Original Article

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Unmasking the silent killer: The hidden aggressiveness of signet-ring cell carcinoma in gallbladder cancer

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SUMMARY The prognostic significance of the signet-ring cell component in gallbladder carcinoma (GBC) has not been systematically evaluated. The aim of this study was to assess the similarities and differences between gallbladder signet-ring cell carcinoma (GBSRCA) and gallbladder adenocarcinoma (GBAC) in terms of clinicopathological features and long-term survival. Using the Surveillance, Epidemiology, and End Results (SEER) database, we analyzed 6,612 patients diagnosed with gallbladder cancer between 2000 and 2021. The cohort included 147 patients with GBSRCA and 6,465 with GBAC. Patients with GBSRCA were significantly younger, with 33.3% being age 60 or younger compared to 23.9% of patients with GBAC ($P = 0.009$). There was a higher proportion of females in the GBSRCA group (77.6%) compared to the GBAC group (70.1%, $P = 0.049$). GBSRCA was associated with a more advanced tumor stage (T3-T4: 56.5% *vs*. 44.4%, $P = 0.004$), higher rates of lymph node metastasis (43.5% *vs*. 28.0%, $P < 0.001$), and poorer differentiation status (poorly to undifferentiated: 80.3% *vs*. 29.7%, $P < 0.001$). Survival analysis revealed that patients with GBSRCA had significantly worse overall survival (OS) and cancer-specific survival (CSS) compared to patients with GBAC ($P < 0.001$). GBSRCA was an independent prognostic factor for OS ($P = 0.001$) in the entire cohort, while the T stage and N stage were independent prognostic factors for OS and CSS in patients with GBSRCA. Even after propensity score matching, patients with GBSRCA still had a poorer prognosis.

Keywords gallbladder carcinoma, adenocarcinoma, signet-ring cell carcinoma, prognosis

1. Introduction

According to the latest (8th) edition of the American Joint Committee on Cancer (AJCC) staging system for gallbladder carcinoma (GBC), in addition to the three most common staging factors – T stage, N stage, and M stage – various other factors can affect the overall prognosis for patients with GBC (*1*). Histological subtypes are considered a crucial prognostic factor that requires additional clinical attention. Cases with papillary differentiation have been associated with a favorable prognosis (*2*). Studies have also shown that gallbladder adeno-squamous/squamous carcinoma has a significantly worse prognosis compared to pure adenocarcinoma (*3*). Moreover, gallbladder mucinous adenocarcinoma (*4*) or sarcomatoid carcinoma (*5*) has been found to have a less favorable prognosis than gallbladder adenocarcinoma (GBAC).

Signet-ring cell carcinoma (SRCC) is a type of adenocarcinoma that produces mucin and is characterized by the presence of significant amounts of mucin within the cytoplasm, which displaces the nucleus towards one side of the cell. When SRCC spreads beyond the submucosa, the signet-ring cells spread widely and establish distant metastases (*6*). This aggressive behavior of SRCC signifies a poor prognosis for adenocarcinoma. Primary SRCC is typically found in the stomach, making up about 15.1-28.2% of cases of primary gastric cancer (*7-9*). It can also develop, although less frequently, in other organs such as the breasts, lungs, esophagus, gallbladder, bladder, and pancreas (*10-16*). To the extent known, few studies have systematically evaluated the clinical significance of the signet-ring component in patients with GBC. Zou *et al*. comparatively analyzed the inconsistencies of clinic-pathological features and long-term survival in patients with GBAC and patients with gallbladder signet-ring cell carcinoma (GBSRCA) (*4*). However, their sample size was too limited to draw a convincing conclusion.

Therefore, the current study evaluated the similarities and differences between patients with GBAC and patients with GBSRCA in terms of short- and long-term outcomes.

2. Materials and Methods

2.1. Data source

The study utilized data from the Surveillance, Epidemiology, and End Results (SEER) database, which collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 34.6% of the US population (*3*). The dataset included patients diagnosed with gallbladder cancer between 2000 and 2021. Patients who were staged according to the 6th AJCC staging system were first evaluated. Moreover, only patients with pathologically confirmed GBAC and GBMCA were considered eligible. In order to guarantee the quality of this study, patients with recorded survival periods less than 1 month were excluded. The specific process of patient selection and identification is shown in Figure 1.

2.2. Identification of variables

Clinical and pathological variables analyzed included age, sex, race, marital status, tumor differentiation grade, pathological subtypes, stage at diagnosis, treatment modalities (radiotherapy, chemotherapy, and surgery), and cancer-related death (CRD). The variables were compared between the GBSRCA and GBAC groups using appropriate statistical tests to identify significant differences. The continuous variable "Age" was categorized into ≤60 and >60. Minor adjustments were also applied to other categorical variables. For instance, Marital status was simplified into two groups: Married and Single/unknown. Race was simplified into two major groups: White and Others. Tumor differentiation status was simplified into three groups: well to moderate differentiated, poorly to undifferentiated, and unknown.

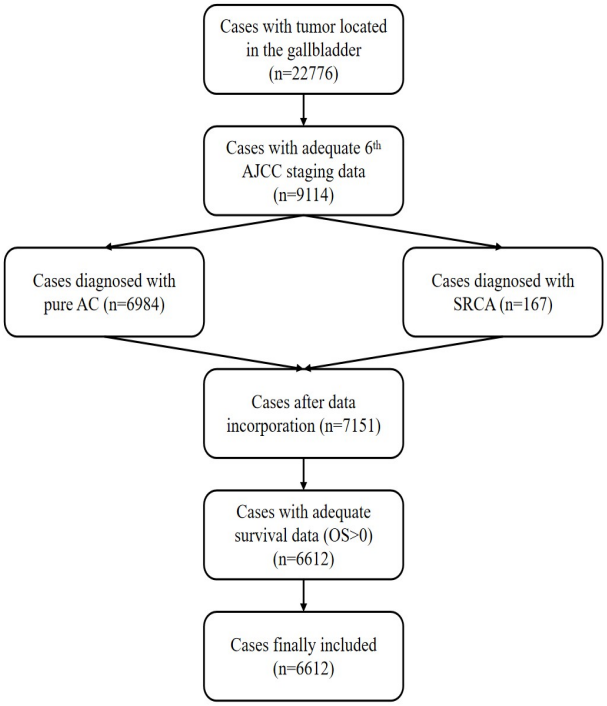

Figure 1. Flowchart illustrating the process of patient selection and identification.

2.3. Statistical analysis

The software R version 4.2.2 was used for statistical analysis. The R package tableone was used for baseline comparison and subsequent table output. Categorical data were expressed as numbers (percentages). Categorical variables were evaluated *via* the chi-squared and Fisher's exact tests. Survival analyses were performed using the R packages survminer and survival. Kaplan–Meier (KM) curves and the corresponding risk tables were generated using the R command ggsurvplot. OS was defined as the time from the date of radical surgery to the date of death or last follow-up. The R packages survminer, dplyr, survival, and rms were used to construct a Cox proportional hazards model, which produced hazard ratios (HR) and their 95% confidence intervals (CI). *P* values lower than 0.05 indicated statistical significance. The PSM analysis was performed using the R package MatchIt with the method="nearest," caliper = 0.05, and ratio = 1, matching factors that mainly consisted of independent prognostic factors for OS.

3. Results

3.1. Clinical and pathological characteristics before and after PSM

Table 1 summarizes the basic clinical and pathological features of the entire cohort. The cohort consisted of 6,612 patients, 147 (2.2%) of whom were diagnosed with GBSRCA and 6,465 (97.8%) of whom were diagnosed with GBAC. The age distribution revealed a significant difference between the two groups. Patients ≤ the age of 60 comprised 24.2% of the total cohort. Of them, 33.3% were in the GBSRCA group, while 23.9% were in the GBAC group, indicating that patients with GBSRCA tended to be younger (P = 0.009). There was also a significant difference in the sex distribution. Males represented 29.8% of the entire cohort. Within the GBSRCA group, males accounted for 22.4%, compared to 29.9% in the GBAC group, indicating a higher prevalence of GBSRCA among females (P = 0.049). Regarding tumor-related pathological features, GBSRCA was associated with a more advanced tumor stage. The proportions of patients with T3-T4 disease (56.5% *vs*. 44.0%, P = 0.004), lymph node metastasis (43.5% *vs*. 28.0%, P < 0.001), and poorly to undifferentiated disease (80.3% *vs*. 29.7%, P < 0.001) were significantly higher in patients with GBSRCA. Moreover, CRD was more frequent in patients with

Table 1. Basic clinical and pathological features in patients with GBSRCA or GBAC

Variables	Overall number (n = 6,612)	GBSRCA (n = 157)	GBAC (n = 6465)	P value
Age (%)				0.009
≤ 60	1,597 (24.2)	49 (33.3)	1,548 (23.9)	
> 60	5,015 (75.8)	98 (66.7)	4,917 (76.1)	
Sex (%)				0.049
Male	1,969 (29.8)	33 (22.4)	1,936 (29.9)	
Female	4,643 (70.2)	114 (77.6)	4,529 (70.1)	
Race (%)				0.708
Asian	694 (10.5)	14 (9.5)	680 (10.5)	
White	5,069 (76.7)	111 (75.5)	4,958 (76.7)	
Other	849 (12.8)	22 (15.0)	827 (12.8)	
Marital status (%)				0.191
No/Unknown	3,231 (48.9)	64 (43.5)	3,167 (49.0)	
Married	3,381 (51.1)	83 (56.5)	3,298 (51.0)	
Grade (%)				< 0.001
Well to moderately differentiated	3,318 (50.2)	13 (8.8)	3,305 (51.1)	
Poorly to undifferentiated	2,038 (30.8)	118 (80.3)	1,920 (29.7)	
Unknown	1,256 (19.0)	16 (10.9)	1,240 (19.2)	
T stage (%)				0.004
T1-T2	3,659 (55.3)	64 (43.5)	3,595 (55.6)	
T3-T4	2,953 (44.7)	83 (56.5)	2,870 (44.4)	
N stage (%)				< 0.001
N-	4,738 (71.7)	83 (56.5)	4,655 (72.0)	
N+	1,874 (28.3)	64 (43.5)	1,810 (28.0)	
M stage (%)				0.133
M-	4,940 (74.7)	102 (69.4)	4,838 (74.8)	
M+	1,672 (25.3)	45 (30.6)	1,627 (25.2)	
Radiotherapy (%)				0.441
Not performed	5,635 (85.2)	122 (83.0)	5,513 (85.3)	
Performed	977 (14.8)	25 (17.0)	952 (14.7)	
Chemotherapy (%)				0.221
Not performed	4,230 (64.0)	87 (59.2)	4,143 (64.1)	
Performed	2,382 (36.0)	60 (40.8)	2,322 (35.9)	
CRD (%)				< 0.001
No	2,558 (38.7)	32 (21.8)	2,526 (39.1)	
Yes	4,054 (61.3)	115 (78.2)	3,939 (60.9)	
Surgery (%)				0.168
Not performed	1,085 (16.4)	18 (12.2)	1,067 (16.5)	
Performed	5,527 (83.6)	129 (87.8)	5,398 (83.5)	

GBSRCA: gallbladder signet-ring cell carcinoma; GBAC: gallbladder adenocarcinoma; CRD: cancer-related death.

GBSRCA (78.2% *vs*. 60.9%, $P < 0.001$).

Table 2 shows the clinical and pathological features of the cohort after PSM, ensuring a balanced comparison between groups. Post-PSM, the age and sex distribution between the GBSRCA and GBAC groups were well balanced, and no significant differences were noted (Age: $p = 1.000$; Sex: $P = 0.657$). Other clinical and pathological features also showed a balanced distribution, ensuring that the survival differences observed are attributable to the histological subtype rather than confounding factors. Provided here is a comprehensive analysis of the differences in clinical characteristics and survival outcomes between patients with GBSRCA and those with GBAC, highlighting the poorer prognosis associated with GBSRCA. The use of PSM helps ensure that these findings are robust and not confounded by baseline differences in patient characteristics.

3.2. Survival analysis before and after PSM

Figure 2 shows the KM survival curves for overall survival (OS) and cancer-specific survival (CSS) before PSM. The median OS for patients with GBSRCA was significantly shorter compared to that for patients with GBAC ($P < 0.001$). The KM curves (Figure 2A) depict a sharp decline in survival for patients with GBSRCA, emphasizing their poorer prognosis. Similarly, CSS analysis (Figure 2B) indicated that patients with GBSRCA had a significantly worse CSS compared to patients with GBAC ($P < 0.001$). Figure 3 shows the KM survival curves for OS and CSS after adjusting for potential confounders through PSM. Even after PSM, the median OS for patients with GBSRCA remained significantly shorter than that for patients with GBAC ($P < 0.001$), as shown in Figure 3A. The CSS results post-PSM (Figure 3B) also indicated that patients with GBSRCA continued to have a significantly poorer prognosis compared to patients with GBAC ($P < 0.001$).

3.3. Univariate and multivariate Cox regression analysis

Table 2. Basic clinical and pathological features in patients with GBSRCA and GBAC after PSM

Variables	Overall number (n = 284)	GBSRCA (n = 142)	GBAC (n = 142)	P value
Age (%)				1.000
≤ 60	90 (31.7)	45 (31.7)	45 (31.7)	
> 60	194 (68.3)	97 (68.3)	97 (68.3)	
Sex (%)				0.657
Male	57 (20.1)	30 (21.1)	27 (19.0)	
Female	227 (79.9)	112 (78.9)	115 (81.0)	
Race (%)				0.881
Asian	26 (9.2)	12 (8.5)	14 (9.9)	
White	218 (76.8)	109 (76.8)	109 (76.8)	
Other	40 (14.1)	21 (14.8)	19 (13.4)	
Marital status (%)				0.720
No/Unknown	127 (44.7)	62 (43.7)	65 (45.8)	
Married	157 (55.3)	80 (56.3)	77 (54.2)	
Grade (%)				1.000
Well to moderately differentiated	26 (9.2)	13 (9.2)	13 (9.2)	
Poorly to undifferentiated	232 (81.7)	116 (81.7)	116 (81.7)	
Unknown	26 (9.2)	13 (9.2)	13 (9.2)	
T stage (%)				1.000
T1-T2	126 (44.4)	63 (44.4)	63 (44.4)	
T3-T4	158 (55.6)	79 (55.6)	79 (55.6)	
N stage (%)				1.000
N-	158 (55.6)	79 (55.6)	79 (55.6)	
N+	126 (44.4)	63 (44.4)	63 (44.4)	
M stage (%)				1.000
M-	198 (69.7)	99 (69.7)	99 (69.7)	
M+	86 (30.3)	43 (30.3)	43 (30.3)	
Radiotherapy (%)				1.000
Not performed	234 (82.4)	117 (82.4)	117 (82.4)	
Performed	50 (17.6)	25 (17.6)	25 (17.6)	
Chemotherapy (%)				0.719
Not performed	161 (56.7)	82 (57.7)	79 (55.6)	
Performed	123 (43.3)	60 (42.3)	63 (44.4)	
CRD (%)				0.399
No	66 (23.2)	30 (21.1)	36 (25.4)	
Yes	218 (76.8)	112 (78.9)	106 (74.6)	
Surgery (%)				1.000
Not performed	32 (11.3)	16 (11.3)	16 (11.3)	
Performed	252 (88.7)	126 (88.7)	126 (88.7)	

GBSRCA: gallbladder signet-ring cell carcinoma; GBAC: gallbladder adenocarcinoma; CRD: cancer-related death; PSM: propensity score matching.

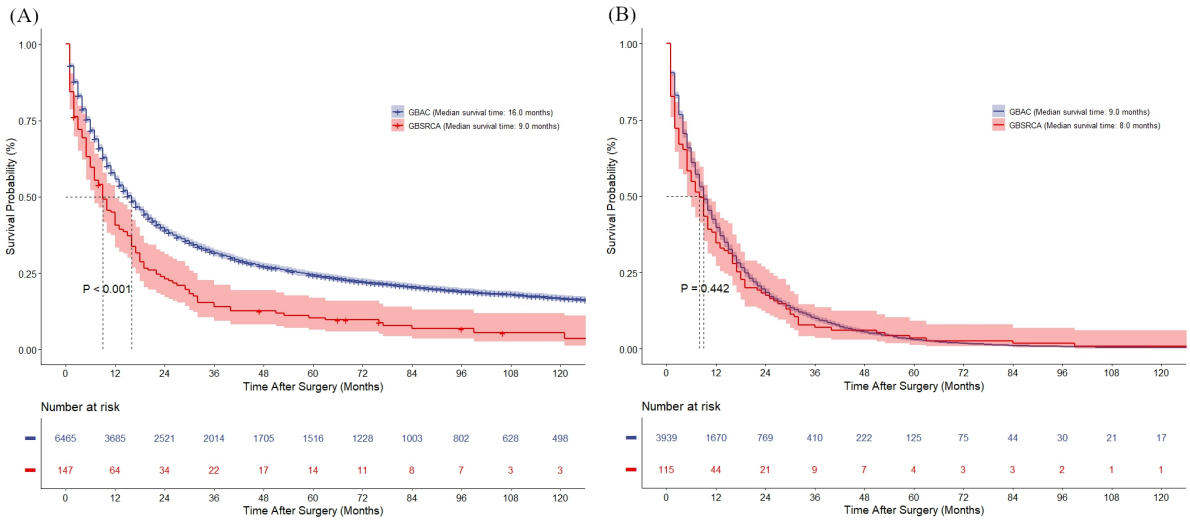

Figure 2. KM curves showing survival differences between patients with GBAC and those with GBSRCA. (A), OS. **(B)**, CSS. GBAC: gallbladder adenocarcinoma; GBSRCA: gallbladder signet-ring cell carcinoma. OS: overall survival. CSS: cancer-specific survival.

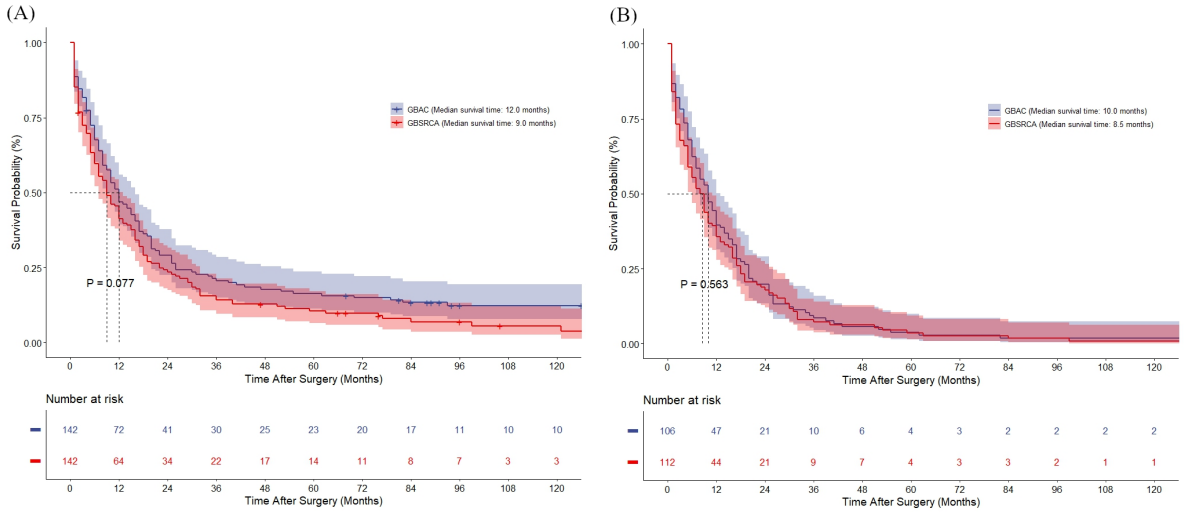

Figure 3. KM curves showing survival differences between patients with GBAC and those with GBSRCA after PSM. (A), OS. **(B)**, CSS. GBAC: gallbladder adenocarcinoma; GBSRCA: gallbladder signet-ring cell carcinoma. OS: overall survival. CSS: cancer-specific survival. PSM: propensity score matching.

Table 3 shows the results of the univariate and multivariate Cox regression analyses for prognostic factors affecting OS and CSS in the entire cohort. In univariate analysis, patients > the age of 60 had an HR for OS of 0.791 (95% CI: 0.552-1.135; $P = 0.204$) and an HR for CSS of 0.765 (95% CI: 0.517-1.134; $P = 0.182$), indicating a trend, albeit not a significant one. Being female was associated with a better OS (HR: 0.786, 95% CI: 0.659-0.937; $P = 0.008$) and CSS (HR: 0.798, 95% CI: 0.667-0.954; $P = 0.013$). In multivariate analysis of the histological subtypes (GBSRCA *vs*. GBAC), GBSRCA was found to be an independent adverse prognostic factor for both OS (HR: 1.839, 95% CI: 1.474-2.297; $P < 0.001$) and CSS (HR: 1.871, 95% CI: 1.494-2.343; $P < 0.001$). Advanced tumor stage was independently associated with a poorer OS and CSS, emphasizing the importance of early detection and treatment.

In the prognostic analyses of cases with GBSRCA, as summarized in Table 4, tumor differentiation grade, T stage, M stage, and surgical status were identified as significant prognostic factors in the univariate analyses. In the multivariate analyses, T stage (HR: 1.721, 95% CI: 1.137-2.605; $P = 0.010$) and M stage (HR: 1.816, 95% CI: 1.192-2.767; $P = 0.005$) emerged as independent prognostic factors. Additionally, while surgery was shown to be a protective factor, it was not found to be an independent prognostic factor (HR: 0.667, 95% CI: 0.373-1.191; $P = 0.171$).

4. Discussion

Previous studies have indicated that the presence of SRCC components is a significantly poor prognostic factor for patients with solid tumors, and particularly in those with gastric cancer (*17-21*). In these patients, early peritoneal dissemination and lymph node metastasis are common, leading to a worse prognosis than that for conventional adenocarcinoma. In GBC, however, the differences in clinicopathological factors and long-term prognosis associated with SRCC compared to conventional adenocarcinoma have not been systematically explored. Using data from the SEER database, the current study has provided an in-depth comparative analysis of these two subtypes, emphasizing differences in demographic characteristics, clinical features, and survival outcomes.

Results revealed significant differences in the age and sex distribution between patients with GBSRCA and those with GBAC. In specific terms, patients with GBSRCA were significantly younger ($p = 0.009$), with a notable 33.3% being age 60 or younger compared to 23.9% of patients with GBAC. This younger age at diagnosis of GBSRCA suggests a potentially distinct etiopathogenesis that might involve genetic predispositions or environmental factors not typically associated with GBAC. This finding is consistent with previous studies indicating that SRCC is more prevalent among younger individuals. The sex distribution also differed significantly, with a higher proportion of females in the GBSRCA group (77.6%) compared to the GBAC group (70.1%, $p = 0.049$). This female predominance aligns with the overall higher incidence of gallbladder disease in women, which is often attributed to hormonal influences and a higher prevalence of gallstones that are known risk factors for gallbladder cancer. In addition, results confirmed that SRCC is associated with a higher likelihood of lymph node metastasis, later-stage diagnosis, and poorer prognosis. Even after PSM, which adjusts for potential confounders such as age, sex, and other clinical variables, patients with GBSRCA continued to share a significantly worse OS and CSS compared to

Table 3. Univariate and multivariate Cox regression of prognostic factors for OS and CSS of the entire cohort

Variables	OS				CSS			
	Univariate		Multivariate		Univariate		Multivariate	
	Crude HR (95%CI)	uni-*P* value	Adj HR (95%CI)	Multi *P* value	Crude HR (95%CI)	Uni *P* value	Adj HR (95%CI)	Multi *P* value
Age								
≤ 60								
> 60	1.409 (1.320,1.505)	< 0.001	1.434 (1.342,1.533)	< 0.001	1.092 (1.016,1.173)	0.017	1.112 (1.033,1.196)	0.005
Sex								
Male								
Female	0.939 (0.886,0.995)	0.032	0.850 (0.801,0.902)	< 0.001	1.006 (0.940,1.076)	0.864		
Race								
Asian								
White	1.120 (1.024,1.226)	0.013	1.083 (0.989,1.184)	0.084	1.054 (0.951,1.168)	0.314		
Other	1.148 (1.026,1.284)	0.016	1.088 (0.972,1.218)	0.143	1.092 (0.960,1.242)	0.179		
Marital status								
No/Unknown								
Married	0.860 (0.815,0.907)	< 0.001	0.801 (0.758,0.847)	< 0.001	0.899 (0.845,0.956)	0.001	0.870 (0.818,0.926)	< 0.001
Grade								
Well to moderately differentiated								
Poorly to undifferentiated	1.788 (1.683,1.900)	< 0.001	1.400 (1.314,1.491)	< 0.001	1.484 (1.384,1.591)	< 0.001	1.368 (1.275,1.469)	< 0.001
Unknown	1.563 (1.455,1.679)	< 0.001	0.943 (0.867,1.026)	0.171	1.968 (1.810,2.141)	< 0.001	1.087 (0.977,1.209)	0.124
T stage								
T1-T2								
T3-T4	2.996 (2.834,3.168)	< 0.001	2.183 (2.046,2.329)	< 0.001	1.835 (1.720,1.957)	< 0.001	1.594 (1.485,1.711)	< 0.001
N stage								
N-								
N+	1.666 (1.572,1.765)	< 0.001	1.266 (1.188,1.348)	< 0.001	1.133 (1.062,1.209)	< 0.001	1.123 (1.049,1.202)	0.001
M stage								
M-								
M+	3.559 (3.345,3.787)	< 0.001	2.320 (2.156,2.497)	< 0.001	2.174 (2.034,2.324)	< 0.001	1.904 (1.763,2.056)	< 0.001
Pathology subtypes								
GBAC								
GBSRCA	1.614 (1.361,1.914)	< 0.001	1.341 (1.127,1.594)	0.001	1.077 (0.894,1.297)	0.434		
Chemotherapy								
Not performed								
Performed	1.283 (1.214,1.356)	< 0.001	0.704 (0.656,0.754)	< 0.001	0.864 (0.811,0.919)	< 0.001	0.578 (0.536,0.624)	< 0.001
Radiotherapy								
Not performed								
Performed	0.816 (0.757,0.880)	< 0.001	0.978 (0.896,1.067)	0.613	0.663 (0.609,0.721)	< 0.001	1.018 (0.924,1.121)	0.717
Surgery								
Not performed								
Performed	0.264 (0.246,0.283)	< 0.001	0.485 (0.442,0.533)	< 0.001	0.405 (0.375,0.437)	< 0.001	0.531 (0.477,0.590)	< 0.001

GBSRCA: gallbladder signet-ring cell carcinoma; GBAC: gallbladder adenocarcinoma; OS: overall survival; CSS: cancer-specific survival.

Table 4. Univariate and multivariate Cox regression of prognostic factors for the OS and CSS of patients with GBSRCA

Variables	OS				CSS			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Age								
≤ 60								
> 60	0.791 (0.552,1.135)	0.204			0.765 (0.517,1.134)	0.182		
Sex								
Male								
Female	0.735 (0.490,1.105)	0.139			0.749 (0.483,1.162)	0.197		
Race								
Asian								
White	0.758 (0.422,1.364)	0.356			1.044 (0.553,1.971)	0.894		
Other	0.827 (0.406,1.681)	0.599			0.985 (0.456,2.131)	0.970		
Marital status								
No/Unknown								
Married	1.050 (0.747,1.477)	0.777			0.868 (0.594,1.268)	0.464		
Grade								
Well to moderately differentiated								
Poorly to undifferentiated	1.514 (0.810,2.829)	0.194	1.538 (0.818,2.892)	0.182	1.110 (0.576,2.138)	0.755		
Unknown	2.353 (1.063,5.208)	0.035	1.705 (0.720,4.036)	0.225	1.446 (0.629,3.325)	0.385		
T stage								
T1-T2								
T3-T4	1.936 (1.354,2.768)	< 0.001	1.720 (1.186,2.494)	0.004	1.798 (1.205,2.683)	0.004	1.721 (1.137,2.605)	0.010
N stage								
N-								
N+	1.197 (0.849,1.688)	0.306			0.835 (0.578,1.208)	0.339		
M stage								
M-								
M+	2.562 (1.754,3.741)	< 0.001	2.421 (1.618,3.623)	< 0.001	1.949 (1.308,2.903)	0.001	1.816 (1.192,2.767)	0.005
Chemotherapy								
Not performed								
Performed	0.964 (0.684,1.360)	0.836			0.753 (0.520,1.091)	0.133		
Radiotherapy								
Not performed								
Performed	0.876 (0.563,1.364)	0.558			0.923 (0.555,1.535)	0.758		
Surgery								
Not performed								
Performed	0.420 (0.245,0.720)	0.002	0.738 (0.387,1.410)	0.358	0.448 (0.259,0.774)	0.004	0.667 (0.373,1.191)	0.171

GBSRCA: gallbladder signet-ring cell carcinoma; OS: overall survival; CSS: cancer-specific survival.

patients with GBAC ($p < 0.001$). This persistent survival disadvantage highlights the inherent aggressiveness of GBSRCA, which may be due to its distinct biological characteristics such as a higher metastatic potential and resistance to conventional therapies.

The clinical implications of this study can be summarized as follows. First, given the younger age at diagnosis of GBSRCA, considering earlier screening of at-risk populations may be worth considering. This could involve more vigilant monitoring of patients with known risk factors such as gallstones or chronic gallbladder inflammation. Second, the distinct survival disadvantage associated with GBSRCA underscores the need for personalized treatment strategies. There is a pressing need for research into targeted therapies that address the unique molecular characteristics of GBSRCA. Third, the higher prevalence of GBSRCA in females suggests that gender-specific factors may influence the development and progression of this subtype. Hormonal influences and their potential role in GBSRCA pathogenesis warrant further investigation. Fourth, comprehensive molecular and genetic profiling of GBSRCA is essential to identifying unique biomarkers and therapeutic targets. Such studies could lead to the development of novel targeted therapies and improve outcomes for patients with this aggressive subtype. Fifth, developing and validating prognostic models that incorporate clinical, pathological, and molecular variables can help predict outcomes more accurately and guide treatment decisions. These models should be tailored to account for the specific characteristics of GBSRCA.

This study had several limitations. First, the retrospective nature of the analysis may have introduced selection bias and limited the ability to establish causality. Second, the reliance on the SEER database means that certain clinical details, such as comorbidities and specific treatment regimens, were not available, potentially affecting the comprehensiveness of the findings. With the advent of adjuvant immunotherapy over the past few years, significant efficacy and improved survival have been achieved in an increasing number of patients with biliary tract malignancies after immunotherapy (*22*). However, the SEER data are not able to provide corresponding detailed raw data, which is undoubtedly a drawback to this study. Third, the relatively small sample of patients with GBSRCA may limit the generalizability of the results and the statistical power to detect differences. Fourth, the study did not include molecular and genetic analyses, which could provide deeper insights into the distinct etiopathogenesis of and therapeutic targets for GBSRCA.

In conclusion, this study has highlighted the significant clinical and pathological differences between GBSRCA and GBAC, emphasizing the poorer prognosis associated with GBSRCA. The findings underscore the need for early detection, personalized treatment strategies, and targeted research efforts to address the unique challenges posed by this rare and aggressive subtype of gallbladder cancer. Enhanced understanding and management of GBSRCA could lead to improved survival outcomes and better quality of life for affected patients.

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