Nomogram to Predict Overall Survival for Gallbladder Cancer Patients With Distant Metastasis

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Research

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Abstract

Background: There are few studies on the relationship between metastatic sites and prognosis of gallbladder cancer (GBC) patients with distant metastasis. In this study, we aimed to analyze the association between metastatic sites and survival of GBC patients with distant metastasis and developed a nomogram to predict the overall survival (OS).

Methods: The information of 1174 GBC patients with distant metastasis was collected from the Surveillance, Epidemiology, and End Results (SEER) database between 2010 and 2015, which was based on the 8th edition of TNM staging system. Then patients were divided into a training set and validation set with ratio 7:3. The Cox proportional hazards analysis was performed to find independent prognostic factors and created a nomogram. Concordance index (C-index) and calibration plots were used to validate the predictive accuracy and discriminatory ability of the nomogram, and risk stratification was established based on the nomogram.

Results: The Cox proportional hazards analysis showed that the T classification, tumor grade, histology, bone metastasis, liver metastasis, brain metastasis, surgery, and chemotherapy were the independent prognostic factors. The C-index of nomogram in training set and validation set were 0.706 (95%CI [0.686-0.726]) and 0.698 (95%CI [0.665-0.731]), respectively. The calibration plots showed satisfactory accuracy of the nomogram, and patients were divided into three groups base on the nomogram. There were significant differences in survival time between groups.

Conclusions: Patients with brain metastasis, liver metastasis, bone metastasis have a poor prognosis, and chemotherapy and surgery may improve the patient's prognosis.

Background

Gallbladder cancer (GBC) accounts for more than 80% of all biliary tract tumors and ranks sixth in the incidence of all gastrointestinal tumors [1]. It has a high mortality rate, the 5-year survival rate may below 5% [2]. With the advent of laparoscopic cholecystectomy, the incidence of gallbladder cancer is on the rise, but only 1/3 of patients can detect GBC preoperatively [3, 4], there are no specific clinical symptoms in the early stage of gallbladder cancer, and GBC is prone to early lymph node metastasis and distant metastasis [5], thus about 40% of the patients have already had metastasis at the time of diagnosis [6], which are not suitable for curative surgery [7]. Even with surgery, less than 15% of GBC patients could be cured [8]. In the 8th edition of TNM staging system, all GBC patients with distant metastasis were defined as M1 classification, included metastasis to periaortic, pericaval, superior mesentery artery, celiac artery lymph nodes, and other distant sites [9], but the prognosis for different site metastasis also varies from site to site [10]. The number of metastatic sites may be related to the length of the patient's disease or the malignancy of the tumor. Hence, it is inappropriate to classify all GBC patients with metastasis at the same level.

The majority of GBC patients die from primary tumors or recurrent cholangitis [11], suffering from illness. Therefore, it is important to accurately estimate the survival time of patients, to facilitate the selection of standardized treatment to extended life span or palliative treatment to alleviate their suffering. There are no large clinical studies to clarify the correlation between metastatic sites and prognosis in GBC patients with distant metastasis.

In order to clarify the influence of different metastatic sites on the prognosis of GBC patients and evaluate the prognosis of patients more accurately, it is necessary to find the risk factor of GBC patients with distant metastasis. In this study, we investigated the impact of different metastatic sites and treatments for patient prognosis, developed a nomogram to predict prognosis for GBC patients with distant metastasis.

Materials And Methods

Data Collection

The GBC patients with distant metastasis were selected from the Surveillance, Epidemiology, and End Results (SEER) program dataset from 2010 to 2015. Inclusion criteria were as follows: a) GBC was the primary and only diagnosis of cancer; b) Patients with distant metastasis based on the 8th edition of TNM staging system; c) Diagnosis with histology; d) Patients received active follow-up. Exclusion criteria were as follows: a) With unknown data of patient characteristics, survival time, tumor information, metastatic sites and cause of death; b) Patients diagnosed at autopsy or via death certificate; c) Survival time less than 1 month.

The data of metastatic sites, surgery of primary tumor, TNM classification, age, race, tumor grade, histology, the status of survival, survival time, and cause of death were included in the analysis. Tumors stage was classified based on the 8th edition of TNM staging system. X-tile analysis provided the optimal age and tumor size cutoff points, the age was divided into 3 groups (25–67 years old; 68–75 years old; >75 years old), and tumor size was also divided into 3 groups ($\leq 36\text{mm}$; $>36\text{mm}$; unknown). 1174 patients were randomly divided into the training set and validation set in a ratio of 7:3.

Statistical analysis

The categorical data were expressed as number and proportion, the Kaplan–Meier curves were drawn by Graph Prism 8, the difference between the training set and validation set were performed using SPSS, version 23.0 for Windows (IBM Corporation, Armonk, NY), univariate Cox regression analysis was performed, and the variables with $P < 0.05$ were included in multivariate Cox regression analysis. Univariate and multivariate Cox regression analysis, nomogram, Concordance index (C-index), the calibration plots were performed by R software (version 3.6.3), and risk stratification was performed by X-tile.

Results

Patient characteristics

A total of 1174 GBC patients with distant metastasis were included in the analysis (Fig. 1), 824 patients were divided into the training set, and 350 patients were divided into the validation set randomly. Patients' baseline characteristics were shown in Table 1. There were no statistically significant differences between the two sets. The ratio of male to female patients was 1:2. About 50% of patients were elder than 65 years old, 73.7% of patients were white, the majority T classification was T3-T4, about 41.9% of patients developed lymph node metastasis, Adenocarcinoma was the most prevalent pathological type, accounting for 76.5%. The proportion of liver metastasis is highest (77.2%), followed by distant lymph node (dLN) metastasis (26.1%), lung metastasis (13.6%), bone metastasis (7.8%), and brain metastasis (1.4%). The distribution of different metastatic sites was shown in Fig. 2A. 907 (77.3%) patients with the single distant metastatic site while 267(22.7%) patients with two or more distant metastatic sites. 41.6% of patients performed surgery, which included tumor destruction, tumor resection, 11.0% underwent radiotherapy and 62.3% underwent chemotherapy.

Table 1
Characteristics of GBC patients with distant metastasis

Characteristics	Total (n = 1174)	Training set (n = 824)	Validation set (n = 350)	P value
Gender n (%)				0.334
Male	359(30.6)	245(29.7)	114(32.6)	
Female	815(69.4)	579(70.3)	236(67.4)	
Age n (%)				0.197
≤ 67 years	630(53.7)	447(54.2)	183(52.3)	
68–75 years	277(23.6)	201(24.4)	76(21.7)	
> 75 years	267(22.7)	176(21.4)	91(26.0)	
Race n (%)				0.770
White	865(73.7)	610(74.0)	255(72.9)	
Black	180(15.3)	127(15.4)	53(15.1)	
Other	129(11.0)	87(10.6)	42(12.0)	
Grade n (%)				0.249
I-II	280(23.9)	205(24.9)	75(21.4)	
III-IV	360(30.7)	242(29.4)	118(33.7)	
Unknown	534(45.5)	377(45.8)	157(44.9)	
Histology n (%)				0.354
Adenocarcinoma	898(76.5)	639(77.5)	259(74.0)	
Squamous cell carcinoma	32(2.7)	20(2.4)	12(3.4)	
Others	244(20.8)	165(20)	79(22.6)	
T classification n (%)				0.947
T0-T2	271(23.1)	189(22.9)	82(23.4)	
T3-T4	631(53.7)	442(53.6)	189(54)	
Unknown	272(23.2)	193(23.4)	79(22.6)	
Lymphatic metastasis n (%)				0.588
No	446(38.0)	303(36.8)	143(40.9)	
Regional lymph node	186(15.8)	131(15.9)	55(15.7)	

Characteristics	Total (n = 1174)	Training set (n = 824)	Validation set (n = 350)	<i>P</i> value
Distant lymph node	307(26.1)	220(26.7)	87(24.9)	
Unknown	235(20.0)	170(20.6)	65(18.6)	
Tumor size n (%)				0.542
≤ 36mm	261(22.2)	186(22.6)	75(21.4)	
> 36mm	336(28.6)	228(27.7)	108(30.9)	
Unknown	577(49.1)	410(49.8)	167(47.7)	
Liver metastasis	906(77.2)	635(77.1)	271(77.4)	0.891
Lung metastasis	160(13.6)	112(13.6)	48(13.7)	0.956
Brain metastasis	17(1.4)	12(1.5)	5(1.4)	0.971
Bone metastasis	92(7.8)	59(7.2)	33(9.4)	0.186
Treatment n (%)				
Surgery	488(41.6)	346(42.0)	142(40.6)	0.652
Radiotherapy	129(11.0)	99(12.0)	30(8.6)	0.084
Chemotherapy	731(62.3)	526(63.8)	205(58.6)	0.089

Metastatic sites and survival.

We analyzed the relationship between the metastatic sites and year, the incidence of metastatic sites did not change with the year significantly (Fig. 2B). Then we analyzed the impact of different metastatic sites on survival, we found that patients with dLN metastasis, liver metastasis, bone metastasis, brain metastasis have a significantly worse prognosis than those without corresponding site metastasis, lung metastasis did not have a significant impact on the prognosis of patients (Fig. 2C, 2D, 2E, 2F, 2G), and the patients with dLN metastasis have best prognosis in all patients (median OS: 7 months) and patients with the single metastatic site (median OS: 10 months) (Fig. 2H, 2I). We also compared whether two and more metastatic sites had a significant effect on patients survival and found no significant difference between the different metastatic sites (Fig. 2J, Fig. 2K). and patients' survival time became shorter with the increasing number of metastatic sites (Fig. 2L).

Prognostic factors for GBC patients with distant metastasis.

Prognostic factors of OS were calculated with univariate and multivariate Cox proportional hazard regression (Table 2). The results of the multivariate Cox analysis showed that higher grade (HR: 1.40,

95%CI[1.14–1.71], $P = 0.001$), Squamous cell carcinoma (HR:2.30, 95%CI[1.46–3.62], $P < 0.001$), higher T classification (HR: 1.28,95%CI[1.05–1.56], $P = 0.016$), liver metastasis (HR:1.33, 95%CI[1.06–1.65], $P = 0.012$), brain metastasis (HR:2.27, 95%CI[1.22–4.22], $P = 0.010$), and bone metastasis (HR:1.64, 95%CI[1.21–2.22], $P = 0.001$) were independent risk factors for survival, surgery (HR:0.60, 95%CI[0.48–0.73], $P < 0.001$) and chemotherapy (HR:0.44, 95%CI[0.37–0.52], $P < 0.001$) were independent protective factors for survival.

Table 2
Univariate and multivariate analysis for overall survival (OS).

Prognostic factors	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P-value	HR (95%CI)	P-value
Gender				
Male	Reference			
Female	0.92(0.79–1.08)	0.314		
Age				
≤ 67 years	Reference		Reference	
68–75 years	1.16(0.98–1.38)	0.094	1.10(0.92–1.31)	0.296
> 75 years	1.52(1.27–1.82)	P < 0.001	1.16(0.96–1.41)	0.129
Race				
White	Reference			
Black	1.09(0.89–1.33)	0.394		
Other	1.06(0.84–1.34)	0.633		
Grade				
I-II	Reference		Reference	
III-IV	1.46(1.20–1.78)	P < 0.001	1.40(1.14–1.71)	0.001
Unknown	1.64(1.37–1.97)	P < 0.001	1.11(0.89–1.39)	0.366
Histology				
Adenocarcinoma	Reference		Reference	
Squamous cell carcinoma	2.64(1.68–4.13)	P < 0.001	2.30(1.46–3.62)	P < 0.001
Others	1.18(0.99–1.41)	0.064	1.02(0.85–1.23)	0.792
T classification				
T0-T2	Reference		Reference	
T3-T4	1.39(1.16–1.67)	P < 0.001	1.28(1.05–1.56)	0.016
Unknown	1.74(1.40–2.15)	P < 0.001	1.06(0.82–1.38)	0.635
Lymphatic metastasis				
No	Reference		Reference	
Abbreviations: HR, hazard ratio; 95%CI, 95% confidence intervals.				

Prognostic factors	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P-value	HR (95%CI)	P-value
Regional lymph node	0.99(0.80–1.22)	0.932	1.01(0.81–1.26)	0.927
Distant lymph node	0.76(0.63–0.91)	0.003	1.04(0.83–1.30)	0.752
Unknown	1.30(1.07–1.57)	0.009	1.15(0.94–1.41)	0.172
Tumor size				
≤ 36mm	Reference		Reference	
> 36mm	1.09(0.89–1.34)	0.390	0.96(0.77–1.20)	0.746
Unknown	1.30(1.08–1.56)	0.005	1.08(0.88–1.32)	0.448
Lung metastasis	1.03(0.84–1.27)	0.776		
Liver metastasis	1.51(1.26–1.79)	P < 0.001	1.33(1.06–1.65)	0.012
Brain metastasis	2.49(1.40–4.41)	0.002	2.27(1.22–4.22)	0.010
Bone metastasis	1.61(1.22–2.12)	0.001	1.64(1.21–2.22)	0.001
Treatment				
Surgery	0.58(0.50–0.68)	P < 0.001	0.60(0.48–0.73)	P < 0.001
Radiotherapy	0.68(0.54–0.84)	0.001	0.89(0.69–1.13)	0.331
Chemotherapy	0.43(0.37–0.50)	P < 0.001	0.44(0.37–0.52)	P < 0.001
Abbreviations: HR, hazard ratio; 95%CI, 95% confidence intervals.				

Nomogram and risk stratification

All independent prognostic factors were used to establish the nomogram (Fig. 3). the C-index for OS prediction was 0.706 (95%CI, 0.686–0.726) in the training set and 0.698 (95%CI, 0.665–0.731) in validation set, respectively. The calibration plots of 1-, 2-, 3- year OS also shown agreement between the prediction by nomogram and actual observation in both sets (Fig. 4A, 4B, 4C, 4D, 4E, 4F). The value for each independent prognostic factor was shown in Table 3. The total score for each patient was calculated and risk stratification was established by using the X-tile, patients were divided into three groups: low-risk group (< 123), medium-risk group (125–187), and high-risk group (> 187). There was a significant difference in survival between the three groups (Fig. 5), with a median OS of 10 months, 5 months, 2months, respectively.

Table 3
Risk scores of all prognostic factors in
the nomogram

Variables	Score
Grade	
I-II	0
III-IV	39
Unknown	12
Histology	
Adenocarcinoma	0
Squamous cell carcinoma	96
Other	0
T classification	
T0-T2	0
T3-T4	27
Unknown	15
Liver metastasis	
No	0
Yes	34
Bone metastasis	
No	0
Yes	57
Brain metastasis	
No	0
Yes	88
Surgery	
No	64
Yes	0
Chemotherapy	
No	100

Variables	Score
Yes	0

Discussion

Existing epidemiological studies show poor prognosis in GBC patients with distant metastasis [4], the 8th edition of TNM staging system rates all GBC patients with distant metastasis as M1 classification, but the prognosis of patients with different metastatic sites are not similar. Miura et al. [10] reported significant survival differences in GBC patients with invasion of the liver, the hepatoduodenal ligament, or lymph node metastasis. A more accurate prognostic assessment model needs to be established, In this study, We analyzed the relationship between metastatic sites and prognosis of GBC patients with distant metastasis from SEER, and revealed that liver metastasis, bone metastasis, and brain metastasis were risk factors for survival, while surgery and chemotherapy can improve patients' prognosis, besides, tumor grade, histology, T classification were also associated with prognosis. A nomogram for GBC patients with distant metastasis was established to show the risk of death more intuitively, and the risk stratification was also developed, which may be useful for doctors in developing an individualized treatment for GBC patients with distant metastasis.

In our study, the incidence of metastasis in different sites, from high to low, were liver, dLN, lung, bone, and brain. The prognosis was not similar in patients with different metastatic sites. For GBC patients with a single metastatic site, patients with dLN metastasis had the best prognosis, patients with brain metastasis had the worst prognosis, and the prognosis of the patients deteriorated with the increasing number of metastatic sites. In multivariate Cox analysis, it was revealed that the occurrence of liver, brain, and bone metastasis had a statistically significant effect on prognosis. After compared the effects of different metastatic sites on prognosis, brain metastasis had the greatest impact on the prognosis of all metastatic sites, so we may need to enhance screening for brain lesions in patients with GBC, to clarify the patient's prognosis, and choose whether to continue with standardized treatment or just palliative care to relieve the patient's suffering. Interestingly, in the multivariate Cox regression analysis, lung metastasis still had no effect on patient survival as the K-M analysis. We speculate that this may be due to that most of the patients (75.63%) who developed lung metastasis had metastasis at other sites, effect of multiple site metastasis made the impact of lung metastasis on prognosis insignificant.

In addition to the patient's metastatic sites, multivariate Cox analysis showed that treatment was associated with prognosis, the surgery and chemotherapy can significantly improve patient prognosis. Although it has been reported that patients who present with N2 lymph node metastasis (defined base on the 7th edition of the AJCC [American Joint Committee on Cancer]) do not benefit from surgery[12], and studies suggested that in patients with unresectable GBC, palliative surgery is not encouraged because of the high risk[13]. But Chen et al. [14] reported that surgical treatment for patients with distant lymph node metastasis could improve the survival of patients, which was consistent with the findings of our study. And He et al. [15] noted that palliative resection has a role in improving the prognosis of GBC patients

with IV stage, but due to the high mortality rate of surgery, cautious evaluation should be performed before surgery. Chemotherapy showed an improved effect on patient prognosis, consistent with the findings of Ma et al. [16]. Interestingly, the therapeutic effect of radiotherapy on patients in multivariate Cox regression was not statistically significant. Some studies revealed that radiotherapy may be considered in patients with local tumors[5], and Verma et al. [17] had shown that radiotherapy plus chemotherapy improve the prognosis of patients with nonmetastatic GBC compared with chemotherapy alone. But Wang et al. [18] compared the survival time between patients treated with surgery plus radiotherapy and surgery alone and there was no significant difference. The current study cohorts which have demonstrated the effectiveness of radiotherapy were mostly based on GBC patients who had not occurred distant metastasis. In GBC patients with distant metastasis, the effect of radiotherapy needs further examination.

There are a lot of GBC related prognostic prediction model, but we can find that they are for all patients with GBC [19], resected GBC [20], or node-negative GBC [21]. These predictive models may not be suitable for GBC patients with distant metastasis, and most are based on the 7th edition of TNM staging system. A more accurate prognostic assessment can help doctors estimate the survival time of GBC patients, which will also help the doctors develop individualized treatment plans. Therefore, we made a nomogram based on the 8th edition of TNM staging system and made the risk stratification based on the nomogram, which can predict the survival time of patients more intuitively, and also help doctors to develop personalized treatments.

However, there are some limitations to our study. Firstly, we can't get information about the patients' metastasis information in other sites, secondly, we don't know the patient's surgical approach, the protocol and dose of radiotherapy or chemotherapy, and the order of different treatment. Thirdly, as a retrospective study, the bias in data collection is inevitable. More clinical cohort studies are needed to refine this model.

Conclusions

We found the brain, liver, bone metastasis lead to a worse prognosis for patients, surgery and chemotherapy can improve the prognosis. We made a nomogram and categorized patients into three groups based on the probability of survival. This may be helpful to doctors in developing treatment plans, but need more clinical research to improve and refine this nomogram.

Abbreviations

GBC: gallbladder cancer; OS: overall survival; SEER: the Surveillance, Epidemiology, and End Results; C-index: Concordance index; dLN: distant lymph node; AJCC: American Joint Committee on Cancer.

Declarations

Acknowledgements

Not applicable.

Authors' contributions

MJW designed, analyzed, wrote, processed and reviewed the manuscript. MZ and YFJ helped in concept, data collection, materials and literature search. LPC designed, supervised, analyzed and reviewed the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Ethics approval and consent to participate

All procedures performed in this study involving the patient were approved by the ethical committee of Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

Figure 1

Flowchart of the patient selection

Figure 2

Number of distant metastatic sites in all patients (A); the incidence of GBC with distant metastasis in different years (B); survival of GBC patients with distant metastasis stratified by dLN metastasis (C), liver metastasis (D), bone metastasis (E), brain metastasis (F), and lung metastasis (G); survival of GBC patients with different metastatic sites (H), single metastatic site (I), two metastatic sites (J), and three

metastatic sites (K); survival of GBC patients with distant metastasis stratified by the number of metastatic sites (L).

Figure 3

Nomograms for predicting 1-year, 2-year, and 3-year OS of GBC patients.

Figure 4

Calibration plots for OS at 1-year, 2-year, 3-year in GBC patients with distant metastasis in the training set (A, B, C) and the validation set (D, E, F), respectively.

Figure 5

Kaplan–Meier curves of OS for different risk stratification of GBC patients with distant metastasis.