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Original Article

Characteristics and prognostic factors of distant metastasis in gallbladder cancer

Jin Zhang[1], Haixiao Wu[1], Sahbi Khaled Taieb[2], Lisha Qi[3], Karl Peltzer[4], Vladimir P Chekhonin[5], Chao Zhang[1]

[1]Department of Bone and Soft Tissue Tumors, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Centre for Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin's Clinical Research Centre for Cancer, Tianjin, China; [2]Tianjin Medical University, Tianjin, China; [3]Department of Pathology, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Centre for Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin's Clinical Research Centre for Cancer, Tianjin, China; [4]Department of Research & Innovation, University of Limpopo, Turfloop, South Africa; [5]Department of Basic and Applied Neurobiology, Federal Medical Research Center for Psychiatry and Narcology, Moscow, Russian Federation

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Abstract: Objective: Gallbladder cancer (GBC) is a rare malignant tumor with high mortality rate. We aimed to describe the distant metastatic patterns and to investigate the risk and prognostic factors of GBC patients with distant metastasis. Methods: Based on the Surveillance, Epidemiology, and End Result (SEER) database, GBC patients with distant metastasis from 2010 to 2015 were involved. Distant metastatic patterns were described in the total cohort and across different organs. Risk factors and prognostic factors of the whole cohort and different metastatic sites were analyzed by logistic regression and Cox hazard regression analysis. Results: 5,907 eligible patients with GBC were included, among which 2,223 patients (37.6%) displayed distant metastasis. Liver was the most common metastatic site being observed in 1525 patients (68.3%), followed by N2 lymph nodes (15.5%), lung (13.0%), bone (6.3%), and brain (1.1%). The age (<71), married status, poorly differentiated grade, adenocarcinoma subtype, T3 and T4 stage were independent risk factors for development of distant metastasis. Median survival of the metastatic GBC was 3.0 (2.68-3.32) months and the 1-year and 3-year survival rates were 15% and 2.8%, respectively. Age (≥71 years), unmarried status, and grade III were negatively associated with survival of metastatic GBC, while surgery can improve it. Distant metastatic sites did not show a correlation with the patient' s overall survival. Conclusions: GBC with distant metastasis indicated poor prognosis. A bundle of risk and prognostic factors were revealed, which may guide metastatic screening for GBC patients with high risk and individualized treatment in clinical practice.

Keywords: Gallbladder cancer, distant metastasis, SEER, characteristics, prognostic factors

Introduction

Gallbladder cancer (GBC) has been known as a rare malignant cancer. The incidence rate of GBC was reported to be 1.31/100,000 person-years in USA from 2001 to 2012 [1]. Compared with other continents, GBC is more common in Asia [2, 3]. Despite of the advances in detection and treatment modalities for GBC, the survival of GBC patients remains poor. It has been estimated that the GBC-related median survival time was only 10 months and the 5-year survival rate was 13% [1, 4]. A large proportion of GBC patients are diagnosed in advanced stages due to its asymptomatic course in early stages, and the lack of a clear screening strategy [5, 6].

Distant metastasis is one of the characteristics of advanced GBC. Reports on breast cancer [7], lung cancer [8], prostate cancer [9], esophagus cancer [10], and ovarian cancer [11] displayed patterns of distant metastases, which had a negative impact on survival. GBC with distant metastasis has seldom been systematically studied. A series of case reports suggested the metastatic ability of GBC to metastasize to brain [12], breast [13], and liver [14]. In a respective single-center retrospective analysis of 340 GBC cases, seven (2.1%) cases dis-

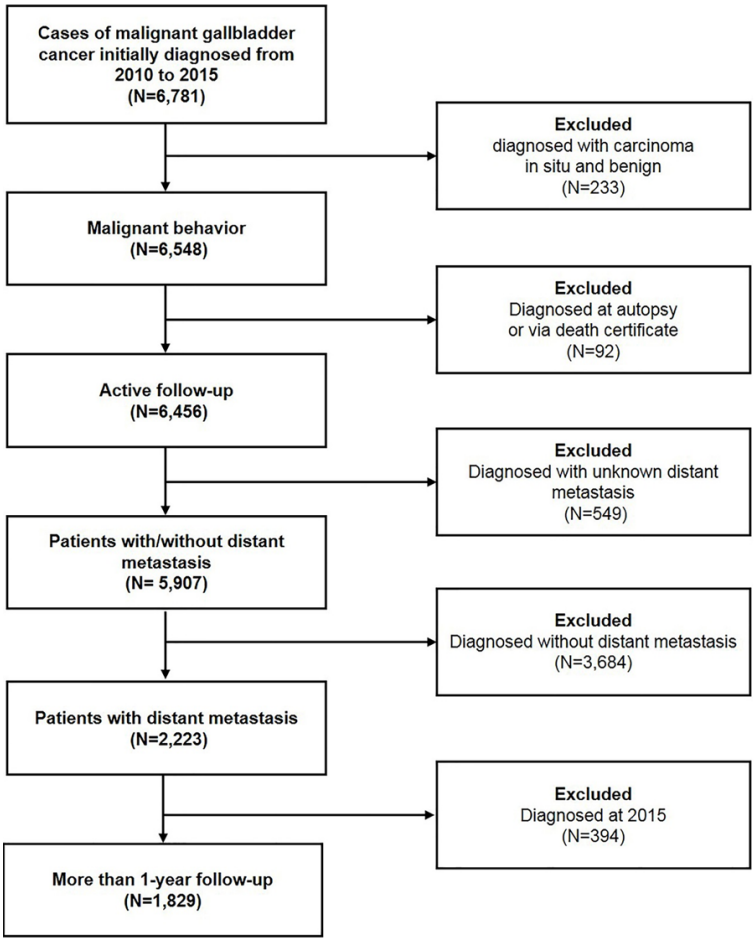

Figure 1. Flowchart of the patient selection for analyzing the risk factors for the morbidity and prognosis of distant metastasis in gallbladder cancer patients.

played skeletal metastasis, including 5 vertebral, 2 pelvic, one skull, and one sternal bone metastases [15]. In order to achieve a comprehensive understanding of GBC with distant metastasis, a large population study on GBC is required. Meanwhile, the survival of GBC patients with distant metastasis has not been estimated yet.

Thus, we performed the present study based on a large cohort of GBC patients. The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database is a commonly used database for evaluation of cancer epidemiology worldwide, which covers around 30% of the total US population. In the present study, based on records from the SEER database, we aimed to investigate the patterns of distant metastases in GBC cancer. Furthermore, the survival and prognostic factors of distant metastases were evaluated.

Materials and methods

Data source and cohort selection

The National Cancer Institute's SEER*Stat software was used to identify patients who were diagnosed as malignant GBC between 2010 and 2015, and the data regarding sites of metastases (including liver, lung, bone, brain) were recorded. The exclusive criteria were as the following: patients diagnosed as carcinoma in situ and benign; patients diagnosed at autopsy or via death certificate; patients diagnosed as unknown distant metastasis. In order to analyze the prognostic factors of metastatic patients with at least 1-year follow up, patients diagnosed without distant metastasis and diagnosed at 2015 were excluded after the logistic regression analysis. The flow-chart of the subjects' selection is listed in **Figure 1**.

SEER database is a freely available database, and the data released by the SEER database do not require informed patient consent, because cancer is a reportable disease in every state of the USA. The present study complied with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Statistical analysis

The patient-related variables included gender (female and male); race (white, black, American Indian/Alaska Native (AI), and Asian or Pacific Islander (API)); age (<71 and ≥71 years); insurance status (insured and uninsured); marital status (married and unmarried); tumor grade (grade I, II, III, and IV); histologic subtypes (adenocarcinoma and non-adenocarcinoma); T stage (T1, T2, T3, and T4); presence or absence of lung, liver, brain, bone, or distant lymph node metastases.

Categorical variables were presented as number and the percentage (N, %) while Pearson

chi-square (χ^2) or Fisher' exact test was used to evaluate the differences between demographic and clinicopathological variables. To identify risk factors for distant metastasis, logistic regression analysis was used. Variables with statistical difference (with $P<0.05$) in univariate logistic regression analysis were further analyzed with the multivariate analysis. In survival analysis, overall survival (OS) was the primary outcome in the present study, which was defined as the time from the diagnosis to all causes of death. To identify prognostic factors of metastatic patients, univariate Cox proportional hazards regression were performed. Factors that were significant (with a *P* value less than 0.05) were then analyzed with multivariate analysis. To evaluate the effect of multiple metastases on the prevalence of metastasis and prognosis of patients, we further calculated the sum of metastatic sites (liver, N2 lymph node, lung, bone and brain). Survival curves were generated using the Kaplan-Meier method; the differences between the curves were tested by a log-rank test.

All the data were obtained using SEER*Stat Software version 8.3.5. All statistical analyses were performed using SPSS 23.0 (IBM Corporation, Armonk, NY, USA), and all survival curves were generated by MedCalc 15.2.2. Two-sided *P*-values <0.05 were considered statistically significant.

Results

Patient characteristics

According to the pre-defined inclusion criteria, 5,907 eligible patients were included with GBC from 2010 to 2015, with the median age of 71 years old (**Table 1**). Female was the predominantly affected gender in the cohort with 68.7% of all patients, while white race (75.1%) was the predominant race. 94.8% of patients got medical insurance. As to the histological subtypes, the adenocarcinoma (83.3%) was the main type in GBC patients. The main grades of primary tumor were grade II (29.8%) and grade III (30.1%) after excluding 31.0% of patients without clear grade information. About 39.7% of the eligible patients were diagnosed with T3 stage, while 28.1% with T2 stage and 14.1% with T1 stage. Totally, 64.8% of the GBC received surgery on gallbladder.

Distant metastatic patterns and risk factors

According to the AJCC 7th edition, for the included patients, 2,223 patients (37.6%) showed distant metastases (M1). The prevalence of DM were successively presented in liver (1525 cases, 68.3%), N2 lymph nodes (344 patients, 15.5%), lung (289 cases, 13.0%), bone (139 cases, 6.3%), and brain (24 cases, 1.1%). Among the cohort, no clear metastasis to liver, lymph nodes (>N2), lung, bone or brain was recorded for 481 (21.6%) patients; 1345 (60.5%) patients suffered from metastasis in only one of the aforementioned sites, while 397 patients (17.9%) suffered more than one site.

Multivariable analysis revealed a bundle of independent risk factors for distant metastasis including the age (<71 years), married status, grade (II, III, and IV), adenocarcinoma type, T3 stage and T4 stage. Gender, race and insurance status did not significantly influence the development of distant metastasis. The associated factors for distant metastasis were not consistent when stratified by different organs. Results showed patients' age (<71 years), poor differentiation grade, T3 stage and T4 stage were independent risk factors for liver metastasis. As to lymph nodes involvement, younger than 71 years old, married status, T3 stage and T4 stage were independent risk factors for metastasis. Lung metastasis was more common in adenocarcinoma type. Besides, patients' age (<71 years) and poor differentiation grade had greater odds to develop bone metastasis. However, no factors were independently associated with brain metastasis. In the present study, multiple metastases were risk factors for metastasis across all of these organs. (**Table 2**).

Survival of patients with distant metastasis and prognostic factors

For the GBC patients diagnosed from 2010 to 2014, the median survival time for patients with and without distant metastasis were 3.0 (2.68-3.32) months and 17.0 (15.81-18.19) months, respectively. The survival curses for patients with and without distant metastasis were illustrated in **Figure 2**. When stratified by different metastatic organs, the median survival for liver was 3.0 (2.65-3.35) months, N2 lymph nodes 6.0 (4.86-7.14) months, lung 2.0

Table 1. Description of the SEER population of patients with GBC by distant metastasis at diagnosis

Subject characteristics	M		Bone-metastasis		Brain-metastasis		Liver-metastasis		Lung-metastasis		N-metastasis		
	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	N0/N1	N2	Nx
Sex (χ^2, *P*-value)	*0.700*	*0.403*	*2.606*	*0.106*	*0.357*	*0.55*	*0.84*	*0.359*	*0.068*	*0.794*	*0.682*	*0.711*	
Female	2,497	1,530	3,941	86	4,012	15	2,973	1,054	3,832	195	3,463	236	328
Male	1,187	693	1,827	53	1,871	9	1,409	471	1,786	94	1,607	108	165
Race (χ^2, *P*-value)	*8.538*	*0.074*	*1.048*	*0.902*	*11.362*	*0.023*	*9.233*	*0.056*	*3.262*	*0.515*	*14.067*	*0.080*	
White	2,783	1,650	4,328	105	4,414	19	3,317	1,116	4,223	210	3,797	262	374
Black	461	329	773	17	789	1	553	237	743	47	688	43	59
API	376	211	572	15	584	3	436	151	561	26	501	35	51
AI	47	28	74	1	75	0	58	17	71	4	69	3	3
Unknown	17	5	21	1	21	1	18	4	20	2	15	1	6
Age (χ^2, *P*-value)	*21.266*	*<0.001*	*5.094*	*0.024*	*2.829*	*0.093*	*6.417*	*0.011*	*0*	*0.985*	*37.477*	*<0.001*	
<71	1,739	1,187	2,844	82	2,910	16	2,128	798	2,783	143	2,453	225	248
≥71	1,945	1,036	2,924	57	2,973	8	2,254	727	2,835	146	2,617	119	245
Insurance Recode (χ^2, *P*-value)	*0.728*	*0.695*	*7.208*	*0.027*	*1.406*	*0.495*	*3.314*	*0.191*	*1.314*	*0.518*	*18.182*	*0.001*	
Insured	3,497	2,105	5,476	126	5,579	23	4,169	1,433	5,329	273	4,823	324	455
Uninsured	114	77	181	10	191	0	132	59	183	8	156	17	18
Unknown	73	41	111	3	113	1	81	33	106	8	91	3	20
Marital status (χ^2, *P*-value)	*9.799*	*0.007*	*3.115*	*0.211*	*4.019*	*0.134*	*0.980*	*0.612*	*0.377*	*0.828*	*10.757*	*0.029*	
Married	1,731	1,135	2,789	77	2,857	9	2,111	755	2,729	137	2,446	194	226
Unmarried	1,775	998	2,718	55	2,761	12	2,068	705	2,636	137	2,393	139	241
Unknown	178	90	261	7	265	3	203	65	253	15	231	11	26
Year of diagnosis (χ^2, *P*-value)	*2.546*	*0.770*	*3.581*	*0.611*	*3.043*	*0.693*	*2.340*	*0.800*	*8.544*	*0.129*	*11.569*	*0.315*	
2010	551	347	877	21	893	5	659	239	866	32	762	49	87
2011	570	348	903	15	916	2	683	235	881	37	767	58	93
2012	628	368	975	21	993	3	736	260	938	58	868	55	73
2013	627	384	985	26	1,005	6	759	252	960	51	869	57	85
2014	683	382	1,037	28	1,062	3	802	263	1,013	52	918	62	85
2015	625	394	991	28	1,014	5	743	276	960	59	886	63	70
Grade (χ^2, *P*-value)	*955.545*	*<0.001*	*71.418*	*<0.001*	*12.679*	*0.013*	*679.940*	*<0.001*	*144.682*	*<0.001*	*347.927*	*<0.001*	
Grade I	520	69	587	2	589	0	555	34	584	5	560	11	18
Grade II	1,388	374	1,749	13	1,760	2	1,522	240	1,723	39	1,635	54	73
Grade III	1,073	552	1,589	36	1,617	8	1,254	371	1,564	61	1,433	96	96
Grade IV	59	43	97	5	102	0	74	28	96	6	90	8	4
Unknown	644	1,185	1,746	83	1,815	14	977	852	1,651	178	1,352	175	302
Histology (χ^2, *P*-value)	*99.836*	*<0.001*	*20.115*	*<0.001*	*4.98*	*0.083*	*91.878*	*<0.001*	*31.709*	*<0.001*	*94.277*	*<0.001*	
Adenocarcinoma	3,108	1,811	4,809	110	4,903	16	3,700	1,219	4,685	234	4,251	295	373
Unadenocarcinoma	393	157	544	6	546	4	439	111	538	12	495	24	31
Unknown	183	255	415	23	434	4	243	195	395	43	324	25	89

T stage (χ^2, *P*-value)	*1268.867*	*<0.001*	*106.272*	*<0.001*	*27.14*	*<0.001*	*896.705*	*<0.001*	*190.252*	*<0.001*	*813.171*	*<0.001*	
T1	642	192	823	11	831	3	691	143	801	33	782	26	26
T2	1,453	237	1,679	11	1,688	2	1,537	153	1,675	15	1,609	35	46
T3	1,342	1,000	2,286	56	2,336	6	1,697	645	2,220	122	1,999	193	150
T4	147	165	305	7	310	2	206	106	295	17	242	39	31
Unknown	100	629	675	54	718	11	251	478	627	102	438	51	240
Number (χ^2, *P*-value)	*705.320*	*<0.001*	*65.942*	*<0.001*	*60.341*	*<0.001*	*42.904*	*<0.001*	*77.203*	*<0.001*	*61.387*	*<0.001*	
≤1	3684	1,826	5,476	110	5,505	13	4,344	1,476	5,431	250	4,882	312	443
>1	0	397	292	29	378	11	38	49	187	39	188	32	50
Vital status (χ^2, *P*-value)	*592.976*	*<0.001*	*28.646*	*<0.001*	*2.503*	*0.114*	*350.207*	*<0.001*	*44.582*	*<0.001*	*132.354*	*<0.001*	
Alive	1,588	282	1,855	15	1,866	4	1,680	190	1,830	40	1,746	65	59
Dead	2,096	1,941	3,913	124	4,017	20	2,702	1,335	3,788	249	3,324	279	434
Surg Prim Site (χ^2, *P*-value)	*1501.544*	*<0.001*	*101.705*	*<0.001*	*16.760*	*<0.001*	*1075.002*	*<0.001*	*314.220*	*<0.001*	*527.492*	*<0.001*	
No Surgery	607	1,471	1,973	105	2,060	18	1,015	1,063	1,836	242	1,492	224	362
Surgery	3,074	751	3,791	34	3,819	6	3,364	461	3,778	47	3,575	120	130
Unknown	3	1	4	0	4	0	3	1	4	0	3	0	1
Median survival time (month)	3.00 (2.68-3.32)		2.00 (1.28-2.72)		2.00 (0.58-3.42)		3.00 (2.65-3.35)		2.00 (1.37-2.63)		6.00 (4.86-7.14)		

Abbreviations: SEER = Surveillance, Epidemiology, and End Result; GBC = Gallbladder cancer; API = Asian or Pacific Islander; AI = American Indian/Alaska Native.

Table 2. Univariable and Multivariable Logistic Regression for analyzing the associated factors for developing distance metastases in patients diagnosed with GBC (Diagnosed between 2010 and 2015)

Subject characteristics	Regression analysis	M		Bone-Met		Brain-Met		Liver-Met		Lung-Met		N-Met	
		OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Sex													
Female	Univariable	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
Male		0.95 (0.85-1.07)	0.403	1.33 (0.94-1.88)	0.108	1.29 (0.56-2.95)	0.551	0.94 (0.83-1.07)	0.360	1.03 (0.80-1.33)	0.794	0.99 (0.78-1.25)	0.908
Race													
White	Univariable	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
Black		1.20 (1.03-1.40)	0.018	0.91 (0.54-1.52)	0.710	0.29 (0.04-2.20)	0.234	1.27 (1.08-1.50)	0.004	1.27 (0.92-1.76)	0.148	0.91 (0.65-1.26)	0.560
API		0.95 (0.79-1.13)	0.548	1.08 (0.62-1.87)	0.781	1.19 (0.35-4.05)	0.776	1.03 (0.85-1.25)	0.773	0.93 (0.61-1.41)	0.741	1.01 (0.70-1.46)	0.947
AI		1.00 (0.63-1.61)	0.984	0.56 (0.08-4.04)	0.563	NA	NA	0.87 (0.51-1.50)	0.620	1.13 (0.41-3.13)	0.810	0.63 (0.20-2.02)	0.436
White	Multivariable	1.00 (Reference)	1.00	NA	NA	NA	NA	1.00 (Reference)	1.00	NA	NA	NA	NA
Black		1.15 (0.91-1.46)	0.251	NA	NA	NA	NA	1.08 (0.83-1.41)	0.576	NA	NA	NA	NA
API		0.77 (0.57-1.02)	0.069	NA	NA	NA	NA	0.83 (0.59-1.15)	0.259	NA	NA	NA	NA
AI		0.74 (0.35-1.57)	0.435	NA	NA	NA	NA	0.57 (0.22-1.48)	0.249	NA	NA	NA	NA
Age													
<71	Univariable	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
≥71		0.78 (0.70-0.87)	<0.001	0.68 (0.48-0.95)	0.025	0.49 (0.21-1.15)	0.100	0.86 (0.77-0.97)	0.011	1.00 (0.79-1.27)	0.985	0.50 (0.39-0.62)	<0.001

<71	Multivariable	1.00 (Reference)	1.00	1.00 (Reference)	1.00	NA	NA	1.00 (Reference)	1.00	NA	NA	1.00 (Reference)	1.00
≥71		0.77 (0.66-0.91)	0.002	0.48 (0.27-0.85)	0.013	NA	NA	0.82 (0.68-0.99)	0.044	NA	NA	0.64 (0.45-0.90)	0.011
Insurance Recode													
Insured	Univariable	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
Uninsured		1.12 (0.84-1.51)	0.443	2.40 (1.24-4.65)	0.009	NA	NA	1.30 (0.95-1.78)	0.100	0.85 (0.42-1.75)	0.665	1.62 (0.97-2.71)	0.065
Insured	Multivariable	NA	NA	1.00 (Reference)	1.00	NA	NA	NA	NA	NA	NA	NA	NA
Uninsured		NA	NA	1.29 (0.39-4.31)	0.673	NA	NA	NA	NA	NA	NA	NA	NA
Marital status													
Married	Univariable	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
Unmarried		0.86 (0.77-0.96)	0.005	0.73 (0.52-1.04)	0.082	1.38 (0.58-3.28)	0.466	0.95 (0.85-1.07)	0.431	1.04 (0.81-1.32)	0.780	0.73 (0.58-0.92)	0.007
Married	Multivariable	1.00 (Reference)	1.00	NA	NA	NA	NA	NA	NA	NA	NA	1.00 (Reference)	1.00
Unmarried		0.80 (0.68-0.94)	0.007	NA	NA	NA	NA	NA	NA	NA	NA	0.68 (0.48-0.96)	0.030
Grade													
Grade I	Univariable	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
Grade II		2.03 (1.54-2.68)	<0.001	2.18 (0.49-9.70)	0.305	NA	NA	2.57 (1.77-3.73)	<0.001	2.64 (1.04-6.74)	0.042	1.68 (0.87-3.24)	0.120
Grade III		3.88 (2.96-5.09)	<0.001	6.65 (1.60-27.70)	0.009	NA	NA	4.83 (3.35-6.96)	<0.001	4.56 (1.82-11.39)	0.001	3.41 (1.81-6.41)	<0.001
Grade IV		5.49 (3.45-8.76)	<0.001	15.13 (2.89-79.08)	0.001	NA	NA	6.18 (3.54-10.77)	<0.001	7.30 (2.18-24.39)	0.001	4.53 (1.77-11.56)	0.002
Grade I	Multivariable	1.00 (Reference)	1.00	1.00 (Reference)	1.00	NA	NA	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
Grade II		1.60 (1.18-2.17)	0.003	1.98 (0.44-8.81)	0.371	NA	NA	2.12 (1.41-3.19)	<0.001	1.58 (0.60-4.15)	0.353	1.16 (0.60-2.28)	0.656
Grade III		2.47 (1.82-3.34)	<0.001	5.69 (1.36-23.83)	0.017	NA	NA	3.53 (2.36-5.29)	<0.001	1.53 (0.59-4.02)	0.384	1.64 (0.85-3.17)	0.140
Grade IV		3.64 (2.06-6.43)	<0.001	10.60 (1.97-57.05)	0.006	NA	NA	4.98 (2.61-9.50)	<0.001	2.43 (0.53-11.22)	0.254	2.49 (0.95-6.53)	0.064
Histology													
Adenocarcinoma	Univariable	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
Unadenocarcinoma		0.69 (0.56-0.83)	<0.001	0.48 (0.21-1.10)	0.084	2.24 (0.75-6.74)	0.149	0.77 (0.62-0.95)	0.017	0.45 (0.25-0.80)	0.007	0.70 (0.46-1.07)	0.099
Adenocarcinoma	Multivariable	1.00 (Reference)	1.00	NA	NA	NA	NA	1.00 (Reference)	1.00	1.00 (Reference)	1.00	NA	NA
Unadenocarcinoma		0.66 (0.50-0.89)	0.006	NA	NA	NA	NA	0.92 (0.68-1.26)	0.618	0.29 (0.09-0.94)	0.039	NA	NA
T stage													
T1	Univariable	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
T2		0.55 (0.44-0.67)	<0.001	0.49 (0.21-1.14)	0.096	0.33 (0.05-1.97)	0.223	0.48 (0.38-0.61)	<0.001	0.22 (0.12-0.40)	<0.001	0.65 (0.39-1.09)	0.106
T3		2.49 (2.08-2.99)	<0.001	1.83 (0.96-3.52)	0.068	0.71 (0.18-2.85)	0.631	1.84 (1.50-2.25)	<0.001	1.33 (0.90-1.98)	0.151	2.90 (1.91-4.41)	<0.001
T4		3.75 (2.85-4.94)	<0.001	1.72 (0.66-4.47)	0.268	1.79 (0.30-10.75)	0.526	2.49 (1.85-3.34)	<0.001	1.40 (0.77-2.55)	0.273	4.85 (2.89-8.13)	<0.001
T1	Multivariable	1.00 (Reference)	1.00	NA	NA	NA	NA	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
T2		1.14 (0.84-1.55)	0.409	NA	NA	NA	NA	0.98 (0.69-1.39)	0.910	0.47 (0.19-1.17)	0.105	2.26 (0.87-5.86)	0.093
T3		3.37 (2.51-4.53)	<0.001	NA	NA	NA	NA	2.33 (1.67-3.26)	<0.001	1.41 (0.65-3.07)	0.384	6.53 (2.61-16.33)	<0.001
T4		4.43 (2.85-6.90)	<0.001	NA	NA	NA	NA	2.57 (1.55-4.26)	<0.001	1.98 (0.70-5.61)	0.201	12.91 (4.57-36.45)	<0.001
Number													
≤1	Univariable	NA	NA	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
>1		NA	NA	4.94 (3.23-7.57)	<0.001	12.32 (5.48-27.69)	<0.001	3.80 (2.47-5.82)	<0.001	6.29 (4.79-8.27)	<0.001	2.66 (1.80-3.94)	<0.001
≤1	Multivariable	NA	NA	1.00 (Reference)	1.00	NA	NA	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
>1		NA	NA	5.73 (2.83-11.61)	<0.001	NA	NA	3.28 (1.38-7.81)	0.007	8.21 (3.36-20.06)	<0.001	2.57 (1.17-5.66)	0.019

Abbreviations: GBC = Gallbladder cancer; API = Asian or Pacific Islander; AI = American Indian/Alaska Native; NA, not available.

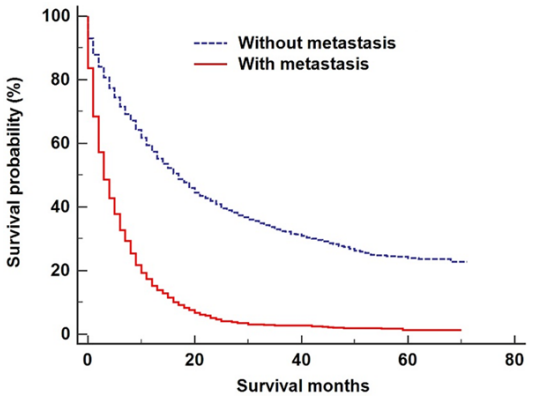

Figure 2. The survival curses for GBC patients with and without distant metastasis.

(1.37-2.63) months, bone 2.0 (1.28-3.72) months and brain 2.0 (0.58-3.42) months, respectively.

Multivariable Cox regression for survival showed that patients with the following factors: age (≥71 years), unmarried status, and differentiated grade III were negatively associated with survival. Surgery can improve patients' life span. Detailed information of Cox hazard regression analysis was shown in **Table 3**. Metastasis limited only to liver, lymph node, lung, bone or brain did not significantly influence the patients' survival. When stratified by metastatic organs, no factors were independently associated with survival for patients with metastasis to lung, bone or brain. However, age (≥71 years), unmarried status, grade III and no surgery on primary site were proven to be independent prognostic factors for liver metastasis. Significant prognostic factors for patients with lymph node metastasis were age (≥71 years) and multiple metastases.

Discussion

Until recently, not many studies have been conducted on GBC patients with distant metastasis. In the current study, we described the patterns of distant metastases of GBC based on a large population. It was shown that initial GBC had a high possibility of distant metastasis (37.6%), and 17.8% of them displayed metastases to more than one site.

We have shown that, the liver was the most common metastatic site (68.3%), followed by N2 lymph nodes, lung, bone, and brain. Due to limitations of large cohort studies, we couldn't obtain confirmatory comparison with other similarly reported results. The recurrence after surgery may offer us some supporting evidence that liver metastasis happened in 14 out of 24 patients (58.3%) [16]. In the current study, more patients with stages T3 and T4 may contribute to more liver metastases even though the hazard risk was not reached statistically. Compared with liver, other organs were significantly less affected with metastasis, and brain metastasis only occupied 1.1% of all cases. The number of metastases was proved to be an independent risk factor to develop further metastases to bone, lung, liver and lymph nodes. Heterogeneous risk factors for different organs were revealed in our study. For liver metastasis, younger age (<71 years), higher grade, and stages T3 and T4 were independent risk factors for the occurrence of liver metastasis. As to lymph nodes involvement, younger than 71 years old, married status, T3 and T4 stages were proven to be independent risk factors. Another study reported more positive lymph nodes involvement in patients younger than 60 years [17]. Although the cutoff age was different due to different calculating methods, there were higher odds of lymph nodes involvement in younger patients. More lung metastasis cases were found with the adenocarcinoma subtype. Besides, patients younger than 71 years old and higher grade displayed greater odds to develop bone metastasis. All these specific factors can be considered to screen for different distant metastases.

One study reported that the 2-year survival rate of the advanced GBC patients was only 29.2%, compared with 100% for those in early stage [18]. Another study reported that the median survival of distant stage was only 2 months [19]. Our results showed that the median survival time of the patients with distant metastasis was 3 months. Further analysis displayed that patients with distant metastasis only to lymph nodes had better survival (6 months) than metastasis to other sites. Nevertheless, the survival of GBC patients with distant metastasis remains poor. Multivariable analysis in the current study demonstrated that age (≥71 years), unmarried status, and grade III and IV were negatively associated with survival. Older patients' comorbidities and less family support may further worsen the poor survival [20]. As

Table 3. Univariable and Multivariable Cox Regression for analyzing the prognosis factors for GBC with distance metastases (Diagnosed between 2010 and 2014)

Subject characteristics	Cox regression	M		Bone-Met		Brain-Met		Liver-Met		Lung-Met		N-Met	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Sex													
Female	Univariable	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
Male		1.09 (0.99-1.21)	0.084	1.53 (1.03-2.27)	0.035	0.88 (0.31-2.53)	0.817	1.06 (0.93-1.19)	0.384	0.97 (0.73-1.29)	0.848	1.18 (0.90-1.56)	0.227
Race													
White	Univariable	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
Black		0.94 (0.83-1.08)	0.394	0.93 (0.52-1.65)	0.804	3.29 (0.38-28.49)	0.279	0.95 (0.81-1.11)	0.500	0.88 (0.62-1.26)	0.478	1.23 (0.85-1.78)	0.279
API		0.95 (0.81-1.12)	0.533	1.19 (0.63-2.25)	0.591	1.15 (0.26-5.22)	0.852	0.98 (0.81-1.19)	0.830	0.87 (0.57-1.35)	0.543	1.07 (0.71-1.62)	0.735
AI		1.20 (0.79-1.81)	0.386	1.19 (0.16-8.60)	0.865			1.04 (0.59-1.84)	0.891	4.89 (0.67-35.56)	0.116	1.28 (0.41-4.01)	0.673
Age													
<71	Univariable	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
≥71		1.59 (1.44-1.74)	<0.001	1.27 (0.86-1.87)	0.236	1.15 (0.43-3.10)	0.783	1.63 (1.45-1.83)	<0.001	1.74 (1.33-2.28)	<0.001	1.79 (1.38-2.33)	<0.001
<71	Multivariable	1.00 (Reference)	1.00	NA	NA	NA	NA	1.00 (Reference)	1.00	NA	NA	1.00 (Reference)	1.000
≥71		1.52 (1.30-1.77)	<0.001	NA	NA	NA	NA	1.51 (1.24-1.83)	<0.001	NA	NA	2.09 (1.53-2.86)	<0.001
Insurance Recode													
Insured	Univariable	1.00 (Reference)	1.00	1.00 (Reference)	1.00	NA	NA	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
Uninsured		0.93 (0.71-1.20)	0.566	1.07 (0.52-2.21)	0.852	NA	NA	0.96 (0.71-1.30)	0.783	0.97 (0.40-2.36)	0.945	0.75 (0.42-1.35)	0.341
Marital status													
Married	Univariable	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
Unmarried		1.31 (1.19-1.44)	<0.001	1.09 (0.73-1.63)	0.668	1.72 (0.57-5.13)	0.334	1.29 (1.15-1.45)	<0.001	1.12 (0.85-1.48)	0.411	1.38 (1.07-1.78)	0.013
Married	Multivariable	1.00 (Reference)	1.00	NA	NA	NA	NA	1.00 (Reference)	1.00	NA	NA	1.00 (Reference)	1.00
Unmarried		1.36 (1.17-1.59)	<0.001	NA	NA	NA	NA	1.33 (1.09-1.62)	0.005	NA	NA	1.05 (0.78-1.42)	0.730
Grade													
Grade I	Univariable	1.00 (Reference)	1.00	1.00 (Reference)	1.00	NA	NA	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
Grade II		0.98 (0.73-1.31)	0.901	0.39 (0.08-1.85)	0.234	NA	NA	0.92 (0.61-1.39)	0.699	0.54 (0.19-1.59)	0.266	1.18 (0.53-2.62)	0.694
Grade III		1.59 (1.20-2.11)	0.001	0.60 (0.14-2.57)	0.495	NA	NA	1.54 (1.04-2.28)	0.033	1.15 (0.41-3.21)	0.785	1.50 (0.69-3.27)	0.309
Grade IV		1.25 (0.79-1.98)	0.336	0.27 (0.05-1.54)	0.142	NA	NA	1.04 (0.57-1.92)	0.888	0.43 (0.09-1.93)	0.269	2.93 (0.97-8.80)	0.056
Grade I	Multivariable	1.00 (Reference)	1.00	NA	NA	NA	NA	1.00 (Reference)	1.00	NA	NA	NA	NA
Grade II		1.04 (1.76-1.42)	0.816	NA	NA	NA	NA	1.04 (0.66-1.61)	0.879	NA	NA	NA	NA
Grade III		1.58 (1.16-2.14)	0.003	NA	NA	NA	NA	1.56 (1.01-2.40)	0.045	NA	NA	NA	NA
Grade IV		1.40 (0.86-2.30)	0.175	NA	NA	NA	NA	1.14 (0.59-2.24)	0.693	NA	NA	NA	NA
Histology													
Adenocarcinoma	Univariable	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
Unadenocarcinoma		1.07 (0.89-1.28)	0.490	0.97 (0.36-2.66)	0.957	1.15 (0.32-4.17)	0.828	1.05 (0.85-1.31)	0.643	1.68 (0.91-3.11)	0.096	0.87 (0.54-1.41)	0.573

Distant metastasis in gallbladder cancer

T stage													
T1	Univariable	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
T2		0.71 (0.57-0.88)	0.002	0.81 (0.33-2.00)	0.645	2.00 (0.18-22.06)	0.571	0.71 (0.54-0.92)	0.011	0.79 (0.40-1.58)	0.510	0.52 (0.28-0.97)	0.040
T3		1.04 (0.88-1.24)	0.634	0.91 (0.44-1.89)	0.802	3.84 (0.45-32.58)	0.218	1.01 (0.82-1.24)	0.926	0.85 (0.56-1.30)	0.451	0.96 (0.60-1.53)	0.862
T4		0.96 (0.76-1.22)	0.747	0.43 (0.14-1.34)	0.143	NA	NA	0.92 (0.69-1.22)	0.556	0.78 (0.41-1.49)	0.457	0.91 (0.52-1.60)	0.744
T1	Multivariable	1.00 (Reference)	1.00	NA	NA	NA	NA	1.00 (Reference)	1.00	NA	NA	1.00 (Reference)	1.00
T2		1.03 (0.74-1.43)	0.856	NA	NA	NA	NA	1.16 (0.78-1.74)	0.459	NA	NA	1.04 (0.51-2.13)	0.920
T3		1.33 (0.99-1.79)	0.060	NA	NA	NA	NA	1.37 (0.95-1.96)	0.093	NA	NA	1.53 (0.90-2.60)	0.114
T4		1.24 (0.82-1.88)	0.315	NA	NA	NA	NA	1.09 (1.65-1.84)	0.746	NA	NA	1.23 (0.67-2.26)	0.498
Number													
≤1	Univariable	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
>1		1.32 (1.13-1.53)	<0.001	1.33 (0.81-2.18)	0.267	1.67 (0.62-4.54)	0.312	1.40 (1.00-1.96)	0.050	1.28 (0.86-1.91)	0.225	2.11 (1.38-3.24)	0.001
≤1	Multivariable	1.00 (Reference)	1.00	NA	NA	NA	NA	NA	NA	NA	NA	1.00 (Reference)	1.00
>1		1.03 (0.82-1.31)	0.78	NA	NA	NA	NA	NA	NA	NA	NA	1.76 (1.04-2.97)	0.034
Surg Prim Site													
No Surgery	Univariable	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
Surgery		0.62 (0.56-0.68)	<0.001	0.88 (0.57-1.36)	0.556	1.08 (0.40-2.91)	0.875	0.58 (0.51-0.66)	<0.001	0.75 (0.52-1.08)	0.123	0.51 (0.39-0.67)	<0.001
No Surgery	Multivariable	1.00 (Reference)	1.00	NA	NA	NA	NA	1.00 (Reference)	1.00	NA	NA	1.00 (Reference)	1.00
Surgery		0.78 (0.65-0.94)	0.008	NA	NA	NA	NA	0.64 (0.51-0.81)	<0.001	NA	NA	0.55 (0.40-0.77)	<0.001

Abbreviations: GBC = Gallbladder cancer; API = Asian or Pacific Islander; AI = American Indian/Alaska Native; NA, not available.

reported previously, higher grade correlates with poorer survival [18, 21]. We noticed that, these studies suggested poorer survival in patients with higher T stage, which was not consistent with our results. Surgery was found to potentially improve patients' life span in our study. As previously reported in patients with advanced diseases, the present results were further strengthened [22]. However, detailed surgery analysis cannot be further performed due to lack of details of surgical information in SEER.

In the current study, distant metastasis limited only to liver, lung, bone or brain did not correlate with worse survival. A previous study reported that lymph node metastasis can significantly decrease disease-free survival of GBC even after radical re-resection [23]. Such difference may be partially explained by only including N2 nodes in our analysis. Further analysis by calculating the number of metastatic sites in our study showed that multiple metastatic sites were not associated with poorer outcome, with the exception of the lymph nodes. However, simple summation of different sites might be incorrect and we cannot provide the detailed patterns of multiple metastases, as showed in a previous study conducted on ovarian cancer [11]. More cases with multiple metastases are required in the future to further estimate the weight of specific organs in evaluating prognosis.

Although the present study identified the largest cohort of distant metastasis in GBC, some limitations should be noticed. Firstly, the included cases were not differentiated as incidental versus non-incidental GBC, possibly leading to bias. Secondly, metastases to other distant sites such as peritoneum were not recorded in the SEER, which results in the inability to precisely describe the metastatic characteristics and prognostic effects on survival. Limited by only a small proportion of brain metastasis, we cannot draw convincing results about the risk and prognostic factors for patients with brain metastasis. Thirdly, locoregional lymph nodes involvement was not discussed according to our main inclusion criteria, even though they may have an influence on survival. Last but not least, the evaluation of multiple metastases was merely conducted by counting numbers. This may lead to bias regarding different organ metastases, which has variable impact on survival.

In conclusion, we demonstrated that initial GBC had a high chance of distant metastasis and the liver was the most common metastatic target. Homogeneous and heterogeneous risk factors and prognostic factors were identified for some specific metastases. Metastasis only to liver, N2 lymph node, lung, bone or brain and multiple metastases did not independently influence patients' overall survival.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Chao Zhang, Department of Bone and Soft Tissue Tumors, Tianjin Medical University Cancer Institute and Hospital, Huanhu Xi Road, Tiyuan Bei, Hexi District, Tianjin 300060, China. E-mail: drzhangchao@tmu.edu.cn

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