



Prognostic factors for resected cases with gallbladder carcinoma: a systematic review and meta-analysis

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Objective: Current meta-analysis was performed to systematically evaluate the potential prognostic factors for overall survival among resected cases with gallbladder carcinoma.

Methods: PubMed, EMBASE, and the Cochrane Library were systematically retrieved and hazard ratio (HR) and its 95% confidence interval were directly extracted from the original study or roughly estimated via Tierney's method. Standard Parmar modifications were used to determine pooled HRs.

Results: A total of 36 studies with 11 502 cases were identified. Pooled results of univariate analyses indicated that advanced age (HR = 1.02, $P = 0.00020$), concurrent gallstone disease (HR = 1.22, $P = 0.00200$), elevated preoperative CA199 level (HR = 1.93, $P < 0.00001$), advanced T stage (HR = 3.09, $P < 0.00001$), lymph node metastasis (HR = 2.78, $P < 0.00001$), peri-neural invasion (HR = 2.20, $P < 0.00001$), lymph-vascular invasion (HR = 2.37, $P < 0.00001$), vascular invasion (HR = 2.28, $P < 0.00001$), poorly differentiated tumor (HR = 3.22, $P < 0.00001$), hepatic side tumor (HR = 1.85, $P < 0.00001$), proximal tumor (neck/cystic duct) (HR = 1.78, $P < 0.00001$), combined bile duct resection (HR = 1.45, $P < 0.00001$), and positive surgical margin (HR = 2.90, $P < 0.00001$) were well-established prognostic factors. Pathological subtypes ($P = 0.53000$) and postoperative adjuvant chemotherapy ($P = 0.70000$) were not prognostic factors. Pooled results of multivariate analyses indicated that age, gallstone disease, preoperative CA199, T stage, lymph node metastasis, peri-neural invasion, lymph-vascular invasion, tumor differentiation status, tumor location (peritoneal side vs hepatic side), surgical margin, combined bile duct resection, and postoperative adjuvant chemotherapy were independent prognostic factors.

Conclusion: Various prognostic factors have been identified beyond the 8th AJCC staging system. By incorporating these factors into a prognostic model, a more individualized prognostication and treatment regime would be developed. Upcoming multinational studies are required for the further refine and validation.

Keywords: adenocarcinoma, surgery, cancer, tumor, carcinoma, cholecystectomy, gallbladder, malignant, neoplasm, surgical resection

Introduction

Gallbladder carcinoma (GBC) is a rare but highly lethal gallbladder epithelium-originated malignant disease with a reported poor 5-year survival rate less than 5%^[1]. Curative-intent surgery has always been regarded the most effective intervention and a pure cholecystectomy has been demonstrated to be especially effective in patients with Tis or T1a disease with a reported 5-year

survival rate reaching 100%^[2,3]. Moreover, the radical cholecystectomy, including gallbladder removal, partial or more extended hepatectomy and a regional or more extensive lymphadenectomy has been widely applied in T1b or more advanced GBC^[1,4]. Promising survival outcomes have been achieved and reported in those received curative surgery^[1,4].

According to the latest 8th American Joint Committee on Cancer (AJCC) staging system, the T stage (the depth of

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invasion), lymph node metastasis, and metastatic disease are the major staging factors and the most important prognostic factors for cases with GBC^[5]. Apart from the three conventional prognostic factors mentioned above, many other potential prognostic factors with inconsistent validity of evidence have also been recommended for clinical care but have not been fully evaluated, including histological grade (differentiation status), pathological subtype, and lymph-vascular invasion^[6-8]. Owing to the complex anatomic features that gallbladder is surrounded by various vital organs and structures, there might also be other hidden predictors for survival. For example, some researchers indicated that an elevated preoperative CA199 level indicated worse prognosis in postsurgical GBC patients^[9-11]. Some easily-ignored predictors, such as age^[12,13] and the level of preoperative fibrinogen level^[14], have also been recommended but not fully evaluated. Just as our previous series indicated that the whole biliary tract was surrounded by dense neural network, it might serve as another potential metastatic route for GBC patients^[15] and prognostic significance of peri-neural invasion has also been validated in numerous previous publications^[16-18]. Moreover, our recent research focusing on the significance of tumor locations (proximal tumor: neck/cystic duct tumors vs distal tumor: body/fundus tumors) in resected GBC indicated that proximal tumors shared much worse prognosis than distal tumors, especially cystic duct tumor^[19]. However, the findings above have not been mentioned by 8th AJCC staging system. Additionally, the prognostic value of the extent of resection, especially the significance of extra-hepatic bile duct resection, has also been systematically evaluated in our previous series^[20] but has not been fully incorporated in the 8th AJCC staging system.

Therefore, current meta-analysis was performed to have a comprehensive evaluation and validation on the potential prognostic factors among surgically-treated GBC patients. Our findings might assist clinicians to stratify patients with different survival outcomes and treatment modalities.

Materials and methods

Search strategy

Eligible studies were retrieved and identified based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA, Supplemental Digital Content 1, <http://links.lww.com/JS9/C299>, Supplemental Digital Content 2, <http://links.lww.com/JS9/C300>)^[21] and Assessing the methodological quality of systematic reviews (AMSTAR, Supplemental Digital Content 3, <http://links.lww.com/JS9/C301>)^[22] guidelines. Comprehensive literature researching was performed in the following databases till 5 February 2024: PubMed, EMBASE, the Cochrane Library. Eligible studies were restricted to publications focusing on the prognostic factors for overall survival (OS) among resected GBC patients. The searching keywords were listed as follows: gallbladder, cancer, tumor, carcinoma, malignant, neoplasm, adenocarcinoma, surgery, surgical resection, and cholecystectomy. In order to broaden our research, we also reviewed any relevant studies listed in previous reviews or meta-analyses. The primary endpoint of current study is the potential prognostic factors for resected cases with GBC through the incorporation of results in univariate analyses. Moreover, all potential independent prognostic factors have also been furtherly evaluated via the incorporation of results reported in multivariate analyses. The current

HIGHLIGHTS

- Current study is the first to systematically evaluate the potential prognostic factors and independent prognostic factors among resected cases with gallbladder carcinoma.
- To date, the sample size of current study is the largest.
- Pooled results validated the prognostic value of conventional staging factors reported by 8th AJCC staging system (T, N).
- Various unmasked potential prognostic factors, such as peri-neural invasion, tumor locations, lymph-vascular invasion, have also been explored and validated.

study was conducted based on published retrospective or prospective studies and was not registered. Additionally, we did not prepare a review protocol.

Inclusion criteria

- (1) Published English literature;
- (2) Only original researches reporting prognostic factors for OS among resected GBC were considered eligible.

Exclusion criteria

- (1) Abstracts, reviews, letters, meetings, and on-going clinical trials would be ruled out.
- (2) For certain studies, despite reporting prognostic factors, if those factors were rare and failed to be meta-analyzed or if the original data failed to be extracted, those studies would be also excluded.
- (3) For originated from the same center and a complete data duplication was detected, only the study with the largest sample size would be included.
- (4) Studies reported prognostic factors for disease-free survival (DFS) or cancer-specific survival but not for OS.
- (5) Studies with inadequate original data for further analysis would also be excluded.

Data extraction

The potential prognostic factors were confirmed via reviewing previous GBC-related publications as well as the latest 8th AJCC staging criteria by the first author (L.T.R) and second author (W.J.K). Based on the results of our own single-center experience^[3,15,23] and findings reported in previous publications, all authors discussed and finally identified sixteen relevant prognostic factors, including age (young vs old), preoperative obstructive jaundice (no vs yes), preoperative CA199 (low vs high), concurrent gallstone disease (no vs yes), T stage (T1-2 vs T3-4), lymph node metastasis (N- vs N+), peri-neural invasion (- vs +), lymph-vascular invasion (- vs +), vascular invasion (- vs +), pathology subtypes (AC vs others), differentiation status (well to moderate vs poor), tumor location (peritoneal side vs hepatic side), tumor location (distal vs proximal), surgical margin (- vs +), concurrent bile duct resection (not performed vs performed), and postoperative adjuvant chemotherapy (not performed vs performed).

Statistical analysis

Tierney' method was the foundation of data extraction, transformation, and incorporation^[24]. When hazard ratio (HR) and

its 95% CI were directly provided, the HR and 95% CI were directly used and were transformed into the lnHR and selnHR for further analysis. However, when HR and 95% CI were not directly provided and only Kaplan–Meier curves were provided with the number of patients in both groups, a rough estimate of HR was performed via Tierney's method using *engauge* software^[24]. When HR and 95% CI as well as survival curves were both not provided, a rough calculation of HR and its 95% CI was conducted based on the number of cases in control group, the number of cases in experimental group, the total number of cases with final event (death), and the *P*-value from log rank test or univariable analysis, which was also based on Tierney's method^[24]. HRs larger than 1 indicated a negative survival impact on OS versus reference. Standard Parmar modifications was the major methodology of data extraction in our analysis^[25]. Acquired lnHR and selnHR were incorporated via RevMan5.3 software. *P*-values lower than 0.05 indicated statistical difference.

Heterogeneity analyses were performed via removing every single study manually to find the major source of heterogeneity. A *P*-value lower than 0.1 and I^2 greater than 50% indicated the existence of significant heterogeneity^[26]. Any single study, which

caused great heterogeneity would be excluded. Sensitivity analysis was also performed in a same manner. Publication bias was systematically evaluated via Stata14.0 software (Begg's and Egger's tests) for the comparison sharing the largest number of included studies. A *P*-value or corrected *P*-value (P^*) lower than 0.05 indicated a significant publication bias^[27].

Results

Preliminary literature search identified a total of 57 097 publications. After removing duplicated articles, we were left with 45 957 unique papers. These papers underwent a screening process based on specific inclusion and exclusion criteria and 374 studies were considered potentially eligible. Full-text screening was furtherly conducted among these 374 articles and ultimately identified 36 studies^[3,9,10,16,17,19,23,28–56] for the final meta-analysis, which had sufficient clinical data (Fig. 1). For studies that performed based on public cancer databases like the Surveillance, Epidemiology, and End Results (SEER) or National Cancer Database (NCDB), we only included the study with the largest sample size. Specifically, we included a recently published study

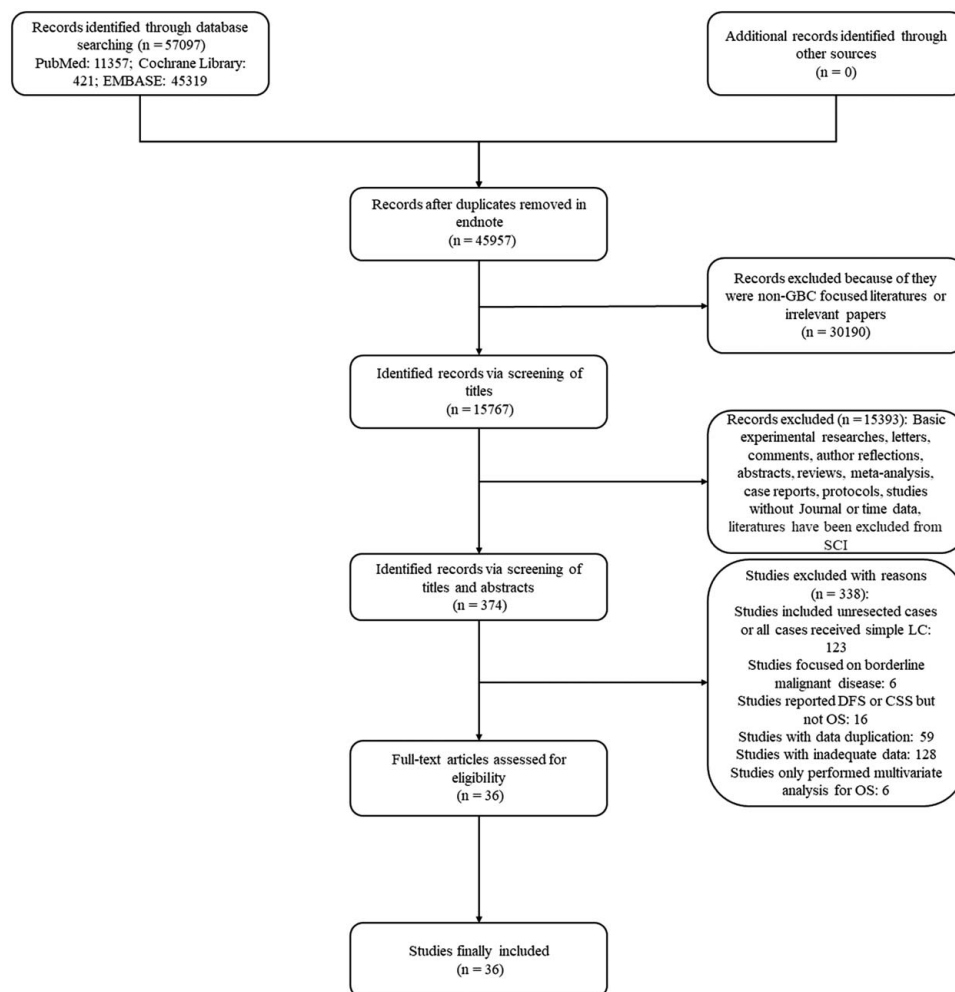


Figure 1. Specific process of literature research, selection, and identification. CSS, cancer-specific survival; DFS, disease-free survival; LC, laparoscopic cholecystectomy; OS, overall survival; SCI, scientific citation index.

by Jiang *et al.*^[37] based on the SEER database with the largest sample size. In cases where multiple studies came from the same center, we applied a similar criterion of including only the study with the largest sample size. In our analysis, we included the study by Gani *et al.*^[36] and the study by Jiang *et al.*^[37], both of which were multicenter studies conducted in America. While there might be some overlap in patient sources between the two studies, their respective study periods differed, and the study by Jiang *et al.* had a significantly larger sample size (5451 vs 449) compared to the study by Gani *et al.* Similarly, multicenter studies by Vega *et al.*, which included cases from Chile and America, were also included due to the similarity of their status. In the case of studies by Li *et al.*, we considered several recent publications focusing on GBC. We included the study with the largest sample size (Lv TR *et al.*, 2023, $n=326$) for further analysis^[23]. However, two additional studies from the same center but with smaller sample sizes were also included. These two studies examined the prognostic value of tumor location (Lv TR *et al.*, $n=259$)^[19] and the prognostic value of combined bile duct resection (Wang JK *et al.*, $n=213$)^[3]. The results of these two studies were included in different outcomes and did not generate any data overlap. The baseline characteristics of finally included studies were summarized in Table 1.

The prognostic value of age

A total of 31 studies^[9,10,16,17,23,28–33,35–38,40–44,46,48–56] with 10 818 cases were incorporated into this comparison. Pooled results indicated that old age was a risk factor for OS among resected cases with GBC (HR = 1.02, 95% CI: 1.01–1.04, $P=0.0002$) (Figure S1A, Supplemental Digital Content 4, <http://links.lww.com/JS9/C302>) (Table 2). Consistently, age has also been demonstrated as an independent prognostic factor (HR = 1.29, 95% CI: 1.17–1.43, $P<0.00001$) (Figure S2A, Supplemental Digital Content 5, <http://links.lww.com/JS9/C303>) (Table 2).

The prognostic value of concurrent gallstone disease

A total of 14 studies^[3,9,10,16,28,31,35,42,43,46,51–53,56] with 2201 cases were incorporated into this comparison. Pooled results indicated that concurrent gallstone disease was a risk factor for OS among resected cases with GBC (HR = 1.22, 95% CI: 1.08–1.39, $P=0.002$) (Figure S1B, Supplemental Digital Content 4, <http://links.lww.com/JS9/C302>) (Table 2). However, only one study incorporated gallstone disease into multivariate analysis and gallstone disease was also an independent prognostic factor (HR = 1.49, 95% CI: 1.16–1.92, $P=0.00200$) (Figure S2B, Supplemental Digital Content 5, <http://links.lww.com/JS9/C303>) (Table 2).

The prognostic value of concurrent obstructive jaundice

A total of 11 studies^[23,28,29,32,35,41,42,49,51–53] with 3134 cases were incorporated into this comparison. Pooled results indicated that the concurrent of preoperative jaundice was a risk factor for OS among resected cases with GBC (HR = 1.93, 95% CI: 1.72–2.18, $P<0.00001$) (Figure S1C, Supplemental Digital Content 4, <http://links.lww.com/JS9/C302>) (Table 2). However, in multivariate analysis, preoperative obstructive jaundice was not an independent prognostic factor (HR = 1.05, 95% CI:

0.75–1.47, $P=0.79000$) (Figure S2C, Supplemental Digital Content 5, <http://links.lww.com/JS9/C303>) (Table 2).

The prognostic value of preoperative CA199 level

A total of 15 studies^[9,10,17,23,29–31,33,41,42,50,53–56] with 2813 cases were incorporated. Pooled results indicated that preoperative CA199 was an indicator of worse prognosis (HR = 2.31, 95% CI: 2.07–2.57, $P<0.00001$) (Figure S1D, Supplemental Digital Content 4, <http://links.lww.com/JS9/C302>) (Table 2). The results of multivariate analyses indicated that preoperative CA199 level was also an independent prognostic factor (HR = 1.50, 95% CI: 1.27–1.77, $P<0.00001$) (Figure S2D, Supplemental Digital Content 5, <http://links.lww.com/JS9/C303>) (Table 2).

The prognostic value of T category

A total of 15 studies^[9,16,23,28–30,34,36,38,41–44,49,54] with 3180 cases were incorporated. Pooled results indicated that T stage was a validating risk factor for OS (HR = 3.09, 95% CI: 2.46–3.88, $P<0.00001$) (Figure S1E, Supplemental Digital Content 4, <http://links.lww.com/JS9/C302>). High heterogeneity was detected ($I^2=65\%$) and the results of heterogeneity analyses indicated that when the study by Lv TR *et al.*^[23] was excluded, a significantly lower heterogeneity value was furtherly acquired (HR = 2.71, 95% CI: 2.38–3.07, $P<0.00001$, $I^2=3\%$) (Table 2). The results of multivariate analyses indicated that T stage was also an independent prognostic factor (HR = 3.74, 95% CI: 2.01–6.97, $P<0.00010$) (Figure S2E, Supplemental Digital Content 5, <http://links.lww.com/JS9/C303>) (Table 2).

The prognostic value of lymph node metastasis

A total of 26 studies^[9,10,16,17,23,28–30,32,33,36,38,39,41–45,47–51,54–56] with 4603 cases were incorporated. Pooled results indicated that lymph node metastasis was a validating risk factor for OS (HR = 2.78, 95% CI: 2.35–3.28, $P<0.00001$) (Figure S1F, Supplemental Digital Content 4, <http://links.lww.com/JS9/C302>) (Table 2). The high heterogeneity was detected and the results of heterogeneity analyses failed to reveal any major source of heterogeneity. The results of multivariate analyses indicated that lymph node metastasis was also an independent prognostic factor (HR = 2.20, 95% CI: 1.74–2.78, $P<0.00001$) (Figure S2F, Supplemental Digital Content 5, <http://links.lww.com/JS9/C303>) (Table 2).

The prognostic value of peri-neural invasion

A total of 15 studies^[16,17,23,28–30,38,41–43,45,46,49,55,57] with 3062 cases were incorporated. Pooled results indicated that peri-neural invasion was a validating risk factor for OS (HR = 2.20, 95% CI: 1.95–2.49, $P<0.00001$) (Figure S1G, Supplemental Digital Content 4, <http://links.lww.com/JS9/C302>) (Table 2). The results of multivariate analyses indicated that peri-neural invasion was also an independent prognostic factor (HR = 1.34, 95% CI: 1.04–1.73, $P=0.02000$) (Figure S2G, Supplemental Digital Content 5, <http://links.lww.com/JS9/C303>) (Table 2).

The prognostic value of lymph-vascular invasion

A total of 13 studies^[9,16,23,28,29,38,41,42,45,46,49,55,57] with 2814 cases were incorporated. Pooled results indicated that lymph-

Table 1

Baseline characteristics of all studies included.

Study author	Year	Study period	Cohort origin	Specific hospitals	No. cases included	Sex ratio (female/male)	Staging criteria	Follow-up time
Schauer <i>et al.</i> ^[47]	2001	1980–1997	Germany	Ludwig-Maximilian University	127	NA	Nevin staging criteria	NA
Shimizu <i>et al.</i> ^[48]	2007	1980–2005	Japan	Graduate School of Medicine, Chiba University	79	50/29	JSBS stage	Median 152, range, 6–288 months
Kohya and Miyazaki ^[39]	2008	1989–2007	Japan	Saga University Hospital	52	36/16	AJCC staging criteria, 2th edition	NA
Murakami <i>et al.</i> ^[44]	2011	1990–2010	Japan	Hiroshima University Hospital	62	30/32	UICC staging criteria, 2010 edition	Median 157, range 2– 255 months
Cziupka <i>et al.</i> ^[34]	2012	2001–2009	Germany	Greifswald University	33	NA	UICC staging criteria, 2010 edition	NA
Choi <i>et al.</i> ^[16]	2013	2000–2010	Korea	Korea University Medical Center	71	39/32	AJCC staging criteria, 7th edition	Till 31 November 2012
Liu <i>et al.</i> ^[43]	2013	1995–2010	China	Liaocheng People's Hospital	78	46/32	AJCC staging criteria, 7th edition	Median 26.5, range: 2–132 months
Abe <i>et al.</i> ^[9]	2016	1996–2014	Japan	Onomichi General Hospital	54	33/21	UICC staging criteria, 2010 edition	Median 3 years, range 0.04–13.8 years
Gani <i>et al.</i> ^[36]	2016	2000–2014	USA	Ten medical centers: Johns Hopkins University; Emory University; Stanford University; University of Wisconsin; Ohio State University; Washington University; Vanderbilt University; New York University; University of Louisville; Wake Forest University	449	292/157	AJCC staging criteria, 7th edition	Median 37.6 months (IQR: 12.3–82.1).
Salman <i>et al.</i> ^[46]	2016	2000–2011	Turkey	Atatürk Training and Research Hospital	47	(35/12)	NA	Till July, 2013
Kurahara <i>et al.</i> ^[17]	2017	2000–2015	Japan	Kagoshima University	80	44/36	AJCC staging criteria, 7th edition	NA
Wang <i>et al.</i>	2017	2008–2013	China	Jinshan Hospital, Fudan University	125	80/45	AJCC staging criteria, 8th edition	Till December 2015
Wen <i>et al.</i> ^[52]	2017	2003–2013	China	Eastern Hepatobiliary Hospital	390	240/150	AJCC staging criteria, 7th edition	Till May 2014
Vega <i>et al.</i> ^[49]	2019	2000–2017	USA/Chile	The University of Texas MD Anderson Cancer Center/ Hospital Sotero del Rio	255	195/60	AJCC staging criteria, 7th edition	Median 70-8, 95% CI: 53-6–87-3 months
Wang <i>et al.</i>	2019	2007–2016	China	West China Hospital	213	139/74	AJCC staging criteria, 7th edition	Every 2–3 months in the first year and 3–6 months thereafter
Zheng <i>et al.</i> ^[56]	2019	2007–2016	China	The Second Affiliated Hospital of Wenzhou Medical University	83	60/23	AJCC staging criteria, 7th edition	Till September 2018
Bao <i>et al.</i> ^[30]	2020	2010–2017	China	Third Affiliated Hospital of Soochow University	144	107/37	AJCC staging criteria, 8th edition	Till October 2020
Lee <i>et al.</i> ^[40]	2020	2001–2013	Korea	National Cancer Center	158	85/73	AJCC staging criteria, 8th edition	Every 3 or 6 months after discharge
Xu <i>et al.</i> ^[53]	2020	2005–2017	China	Peking Union Medical College Hospital	154	91/63	AJCC staging criteria, 8th edition	Every 3 months during the first 2 years, every 6 months during the next 3 years, and annually after 5 years
Ando <i>et al.</i> ^[28]	2021	1982–2019	Japan	Niigata University Medical and Dental Hospital and Niigata Cancer Center Hospital, Japan	207	117/90	AJCC staging criteria, 8th edition	Median 107, range: 0.5–424 months
Chaudhary <i>et al.</i> ^[32]	2021	1985–2016	Japan	Tokyo Womens' Medical University Hospital	348	208/140	AJCC staging criteria, 8th edition	NA
Chen <i>et al.</i> ^[33]	2021	2012–2020	China	Affiliated Hospital of the Southwest Medical	93	31/62	AJCC staging criteria, 8th edition	Till July 2020
Gupta <i>et al.</i> ^[10]	2021	2014–2018	India	George's Medical University	115	91/24	AJCC staging criteria, 7th edition	Median 30, range 8–62 months
Kim <i>et al.</i> ^[38]	2021	2002–2018	Korea	Korea University Guro Hospital	78	52/26	AJCC staging criteria, 8th edition	Median 31, range: 0.5–147 months
Li <i>et al.</i> ^[41]	2021	2002–2019	China	Chinese Research Group of gallbladder Cancer	691	421/270	AJCC staging criteria, 8th edition	Till June 2019
Yao <i>et al.</i> ^[54]	2021	2000–2016	China	Xinhua Hospital	104	69/35	AJCC staging criteria, 8th edition	Till June 2020
Ashida <i>et al.</i> ^[29]	2022	2002–2014	Japan	Shizuoka Cancer Center	88	35/53	AJCC staging criteria, 8th edition	Median 43.8 months
Wang <i>et al.</i> ^[51]	2022	2012–2020	China	Shanghai Jiao Tong University Affiliated Sixth People's Hospital and Renji Hospital	55	35/27	AJCC staging criteria, 7th edition	Till November 2020
You <i>et al.</i> ^[55]	2022	2013–2018	China	Eastern Hepatobiliary Surgery Hospital/Affiliated Hospital of North Sichuan Medical College	102	59/43	AJCC staging criteria, 8th edition	Till December 2019

Cao et al. ^[31]	2023	2011–2018	China	Sir Run-Run Shaw Hospital	114	82/32	AJCC staging criteria, 7th edition	Till January 2020
Fan et al. ^[35]	2023	2014–2022	China	81st Group Army PLA/the First Affiliated Hospital of Hebei North University	80	60/20	AJCC staging criteria, 8th edition	NA
Jiang et al. ^[37]	2023	2004–2015	USA	SEER	5451	3825/1626	AJCC staging criteria, 7th edition	NA
Li et al. ^[42]	2023	2011–2020	China	The First Affiliated Hospital of Xi'an Jiaotong University	540	367/173	AJCC staging criteria, 8th edition	Till January 2022
Lv et al.	2023	2010–2020	China	West China hospital	259	178/81	AJCC staging criteria, 8th edition	Till September 2022
Lv et al.	2023	2010–2021	China	West China hospital	326	221/105	AJCC staging criteria, 8th edition	Till September 2022
Park et al. ^[45]	2023	2010–2020	Korea	Three tertiary referral hospitals	197	100/97	AJCC staging criteria, 8th edition	NA

AJCC, American Joint Committee on Cancer; NA, not available; No, the number of; SEER, Surveillance, Epidemiology, and End Results; UICC, International Union Against Cancer; USA, The United States of America.

vascular invasion was a risk factor for OS among resected cases with GBC (HR = 2.37, 95% CI: 2.07–2.77, $P < 0.00001$) (Figure S1H, Supplemental Digital Content 4, <http://links.lww.com/JS9/C302>) (Table 2). The results of multivariate analyses indicated that lymph-vascular invasion was also an independent prognostic factor (HR = 1.41, 95% CI: 1.02–1.95, $P = 0.04000$) (Figure S2H, Supplemental Digital Content 5, <http://links.lww.com/JS9/C303>) (Table 2).

The prognostic value of vascular invasion

A total of 8 studies^[28,29,32,38,42,43,45,48] with 1615 cases were incorporated. Pooled results indicated that vascular invasion was a risk factor for OS among resected cases with GBC (HR = 2.28, 95% CI: 1.87–2.79, $P < 0.00001$) (Figure S1I, Supplemental Digital Content 4, <http://links.lww.com/JS9/C302>) (Table 2). However, in multivariate analysis, vascular invasion was not an independent prognostic factor (HR = 1.29, 95% CI: 0.80–2.10, $P = 0.30000$) (Figure S2I, Supplemental Digital Content 5, <http://links.lww.com/JS9/C303>) (Table 2).

The prognostic value of tumor differentiation status

A total of 27 studies^[9,10,17,23,28–33,35,37,38,40–44,46,49,50,52–57] with 10 164 cases were incorporated. Pooled results indicated that poorly differentiated tumor was a risk factor for OS among resected cases with GBC (HR = 3.22, 95% CI: 1.65–2.87, $P < 0.00001$) (Figure S1J, Supplemental Digital Content 4, <http://links.lww.com/JS9/C302>) (Table 2). The high heterogeneity ($I^2 = 76%$) was detected and the results of heterogeneity analyses failed to reveal any major source of heterogeneity. The results of multivariate analyses indicated that tumor differentiation status was also an independent prognostic factor (HR = 2.02, 95% CI: 1.59–2.56, $P < 0.00001$) (Figure S2J, Supplemental Digital Content 5, <http://links.lww.com/JS9/C303>) (Table 2).

The prognostic value of tumor pathological subtypes

A total of 7 studies^[23,28,37,41–43,52] with 7683 cases were incorporated. Pooled results indicated that pathological subtypes were not a risk factor for OS among resected cases with GBC (HR = 1.09, 95% CI: 0.84–1.41, $P = 0.53$) (Figure S1K, Supplemental Digital Content 4, <http://links.lww.com/JS9/C302>) (Table 2). The high heterogeneity ($I^2 = 78%$) was detected and the results of heterogeneity analyses failed to reveal any major source of heterogeneity. In multivariate analysis, pathological subtypes were not an independent prognostic factor (HR = 1.09, 95% CI: 0.97–1.23, $P = 0.15000$) (Figure S2K, Supplemental Digital Content 5, <http://links.lww.com/JS9/C303>) (Table 2).

The prognostic value of tumor location (peritoneal side vs hepatic side)

A total of 3 studies^[50,52,55] with 617 cases were incorporated. Pooled results indicated that hepatic tumor shared more worse prognosis than peritoneal tumor and tumor location (peritoneal side vs hepatic side) was a prognostic factor for resected GBC (HR = 1.85, 95% CI: 1.51–2.28, $P < 0.00001$) (Figure S1L, Supplemental Digital Content 4, <http://links.lww.com/JS9/C302>) (Table 2). The results of multivariate analyses indicated that hepatic tumor was also an independent prognostic factor (HR = 1.52, 95% CI: 1.19–1.95, $P = 0.0090$) (Figure S2L,

Table 2

Pooled results of prognostic factors and independent prognostic factors for OS among resected patients with GBC.

Outcomes	No. studies	No. patients	Model (Fixed/random)	HR	95% CI	P (overall test)	P ^c (overall test)	Heterogeneity		Begg's test		Egger's test
								I ² (%)	P	Pr > z ^a	Pr > z ^b	P > t ^a
Pooled results of univariate analyses												
Age (young ^R vs old)	31	10818	Fixed	1.02	1.01–1.04	0.00020	0.00020	49	0.00100	0.634	0.646	< 0.001
Gallstone disease (no ^R vs yes)	14	2201	Fixed	1.22	1.08–1.39	0.00200	0.00200	0	0.93000	—		
Preoperative jaundice (no ^R vs yes)	11	3134	Fixed	1.93	1.72–2.18	< 0.00001	< 0.00001	30	0.16000			
Preoperative CA199 (low ^R vs high)	15	2813	Fixed	2.31	2.07–2.57	< 0.00001	< 0.00001	45	0.03000			
T stage (T1-2 ^R vs T3-4)	15	3180	Random	3.09	2.46–3.88	< 0.00001	< 0.00001	65	0.00030			
Node stage (N- ^R vs N+)	26	4603	Random	2.78	2.35–3.28	< 0.00001	< 0.00001	60	< 0.0001			
Peri-neural invasion (- ^R vs +)	15	3062	Fixed	2.20	1.95–2.49	< 0.00001	< 0.00001	3	0.42000			
Lymph-vascular invasion (- ^R vs +)	13	2814	Fixed	2.37	2.02–2.77	< 0.00001	< 0.00001	38	0.08000			
Vascular invasion (- ^R vs +)	8	1615	Fixed	2.28	1.87–2.79	< 0.00001	< 0.00001	25	0.23000			
Differentiation status (well to moderate ^R vs poor)	27	10164	Random	3.22	1.65–2.87	< 0.00001	< 0.00001	76	< 0.00001			
Pathology subtype (Others ^R vs AC)	7	7683	Random	1.09	0.84–1.41	0.53000	0.53000	78	0.00010			
Tumor location (peritoneal side ^R vs hepatic side)	3	617	Fixed	1.85	1.51–2.28	< 0.00001	< 0.00001	10	0.33000			
Tumor location (distal ^R vs proximal)	6	1244	Fixed	1.78	1.47–2.14	< 0.00001	< 0.00001	3	0.40000			
Surgical margin (negative ^R vs positive)	20	3846	Random	2.90	2.42–3.47	< 0.00001	< 0.00001	60	0.00030			
Bile duct resection (not performed ^R vs performed)	10	1756	Fixed	1.28	1.10–1.48	0.00100	< 0.00001	50	0.04000			
Adjuvant chemotherapy (not performed ^R vs performed)	14	7929	Random	0.96	0.80–1.16	0.70000	0.70000	57	0.00400			
Pooled results of multivariate analyses												
Age (young ^R vs old)	5	6138	Fixed	1.29	1.17–1.43	< 0.00001	< 0.00001	48	0.10000	—		
Gallstone disease (no ^R vs yes)	1	540	NA	1.49	1.16–1.92	0.00200	NA	NA	NA			
Preoperative jaundice (no ^R vs yes)	2	470	Fixed	1.05	0.75–1.47	0.79000	0.79000	0	0.33000			
Preoperative CA199 (low ^R vs high)	10	1896	Fixed	1.50	1.27–1.77	< 0.00001	< 0.00001	0	0.62000			
T stage (T1-2 ^R vs T3-4)	6	1431	Random	3.74	2.01–6.97	< 0.00010	< 0.00001	72	0.00300			
Node stage (N- ^R vs N+)	14	2961	Random	2.20	1.74–2.78	< 0.00001	< 0.00001	56	0.00500			
Peri-neural invasion (- ^R vs +)	7	1015	Fixed	1.34	1.04–1.73	0.02000	0.02000	3	0.40000			
Lymph-vascular invasion (- ^R vs +)	5	791	Fixed	1.41	1.02–1.95	0.04000	0.04000	0	0.51000			
Vascular invasion (- ^R vs +)	2	436	Fixed	1.29	0.80–2.10	0.30000	0.30000	0	0.86000			
Differentiation status (well to moderate ^R vs poor)	16	8461	Random	2.02	1.59–2.56	< 0.00001	< 0.00001	72	< 0.00001			
Pathology subtype (Others ^R vs AC)	4	6255	Fixed	1.09	0.97–1.23	0.15000	0.15000	0	0.90000			
Tumor location (peritoneal side ^R vs hepatic side)	2	492	Fixed	1.52	1.19–1.95	0.00090	0.00090	0	0.78000			
Tumor location (distal ^R vs proximal)	3	427	Random	1.78	0.84–3.78	0.13000	0.13000	67	0.05000			
Surgical margin (negative ^R vs positive)	11	2067	Fixed	2.28	1.91–2.73	< 0.00001	< 0.00001	0	0.60000			
Bile duct resection (not performed ^R vs performed)	4	795	Fixed	1.73	1.55–1.93	< 0.00001	< 0.00001	0	0.64000			
Adjuvant chemotherapy (not performed ^R vs performed)	4	6190	Random	0.68	0.48–0.96	0.03000	0.01000	77	0.00500			

^aP-value.^bP-value (continuity corrected).

GBC, gallbladder carcinoma; HR, hazard ratio; NA, not applicable; No, the number of; OR, odds ratio; OS, overall survival; PC, corrected P-value after the sensitivity analysis; R, reference.

Supplemental Digital Content 5, <http://links.lww.com/JS9/C303> (Table 2).

The prognostic value of tumor location (distal vs proximal)

A total of 6 studies^[17,23,29,35,40,42] with 1244 resected cases were incorporated. Pooled results indicated that proximal tumors (neck/cystic duct) shared more worse prognosis than distal tumors (body/fundus) and tumor location (distal vs proximal) was a prognostic factor for resected GBC (HR = 1.78, 95% CI: 1.47–2.14, $P < 0.00001$) (Figure S1M, Supplemental Digital Content 4, <http://links.lww.com/JS9/C302>) (Table 2). However, in multivariate analysis, proximal tumor was not an independent prognostic factor (HR = 1.78, 95% CI: 0.84–3.78, $P = 0.13000$) (Figure S2M, Supplemental Digital Content 5, <http://links.lww.com/JS9/C303>) (Table 2).

The prognostic value of surgical margin

A total of 20 studies^[9,17,23,28,32,35,36,38,41,44,46–49,51–55,57] with 3864 cases were incorporated. Pooled results indicated that positive margin was a risk factor for OS among resected GBC (HR = 2.90, 95% CI: 2.42–3.47, $P < 0.00001$) (Figure S1N, Supplemental Digital Content 4, <http://links.lww.com/JS9/C302>) (Table 2). High heterogeneity ($I^2 = 60\%$) was detected and the results of heterogeneity analyses failed to reveal any major source of heterogeneity. The results of multivariate analyses indicated that surgical margin was also an independent prognostic factor (HR = 2.28, 95% CI: 1.91–2.73, $P < 0.00001$) (Figure S2N, Supplemental Digital Content 5, <http://links.lww.com/JS9/C303>) (Table 2).

The prognostic value of combined extra-hepatic bile duct resection

A total of 10 studies^[3,9,16,17,29,36,39,49,52,54] with 1756 cases were incorporated. Pooled results indicated that the combined bile duct resection was a risk factor for OS among resected GBC (HR = 1.28, 95% CI: 1.10–1.48, $P = 0.001$) (Figure S1O, Supplemental Digital Content 4, <http://links.lww.com/JS9/C302>) (Table 2). Moderate heterogeneity ($I^2 = 50\%$) was detected and the results of heterogeneity analyses indicated that when the study by Wang *et al.*^[3] was excluded, a more significant P -value with lower heterogeneity was acquired (HR = 1.45, 95% CI: 1.23–1.71, $P < 0.00001$, $I^2 = 0\%$). The results of multivariate analyses indicated that combined bile duct resection was also an independent prognostic factor (HR = 1.73, 95% CI: 1.55–1.93, $P < 0.00001$) (Figure S2O, Supplemental Digital Content 5, <http://links.lww.com/JS9/C303>) (Table 2).

The prognostic value of postoperative adjuvant chemotherapy

A total of 14 studies^[9,16,17,23,28,32,37,42,44,45,49–51,57] with 7929 cases were incorporated. Pooled results indicated that postoperative adjuvant chemotherapy was a protective factor but was not a prognostic factor for OS among resected GBC (HR = 0.96, 95% CI: 0.80–1.16, $P = 0.70000$) (Figure S1P, Supplemental Digital Content 4, <http://links.lww.com/JS9/C302>) (Table 2). High heterogeneity ($I^2 = 57\%$) was detected and the results of heterogeneity analyses failed to reveal any major source of heterogeneity. However, in multivariate analysis, postoperative adjuvant chemotherapy was proved to be a protective factor as

well as an independent prognostic factor (HR = 0.68, 95% CI: 0.48–0.96, $P = 0.03000$) (Figure S2P, Supplemental Digital Content 5, <http://links.lww.com/JS9/C303>) (Table 2).

Publication bias, heterogeneity analysis, and sensitivity analysis

The potential publication bias in the outcome with the highest number of studies included was assessed through several analyses. Initially, Begg's test and Egger's test were conducted to evaluate the presence of publication bias in the age (young vs old) comparison. As summarized in Table 2, publication bias was detected in Egger's test. To further assess the potential publication bias, Begg's filled funnel plot and Egger's linear regression (meta-trim command) were utilized (Figure S3B, Supplemental Digital Content 6, <http://links.lww.com/JS9/C304>). The results were consistent before and after trimming, with both P -values being lower than 0.05. This suggests that the identified publication bias could be disregarded. Heterogeneity analyses and sensitivity analyses were performed via removing every single study manually and their results were documented in each relevant outcome. Additionally, the sensitivity analysis for the outcome with the highest number of studies included was furtherly validated via using the *db metainf* command (Figure S3A, Supplemental Digital Content 6, <http://links.lww.com/JS9/C304>). The stepwise exclusion of included studies did not result in any significant differences.

Discussion

This meta-analysis represents the first systematic evaluation of potential prognostic factors for OS among cases with resected GBC. Our findings not only reinforce the significance of prognostic factors outlined in the latest 8th edition of the AJCC staging system, such as the T category, lymph node metastasis, lymph-vascular invasion, differentiation status, and surgical margin, but also uncover other potentially useful predictors. These additional predictors include peri-neural invasion, preoperative CA199 level, preoperative jaundice, concurrent gallstone disease, tumor locations, and age. Notably, postoperative adjuvant chemotherapy was shown to be a protective factor for OS (HR = 0.96000) but can provide limited survival benefit ($P = 0.70000$). However, the pooled results of multivariate analyses indicated that postoperative adjuvant chemotherapy was an independent protective factor (HR = 0.68, 95% CI: 0.48–0.96, $P = 0.03000$). Additionally, the inconsistency in pathological subtype was also not found to be a prognostic factor for OS among resected GBC cases. The findings of this study could contribute to a more in-depth understanding of the prognostic factors as well as independent prognostic factors for OS among surgically-treated cases with GBC and provide insights into potentially valuable predictors beyond those included in the current AJCC staging system.

The prognostic value of age (young vs old)

Theoretically, older patients often have more severe preoperative comorbidities, especially respiratory and cardiovascular conditions, and their immune system may be weakened. As a result, their postoperative recovery is typically slower compared to younger patients. Additionally, surgery itself is considered a form

of trauma to the body, and older patients generally share lower tolerance for surgical procedures compared to younger individuals. Consequently, it is expected that older patients would have a less favorable prognosis, and our findings supported this hypothesis by showing a slight yet significant difference in survival between younger and older patients. Our analysis revealed a HR of 1.02 in the univariate analyses, indicating that older patients had a 1.02 times higher risk of death compared to their younger counterparts. Moreover, in multivariate analyses, advanced age was furtherly demonstrated to be an independent prognostic factor. However, due to the relatively small impact on survival compared to other tumor-related factors, limited attention has been given to this issue, and therefore, we will not delve further into this aspect.

The prognostic value of concurrent gallstone disease

Accumulating evidence has indicated that the presence of concurrent gallstone disease is a risk factor for GBC, particularly in cases where there has been a prolonged tolerance of chronic inflammation, hyperplasia, and atypical differentiation resulting from gallstone-related factors^[3,42,43,46,51,56]. The latest 8th AJCC staging system has also indicated that cholelithiasis is associated with carcinoma of the gallbladder in most cases. Recently, according to the analysis based on Chilean and European Genotype Data, gallstone disease was the major risk factor in the prevention of GBC^[58]. Additionally, Ryu *et al.* analyzed 396 720 cases from south Korea between 2002 and 2012 and demonstrated that gallstone disease was associated with an elevated risk of mortality in hepatobiliary cancer, particularly liver and intrahepatic cancer, as well as mortality specifically related to gallbladder cancer. These associations remained regardless of other potential confounding factors^[59]. Further epigenome-wide analysis focusing on methylation status revealed that gallstone disease was often accompanied by low-grade dysplasia^[60]. Consequently, the evidence above collectively validated the fact the gallstone disease is a key factor in the development and prognosis of GBC.

The prognostic value of concurrent preoperative jaundice

Our previous meta-analysis has systematically evaluated the prognostic value of preoperative jaundice in radically-resected cases with GBC, that is, jaundice was associated with a lower resectability rate, a lower R0 rate, more postoperative complications and mortalities^[61]. In consistent with our previous findings, current meta-analysis demonstrated that preoperative jaundice was a risk factor for OS among resected GBC cases (HR = 1.93, $P < 0.00001$). However, when results in multivariate were pooled together, preoperative jaundice failed to be an independent prognostic factor (HR = 1.05, $P = 0.79000$). We think this might be accounted for the limited number of studies ($n = 2$) and patients included ($n = 470$). Preoperative jaundice was previously regarded as a contraindication of curative surgery for advanced lesions^[62]. Hyper bilirubin level in the blood could lead to liver dysfunction, which often greatly increase the risk of surgery and anesthesia, especially for surgical candidates with GBC who are considering receiving the combined partial or extended hepatectomy. Undoubtedly, preoperative percutaneous or nasobiliary drainage is extremely necessary for jaundiced cases.

The prognostic value of preoperative CA199

CA199 is a common and classical serum tumor biomarker of biliary malignancies and its obvious elevation can often be regarded as an indicator of early diagnosis and worse prognosis in various biliary malignancies^[63–65]. Wen *et al.* reported an extremely satisfactory area under curve (AUC) value of 0.77 regarding the predictive value of preoperative CA199 level in 5-year survival rate in resected GBC patients^[52]. In line with previous publications^[3,9,10,14,17,63–66], our pooled results furtherly validated the prognostic value of CA199 that patients with an elevated preoperative CA199 level shared a 2.31 times risk of death than those with lower level of CA199. Moreover, the pooled result of multivariate analyses also demonstrated it to be an independent prognostic factor. However, the prognostic value of preoperative CA199 was not fully-reflected in the 8th AJCC staging system, not even to be mentioned. Currently, the optimal cut-off value of survival-related CA199 level remains debating and a cut-off value of around 37 mmol/l has been widely applied in various studies^[3,9,10,17,66]. Others have also put forward inconsistent cut-off values and they were also demonstrated to be effective to stratify patients with different survival outcomes^[14,67]. The prognostic value of preoperative CA199 is expected to be officially-recognized in the upcoming AJCC staging system and more powerful well-designed controlled studies are required for further validation.

The prognostic value of peri-neural invasion

Anatomically, just as our previous series has indicated, the whole biliary tract was regulated by the sympathetic as well as parasympathetic nerves, which were primarily distributed around the portal hepatis, along with hepatic artery and extra-hepatic bile duct^[15]. Due to the extensive attachment neural network to biliary system, the pathological or physiological functions of biliary epithelium are inevitably influenced. The interaction between the neural network and tumors originating from organs set up an anatomic foundation of peri-neural invasion-mediated metastasis. Previous multicenter studies have evaluated the significance of peri-neural invasion in patients with resected intrahepatic cholangiocarcinoma^[68]. Peri-neural invasion was demonstrated to be an independent prognostic factor on OS or DFS in resected patients with intrahepatic cholangiocarcinoma^[68]. Similarly, based on the evidence regarding GBC patients, peri-neural invasion also indicated a worse prognosis^[13,16–18,23,28–30,38,41–43,45,46,49,55,57]. Subsequently, when their results were pooled together, we were surprisingly to find that patients with peri-neural invasion shared a two times risk of death than those without peri-neural invasion (HR = 2.20, $P < 0.00010$) and it also served as an independent prognostic factor (HR = 1.34, $P = 0.02000$)

The prognostic value of lymph-vascular invasion

Lymph-vascular invasion is defined as the micro invasion of tumor cells in endothelial-lined spaces, such as lymphatic or blood vessels^[69]. The prognostic significance of lymph-vascular invasion has been demonstrated in oral cancer^[70], melanoma and breast cancer^[71], and bladder cancer^[72]. According to the 8th AJCC staging system, lymph-vascular invasion was regarded as an additional factor requiring clinical care (1366 cases, AJCC level of evidence II) in cases with GBC^[8]. Our analysis, however, with a much larger sample size ($n = 2814$), furtherly validated its

prognostic value in resected GBC patients (HR = 2.37, $P < 0.00001$). Lymph-vascular invasion also served as an independent prognostic factor (HR = 1.41, $P = 0.04000$). Our findings would provide a much higher level of evidence regarding the significance of lymph-vascular invasion in GBC patients.

The prognostic value of tumor differentiation status

Accumulating evidence has consistently indicated that a poor or moderate to poor differentiation status indicated a worse OS or DFS than those with well differentiation disease^[9,10,13,14,17,18,23,28–33,35,37,38,40–44,46,49,50,52–57,66,73]. When their results were pooled together, a significant risk factor was furtherly validated (HR = 3.22, $P < 0.00001$). Tumor differentiation status (well to moderate vs poor) has also been suggested as an independent prognostic factor on OS or DFS in the 8th AJCC staging system (level of evidence II)^[7]. Our study with 10 164 resected patients included furtherly validated its prognostic significance.

The prognostic value of pathological subtypes

Current meta-analysis revealed that tumor pathological subtypes were not a prognostic factor for resected GBC cases. The inconsistency of pathological subtypes in the comparison with adenocarcinoma might account for this phenomenon. Accumulating evidence have suggested that gallbladder adeno-squamous/squamous carcinoma shared a worse prognosis than those with adenocarcinoma^[74–79]. Gallbladder mucinous adenocarcinoma^[80] and sarcomatoid carcinoma^[81] have also been demonstrated to share a worse prognosis than adenocarcinoma. However, there are also pathological subtypes that show a comparable or even more favorable prognosis compared to gallbladder adenocarcinoma. A study conducted by Do *et al.*^[82] revealed that gallbladder neuroendocrine carcinoma had a comparable prognosis to gallbladder adenocarcinoma after matching. Our previous research focusing on extra-hepatic cholangiocarcinoma also acquired the similar phenomenon^[83]. Consequently, the inconsistency regarding pathological subtypes might serve as a confounding factor, and the prognostic value of pathological subtypes needs to be furtherly investigated more specifically, especially when focused on different subtypes.

The prognostic value of tumor locations

Compared with the 7th AJCC staging system for GBC, the latest 8th AJCC staging system furtherly classified T2 diseases into T2a (peritoneal side) and T2b (hepatic side) disease. Our research incorporated 3 studies with 617 cases included furtherly validated the reasonability of this novel classification criteria in terms of univariate analysis (HR = 1.85, $P < 0.00001$) and multivariate analysis (HR = 1.52, $P = 0.00090$). However, the 8th AJCC staging system does not mention the prognostic value brought by another type of classification criteria of tumor locations, which includes tumor located in the body, fundus, neck, and cystic duct of the gallbladder. Anatomically, tumors located in the neck or the cystic duct of the gallbladder are closer to the porta hepatis, adjacent to numerous major blood vessels and organs. Consequently, proximal tumors (neck/cystic duct tumor) have a high tendency to develop multiorgan infiltrations and metastasis versus distal tumors (body/fundus tumor). Therefore, proximal tumors of the gallbladder often require a more extended range of surgical resection, share a more advanced stage, and a worse

prognosis. The prognostic value of tumor locations (distal vs proximal) has been validated in our previous research (HR = 2.5, $P = 0.003$)^[19], which has also been validated in the current meta-analysis (HR = 1.85, $P < 0.00001$). However, in multivariate analysis, proximal tumor was shown to be a risk factor as well but not an independent prognostic factor ((HR = 1.78, $P = 0.13000$). Further analysis on the potential reasons, we found that only two studies were incorporated into the analysis of multivariate analysis. Consequently, the prognostic value of tumor location (distal vs proximal) still requires to be furtherly validated in large multicenter studies.

The prognostic value of surgical margin and the combined EHBDR

A radical resection with a clear margin has always been linked with improved survival^[84,85]. A lymphadenectomy along with the hepatoduodenal ligament combined with partial hepatectomy has been strongly recommended as the standard surgical procedures for patients with progressive GBC disease. A clear margin without residual disease microscopically or macroscopically has been proved to be closely-associated with improved survival than those with positive margin^[3,9,12–14,17,36,44,46,48,49,52,73], which was also validated in our synthetic results with an extremely significant P -value combined with a high level of risk of death in terms of univariate analysis (HR = 2.90, $P < 0.00001$) and multivariate analysis (HR = 2.28, $P < 0.00001$).

The prognostic significance of concurrent extra-hepatic bile duct resection in cases with GBC has always been discussed and remains debating. According to findings reported in previous in previous publications, EHBDR was not correlated with an improved survival and was even harmful in cases with early-staged disease^[15,20,86–88]. However, some Asian surgeons, especially Japanese researches, have always insisted on performing EHBDR aggressively due to its potential contribution in tumor clearance as well as a more thorough lymph yield^[36,89–91]. In current analysis, bile duct resection was a predictor of worse prognosis (HR = 1.28, $P < 0.00001$) and also served as an independent prognostic factor (HR = 1.73, $P < 0.00001$). According to the National Comprehensive Cancer Network (NCCN) (Version: 1.2022 to 29 March 2022, www.nccn.org/patients) guidelines, EHBDR should be only performed when there is an obvious positive cystic duct margin or extra-hepatic bile duct infiltration. Clinically, patients who received RHBDR were generally in a more advanced stage and therefore shared a worse prognosis^[20]. What truly determines the prognosis is the tumor staging rather than the combined extra-hepatic bile duct resection. Bile duct resection is primarily performed to achieve curative resection.

The prognostic value of postoperative adjuvant chemotherapy

According to a previous NCDB-based retrospective study, adjuvant therapy was associated with an improved 3-year survival rate in resected GBC patients but only less than one thirds GBC patients were eligible for receiving adjuvant therapies^[92]. Currently, according to the latest NCCN guidelines, postoperative adjuvant chemotherapy or chemo-radiotherapy were only recommended in resected GBC patients with positive margins or those with positive lymph node status^[93]. Horgan *et al.* performed a meta-analysis with 6712 patients with biliary

malignancies included focusing on the effect of postoperative adjuvant chemotherapies and found a moderate but not significant survival benefit in patients with positive surgical margin or node status^[93]. Ma *et al.*^[94] also indicated that postoperative adjuvant therapies could bring survival benefit in patients with positive margin, positive node status or patients with II/III disease. Wang *et al.*^[95] also indicated adjuvant chemo-radiotherapy was beneficial in T3 or N1 GBC patients. Mantripragada *et al.*^[96] performed a propensity score matching analysis to evaluate the effect of adjuvant therapies in resected GBC patients and reported a moderate survival benefit in T3 or N1 GBC patients but was not correlated with survival benefit in the entire cohort, which was in consistent with our results in univariate analysis (HR = 0.96, $P = 0.70000$). The results of multivariate analysis indicated that postoperative adjuvant chemotherapy was an independent risk factor as well as a protective factor (HR = 0.68, $P = 0.01000$), which was consistent with the findings reported by Jiang *et al.* based on a SEER cohort ($n = 6712$). However, inconsistent with our research, in order to avoid the survival impact brought by various confounding factors, Jiang *et al.* performed further investigation via propensity score matching and revealed that postoperative adjuvant chemotherapy was a prognostic factor as well as a protective factor ($P = 0.002$). The propensity score matching analyses and subgroup analyses focusing on R1 or N1 patients were not feasible in current meta-analysis due to the inadequate original data.

Currently, there is a growing trend of strongly recommending a multidisciplinary approach for cases with biliary tract cancers, particularly for those with advanced GBC. Novel and emerging adjuvant strategies, including immunotherapy, targeted therapy, and combination strategies, are being investigated for GBC and the results of these studies are eagerly awaited^[97–99]. In order to enhance the effectiveness of antitumor treatment, the combination of immune checkpoint inhibitors with chemotherapy has been investigated. It was found that chemotherapeutic agents could upregulate the expression of checkpoint proteins^[100–102]. A current phase III, double-blind clinical trial called TOPAZ-1 is evaluating the role of chemotherapy agents in combination with the immunotherapy agent durvalumab compared to chemotherapy agents with a placebo. Undoubtedly, considering the evidence presented above, postoperative adjuvant chemotherapy should be considered a crucial prognostic factor for OS among resected GBC. To further evaluate its effectiveness, it is imperative to conduct more robust and well-designed studies. Randomized controlled trials, in particularly, would be invaluable in this regard.

Other potential prognostic factors

The significance of preoperative fibrinogen in resected GBC patients have also been discussed and validated^[14,103–105]. However, the majority publications were based on Asian populations and therefore its prognostic value was less powerful and applicable^[14,103–105]. Other nonconventional prognostic factors based on a small cohort, such as the level of survivin expression^[46], platelet to lymphocyte ratio^[66], or preoperative systemic inflammation status^[9], have also been reported. Moreover, the prognostic value of nutrition-related indicators has also been demonstrated in patients with GBC, such as sarcopenia^[57]. Additionally, in the era of minimally surgery, numerous studies have focused on the surgery approaches,

including laparotomy, laparoscopic surgery, or robotic surgery. Laparoscopic radical cholecystectomy has been demonstrated to be effective in T1/2 GBC patients that equivalent oncological adequacy and long-term survival has been achieved via laparoscopic approach versus conventional laparotomy approach^[106]. However, for patients with more advanced disease, laparoscopic surgery seems to be less applicable^[106].

Limitations

Current study has to be interpreted with several limitations. Firstly, a rough estimate of HR and its 95% CI via Tierney's method would introduce bias to some extent. Secondly, the inconsistency on the predictors selected for model establishment would also introduce bias. Some studies might have selectively avoided reporting negative results, which can have a certain impact on our research outcomes. Thirdly, our study not only assessed all potential prognostic factors but also evaluated all potential independent prognostic factors at the same time. However, independent prognostic factors in current study were evaluated via incorporating HRs and 95% CIs in multivariate analyses, which might introduce certain statistical limitations. The appropriate approach should involve collecting clinical information from all patients included in all included studies, merging the clinical information of all cases, and then conducting univariate and multivariate Cox regression analysis. This issue is expected to be addressed in future large-sample multicenter studies, which will provide more conclusive results. Fourth, in order to maximize the sample size and gather more compelling evidence, we included some studies where there might have been some overlapping data after evaluation across studies. While this approach did increase the overall sample size to some extent and provide more significant evidence, it is important to acknowledge that the presence of data overlap could somewhat weaken the robustness of our study. Fifth, there are also many other potential prognostic factors to be explored, such as the evolvement in the surgical techniques, peri-operative management, and adjuvant therapies in GBC in the past few decades. However, the inadequate original data has hindered us from further exploration.

Conclusion

Current systematic review and meta-analysis firstly evaluated and validated all potential prognostic factors as well as independent prognostic factors for OS among resected GBC patients. Our findings not only validated previously-approved prognostic factors such as lymph node metastasis, but also revealed other nonconventional and rarely-reported prognostic factors, such as peri-neural invasion, tumor locations, and lymph-vascular invasion. Due to the multicollinearity and interdependence between prognostic factors, the inconsistency regarding the factors selected for modeling were unavoidable. Future multinational studies are required for a better model establishment and evaluation.

Ethical approval

Current study was performed based on previously-published studies and the ethical approval was not required.

Consent

Current study was performed based on previously-published studies and the informed consent was not required.

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Author contribution

T.-R.L. and J.-K.W.: contributed equally to the study; T.-R.L.: contributed to data acquisition and drafted the manuscript; J.-K.W.: contributed to the literature review, manuscript editing, and subsequent minor revision; H.-J.H.: was involved in editing the manuscript; F.-Y.L.: contributed to the study design and revision of the manuscript.

Conflicts of interest disclosure

The authors declare that they have no conflicts of interest.

Research registration unique identifying number (UIN)

Current study was performed based on previously-published studies and the registered number is not available and required.

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

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