes; BM, bone metastases; CSS, cancer-specific survival; HR, hazard ratio; CI, confidence interval; R, reference; NA, not applicable; NI, not included.

had not received chemotherapy [14, 31-33]. Therefore, performing chemotherapy should be considered to improve the prognosis of GC patients with BM. In terms of primary tumor site, BM patients with cardia cancer also had favorable CSS. As a result, the presence of RLN metastases independently predicted worse OS and CSS in BM patients. This is also in accordance with Kodera's study [34]. Clinical physicians should pay more attention to GC patients with the presence of RLN metastases. Interestingly, we found that BM patients with T2 stage showed better OS and CSS than other tumor stage groups. The reasons were unclear and we thought that the inaccuracy of clinical staging might explain this phenomenon. Moreover, previous studies revealed that high level of serum alkaline phosphatase (ALP), lactate dehydrogenase (LDH), carcinoembryonic antigen 19-9 (CA19-9), carcinoembryonic antigen (CEA), and calcium represented as poor prognostics factors of BM patients [12, 15, 20, 22, 35]. Further studies should be conducted to find more prognostic factors to construct a predictive system for GC patients with BM.

From a clinical perspective, these findings emphasize the need for a multimodal management approach. Integrating bone-targeted agents alongside systemic chemotherapy, as guided by our prognostic data, may not only improve survival but also enhance the quality of life by reducing bone pain and preventing pathological fractures. Our study serves as a clinical reminder that BM management in GC should be comprehensive, combining early detection in high-risk groups with optimized systemic and supportive care.

Our study had some limitations. Firstly, the BM prevalence might be underestimated due to the potential under-reporting of asymptomatic BM patients in the SEER database. Secondly, the SEER database did not record information regarding the specific site of BM or the specific treatment modality for these metastases. Thirdly, data on serum tumor markers, skeletal-related events, comorbidities, HER2 status, and performance status were unavailable. Fourthly, a significant limitation regarding systemic therapy is that the SEER database records chemotherapy status only as 'Yes' or 'No/Unknown.' Consequently, we were unable to distinguish between specific treatment regimens, such as targeted therapies (e.g., trastuzumab or ramucirumab) versus traditional cytotoxic drugs. Therefore, our findings should be interpreted as reflecting the general survival benefit of systemic treatment rather than the efficacy of a specific clinical protocol. Lastly, excluding patients with incomplete information might have introduced selection bias. Additionally, external validation using a separate dataset was not performed in our study. Hence, further prospective studies are needed to confirm these results and provide more granular data in the future.

In conclusion, our study demonstrated the prevalence of BM, several risk factors for BM development and prognostic factors for BM patients. Despite the dismal prognosis of BM, chemotherapy showed a significant

benefit to BM patients' OS and CSS. Our findings could be helpful for clinical surveillance and individualized treatment of BM.

Author Contribution Statement

All authors contributed equally in this study.

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Ethical Declaration

Because the SEER database is an open-access database, after signing the Data Use Agreement for the SEER 1975–2016 Research Data we were allowed to access to the SEER database to abstract the data, so we did not need to acquire patient' informed consent or ethical review committee statement.

Data Availability

The datasets used and/or analyzed during the current study will be made available from the corresponding author on reasonable request.

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