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RESEARCH

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Novel multifactor predictive model for postoperative survival in gallbladder cancer: a multi-center study

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Abstract

Background Gallbladder cancer (GBC) is a highly aggressive malignancy, with limited survival profiles after curative surgeries. This study aimed to develop a practical model for predicting the postoperative overall survival (OS) in GBC patients.

Methods Patients from three hospitals were included. Two centers ($N=102$ and 100) were adopted for model development and internal validation, and the third center ($N=85$) was used for external testing. Univariate and stepwise multivariate Cox regression were used for feature selection. A nomogram for 1-, 3-, and 5-year postoperative survival rates was constructed accordingly. Performance assessment included Harrell's concordance index (C-index), receiver operating characteristic (ROC) curves and calibration curves. Kaplan-Meier curves were utilized to evaluate the risk stratification results of the nomogram. Decision curves were used to reflect the net benefit.

Results Eight factors, TNM stage, age-adjusted Charlson Comorbidity Index (aCCI), body mass index (BMI), R0 resection, blood platelet count, and serum levels of albumin, CA125, CA199 were incorporated in the nomogram. The time-dependent C-index consistently exceeded 0.70 from 6 months to 5 years, and time-dependent ROC revealed an area under the curve (AUC) of over 75% for 1-, 3-, and 5-year survival. The calibration curves, Kaplan-Meier curves and decision curves also indicated good prognostic performance and clinical benefit, surpassing traditional indicators TNM staging and CA199 levels. The reliability of results was further proved in the independent external testing set.

Conclusions The novel nomogram exhibited good prognostic efficacy and robust generalizability in GBC patients, which might be a promising tool for aiding clinical decision-making.

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Highlights

- A representative surgical cohort of GBC was retrospectively established.
- Clinical variables related to surgical management were comprehensively collected and analyzed.
- The study introduced the independent prognostic significance of aCCI and CA125 in GBC.
- A novel multi-factor nomogram was developed with satisfactory prognostic performance, as confirmed by internal and external validations.

Keywords Gallbladder cancer (GBC), Surgery, Survival, Predictive model, Nomogram, Tumor markers, Comorbidities

Introduction

Gallbladder cancer (GBC) is a rare yet highly malignant tumor that is more prevalent in women. The adjusted incidence rate of GBC in women is approximately 1.4/100,000, whereas that in men is approximately 0.8/100,000 [1]. GBC constitutes approximately 1.2% of the global cancer incidence and 1.7% of all cancer-related deaths [2]. It is the most common cancer of the biliary system, comprising 80–95% of cases [3], with adenocarcinoma being the most common pathological type [4]. Compared to other biliary tract malignancies, GBC has a worse prognosis, with an average survival period of less than 1 year and a 5-year overall survival (OS) rate of less than 5% [3, 5, 6]. Studies based on the Surveillance Epidemiology and End Results (SEER) database have shown a significant decrease in the incidence of GBC in the United States over the past 40 years, followed by a stable trend. Incidence-based mortality (IBM) has also experienced an average annual decrease of 1.69%, which may be related to advancements in surgical techniques and adjuvant and neoadjuvant therapies [7, 8]. However, an increase in the incidence of GBC has been observed in the population aged < 45 years [9].

GBC primarily results from chronic inflammation owing to various causes. Key contributing factors include gallstones, large gallbladder polyps, obesity, advanced age, female sex, hereditary factors, exposure to specific toxins, and certain microbial infections [1]. Most GBC cases are incidentally found during cholecystectomy for gallstones, with approximately 0.25–0.89% of cholecystectomy specimens revealing GBC upon pathological examination [1, 10]. Curative resection remains the main therapeutic approach for early-stage tumors and is the primary means of achieving long-term survival. The implementation of curative surgery relies heavily on standardized preoperative clinical staging to guide potential lymphadenectomy, hepatic resection, and bile duct excision [11]. In patients with R1 resection (non-curative resection) or stages III-IV disease, advances in high-throughput sequencing techniques and systemic therapies, including chemotherapy, targeted therapy, and immunotherapy, have shown promise in improving prognosis [11–13].

In patients undergoing surgery for GBC, prognosis is still affected by the risk of tumor recurrence and progression, with overall survival significantly decreasing as TNM staging advances [14]. Surgical intervention compared to non-surgical approaches [6], curative resection with negative margins [15], and incidental discovery of GBC during surgery [16] are associated with better postoperative survival. Chang et al. suggested that for stage IV patients, simple excision offers superior survival benefits compared to curative resection; however, in patients across all stages, the choice between curative and palliative resection did not emerge as an independent predictor of postoperative survival [17]. Furthermore, researchers have developed and validated a series of novel prognostic markers and models to aid the comprehensive management of GBC. They identified factors such as higher preoperative serum carbohydrate antigen 199 (CA199) levels [17], elevated serum fibrinogen levels [18], liver invasion [19], and certain preoperative cross-sectional imaging features [20] as potential predictors of poorer postoperative survival. The newly developed predictive models exhibited promising effectiveness compared to traditional TNM staging systems, demonstrating good discriminative power, accuracy, and generalizability [18–20]. These tools hold promise for driving advancements in precision medicine for GBC. However, to date, a reliable predictive system for postoperative prognosis in GBC has yet to be established, prompting clinicians to seek effective prognostic factors and robust models to assist in individualized surgical decision-making. This retrospective study aimed to establish and validate a postoperative survival prediction model based on common clinical data in a multicenter GBC cohort, thus supporting the surgical management of patients with GBC.

Materials and methods

Study population

This study was conducted in accordance with the STROCSS criteria [21]. Three tertiary hospitals in China were involved: institution PU, institution BJ from

Beijing, and institution WC from Chengdu. Patients with GBC who were initially treated surgically in these three institutions were retrospectively reviewed. In all three medical centers, the operations were performed by experienced hepatobiliary surgeon teams. All surgical procedures were decided according to the clinical guidelines for GBC management [1, 22, 23] to ensure procedural consistency, which included gallbladder resection, certain extent of hilar lymphadenectomy, hepatic resection, and bile duct excision. The inclusion criteria for this study were: (1) patients with a pathologically confirmed diagnosis of GBC, (2) patients who underwent surgery as the primary treatment, and (3) patients with full postoperative follow-up records. The exclusion criteria were as follows: (1) patients with non-primary gallbladder tumors; (2) patients without surgical pathological reports; and (3) patients with concurrent malignancies at other sites. In institutions PU and BJ, consecutive medical records from 2005 to 2019, including the scanned handwritten documents, were independently extracted from electronic medical record systems by two authors using structured forms. Discrepancies were resolved by further verification. Data from PU and BJ were analyzed for model development and internal validation. Similarly, consecutive medical records from 2010 to 2015 were collected from the WC institution as the external validation dataset. Survival data were obtained from hospital or telephone follow-up records. A total of 202 patients were included in the process of model development and internal validation, with 102 cases from PU and 100 cases from BJ. A total of 85 patients from institution WC were included in the external validation dataset (Supplementary Fig. 1).

Data collection and follow-up

For the included patients, the following five categories of factors were collected for data analysis (Supplementary Fig. 1). (1) Demographic factors: sex, age, and body mass index (BMI). (2) Comorbidities: diabetes mellitus (DM), gallstones (GS), jaundice (JAU), hypertension (HTN), heart disease (HD), and age-adjusted Charlson Comorbidity Index (aCCI) [24]. (3) Laboratory factors (preoperative blood test results): i. neutrophils (NEU), monocytes (Mono), lymphocytes (LYM), and platelet count (PLT). ii. Total bilirubin (TBIL), albumin (ALB), total cholesterol (TC), and fibrinogen (FIN). iii. Carcinoembryonic antigen (CEA), carbohydrate antigen 199 (CA199), carbohydrate antigen 125 (CA125). (4) Perioperative factors: American Society of Anesthesiologists (ASA) physical status, operation duration (OD), blood loss (BLD), intraoperative blood transfusion (TRF), postoperative hospital days (POD), and Clavien-Dindo classification of postoperative complications (POC) [25]. (5) Clinico-pathological factors: American Joint Committee on Cancer (AJCC) TNM stages [26], tumor differentiation (DF), lymph node metastasis (LN), and radical resection with pathologically negative margins (R0 resection). The survival status of all patients was confirmed through medical records or additional telephone follow-up.

Statistical analysis

All statistical analyses were performed using R software (version 4.1.3) [27]. Statistical significance was defined as a two-tailed P-value of < 0.05. The results are presented with 95% confidence intervals (95% CI). Continuous variables were described using mean ± standard deviation and compared using t-tests, whereas categorical variables were presented as numbers and percentages and compared using chi-square tests or Fisher's exact tests. Prognostic factors were initially screened using univariate Cox regression, and variables showing significant risk or protective effects (P-value < 0.05) were then entered into a stepwise multivariate Cox regression (bidirectional) to adjust confounders and select model features, which was based on the Akaike information criterion (AIC) for goodness of fit. The best multivariate Cox regression model output by stepwise regression was then utilized to construct a predictive nomogram for 1-year, 3-year, and 5-year postoperative survival.

The performance of the nomogram was then evaluated. The discriminative power of the nomogram for 1-, 3-, and 5-year survival status was evaluated using the time-dependent Harrell's concordance index (C-index) and time-dependent receiver operating characteristic (ROC) curves. The predictive accuracy of the nomogram for 1-, 3-, and 5-year survival rates was assessed using calibration curves. The risk stratification function of the nomogram was based on the individualized risk score, and the optimal threshold for determining the high-risk and low-risk groups was chosen according to the maximum Youden's index. Survival outcomes were compared between the risk groups using Kaplan-Meier curves and log-rank tests. Decision curve analysis (DCA) was used to evaluate the clinical utility of the prognostic models. 1000-time bootstrap resampling was utilized to adjust the risk of bias when calculating the C-index and calibration curves.

The reliability and generalizability of the nomogram were further assessed using internal and external validations. The nomogram was first fitted in the PU dataset, and the performance of the nomogram was further tested on the BJ dataset for internal validation and on the WC dataset for external validation using the same approaches, including time-dependent C-index, time-dependent ROC curves, calibration curves, and Kaplan-Meier curves (Supplementary Fig. 1).

Results

Clinical characteristics of the study population

Clinical information of the cohorts from the PU and BJ institutions is presented in Table 1. In these two cohorts, the median follow-up time the total of the 202 patients was 27.9 months, a total of 123 patients reached the endpoint, while the remaining patients were still alive at the last follow-up. The median overall survival time was 24.9 months (95% CI: 18.7–41.3 months) in institution PU and 25.0 months (95% CI: 18.0–36.0 months) in institution BJ, with no significant inter-institution difference (Fig. 1). Most demographic and preoperative laboratory characteristics were not significantly different between the two institutions. In institution PU, the rates of patients with higher ASA levels, gallstones, jaundice, hypertension, heart disease, and well-differentiated tumors were higher than those in BJ. In contrast, patients from institution BJ exhibited higher aCCI scores, postoperative complication rates, Clavien-Dindo levels, intraoperative blood loss, R0 resection rates, and postoperative hospital days than patients with PU. In addition, the patient characteristics of the external validation dataset (institution WC) are listed in Supplementary Table 1 and compared with the PU and BJ datasets. The characteristics of the three cohorts showed considerable diversity.

Identification of risk factors for poor prognosis after surgery

Univariate Cox regression analysis revealed that 18 factors were significantly associated with postoperative survival. These factors included BMI, DM, PLT, TBIL, ALB, FIN, CEA, CA125, CA199, ASA, OD, TRF, DF, LN, R0, TNM, aCCI, and POC. Among demographic factors, increased BMI was identified as a protective factor for postoperative survival. The year of operation showed an insignificant correlation with overall postoperative survival, favoring those who underwent surgeries in recent years. Regarding comorbidities, diabetes mellitus and a higher aCCI were identified as risk factors. Laboratory findings revealed that higher platelet, bilirubin, and fibrinogen levels, as well as lower albumin levels, were associated with poorer prognosis. Elevated levels of the tumor markers CEA, CA125, and CA199 were correlated with adverse outcomes. Clinicopathological factors, such as poorly-to-moderately differentiated tumors, positive lymph node metastasis, R1 resection, and higher TNM stage, predicted worse postoperative survival. Perioperative factors, including higher ASA levels, longer operation duration, intraoperative transfusions, and higher Clavien-Dindo levels of postoperative complications, were associated with a poorer prognosis. These factors were included in bidirectional stepwise multivariate Cox regression analysis for feature selection. Stepwise regression revealed the minimization of the AIC value (1067.5) upon the inclusion of eight variables: TNM stage, CA125, CA199, R0 resection, BMI, ALB, aCCI score, and PLT, which were ranked by their contributing effect in the model. The results of the univariate and stepwise multivariate Cox regression analyses are presented in Table 2. The feature selection process is presented in Supplementary Material 1.

Predictive nomogram for 1-, 3-, and 5-year survival

According to the optimal multivariate Cox regression model output from stepwise regression (Supplementary Material 1), we constructed a nomogram predicting the risk of mortality at 1, 3, and 5 years postoperatively (Fig. 2). Schoenfeld residual tests indicated fine adherence to the proportional hazard assumption within the predictive model (Supplementary Fig. 2), while Dfbetas residual tests demonstrated no significant bias caused by outliers in the model (Supplementary Fig. 3).

Evaluation of the nomogram

Next, we evaluated the performance of the novel nomogram using the dual-center cohort (PU and BJ). Harrell's C-index of the nomogram was 0.770 (95% CI: 0.724–0.815) and 0.757 (95%CI: 0.712–0.802) before and after adjusting for the risk of bias, respectively, demonstrating moderate discriminative capability. The nomogram was then compared to classic prognostic indicators, TNM stages and CA199 levels. Both TNM stages and CA199 levels exhibited a C-index < 0.70 before and after bootstrap resampling (Table 3). Additionally, we assessed the time-dependent C-index of the novel nomogram in the predictive work span of 6 to 60 months. The nomogram consistently maintained a C-index above 0.70 in the work span, significantly outperforming TNM stages and CA199 levels (Fig. 3A-B). Time-dependent ROC at 1 year, 3 years, and 5 years showed an area under curve (AUC) of 82.1%, 79.5%, and 84.23%, respectively, signifying the fine prognostic power of the nomogram (Fig. 3C-E).

The predictive accuracy of the nomogram was assessed using calibration curves with 1000-time bootstrap resampling. The results are illustrated in Fig. 3F-H, showing good adherence of the predicted survival rates at 1, 3, and 5 years to the actual rates. Finally, the function of the nomogram for risk stratification was tested. When the cut-off risk score was 4.616 (the risk score alculated by the multivariate Cox regression model), Youden's index peaked, and the corresponding cut-off total score of the nomogram was 257 (the total score of the nomogram, illustrated in Fig. 2). Using the calculated optimal cut-off value, patients were stratified into high- and low-risk groups. Significant differences

Table 1 Patient characteristics of the two centers used for model development

Variables (unit)	Total (*N* = 202)	BJ (*N* = 100)	PU (*N* = 102)	*P* value
Demographic factors				
Age (year)	65.1 (10.5)	65.9 (10.6)	64.3 (10.4)	0.272
Sex				0.491
Male	81 (40.1%)	43 (43.0%)	38 (37.3%)	
Female	121 (59.9%)	57 (57.0%)	64 (62.7%)	
POD (day)	16.0 (13.5)	20.2 (15.1)	11.9 (10.4)	<0.001*
BMI (kg/m^2)	24.5 (3.29)	24.6 (3.42)	24.4 (3.18)	0.601
Comorbidities				
Gallstones (GS)				<0.001*
No (n)	137 (67.8%)	83 (83.0%)	54 (52.9%)	
Yes (n)	65 (32.2%)	17 (17.0%)	48 (47.1%)	
Jaundice (JAU)				0.001*
No (n)	170 (84.2%)	93 (93.0%)	77 (75.5%)	
Yes (n)	32 (15.8%)	7 (7.00%)	25 (24.5%)	
Diabetes mellitus (DM)				0.797
No (n)	172 (85.1%)	84 (84.0%)	88 (86.3%)	
Yes (n)	30 (14.9%)	16 (16.0%)	14 (13.7%)	
Hypertension (HTN)				<0.001*
No (n)	157 (77.7%)	94 (94.0%)	63 (61.8%)	
Yes (n)	45 (22.3%)	6 (6.00%)	39 (38.2%)	
Heart disease (HD)				0.001*
No (n)	190 (94.1%)	100 (100%)	90 (88.2%)	
Yes (n)	12 (5.94%)	0 (0.00%)	12 (11.8%)	
aCCI	7.52 (13.9)	9.49 (10.5)	3.80 (9.54)	<0.001*
Laboratory results				
Mono (×10^9/L)	0.49 (0.65)	0.47 (0.18)	0.50 (0.89)	0.739
NEU (×10^9/L)	4.55 (4.34)	4.34 (2.55)	4.77 (5.57)	0.477
LYM (×10^9/L)	1.70 (0.99)	1.75 (1.24)	1.66 (0.67)	0.549
PLT (×10^9/L)	233 (55.6)	236 (27.6)	230 (73.4)	0.495
TBIL (μmol/L)	35.8 (74.6)	39.8 (81.7)	31.8 (67.0)	0.445
ALB (g/L)	40.0 (4.68)	39.4 (4.77)	40.6 (4.54)	0.085
TC (mmol/L)	4.76 (1.14)	4.67 (1.02)	4.85 (1.25)	0.279
FIN (g/L)	3.67 (1.11)	3.72 (1.16)	3.63 (1.07)	0.609
CEA (μg/L)	15.6 (42.2)	18.3 (52.3)	12.9 (29.2)	0.360
CA125 (U/mL)	36.1 (39.6)	37.8 (49.7)	34.4 (26.2)	0.542
CA199 (U/mL)	561 (1488)	572 (1730)	550 (1213)	0.916
Perioperative factors				
ASA levels				<0.001*
1	97 (48.0%)	78 (78.0%)	19 (18.6%)	
2	93 (46.0%)	22 (22.0%)	71 (69.6%)	
3	12 (5.94%)	0 (0.00%)	12 (11.8%)	
OD (min)	195 (108)	202 (113)	187 (104)	0.323
BLD (mL)	324 (353)	409 (430)	240 (230)	0.001*
TRF				0.222
No	166 (82.2%)	86 (86.0%)	80 (78.4%)	
Yes	36 (17.8%)	14 (14.0%)	22 (21.6%)	
POC (Clavien-Dindo levels)				<0.001*
0	133 (65.8%)	53 (53.0%)	80 (78.4%)	
1	25 (12.4%)	10 (10.0%)	15 (14.7%)	

Table 1 (continued)

Variables (unit)	Total ($N=202$)	BJ ($N=100$)	PU ($N=102$)	*P* value
2	38 (18.8%)	35 (35.0%)	3 (2.94%)	
3	1 (0.50%)	0 (0.00%)	1 (0.98%)	
4	2 (0.99%)	2 (2.00%)	0 (0.00%)	
5	3 (1.49%)	0 (0.00%)	3 (2.94%)	
Clinico-pathological factors				
DF				<0.001*
High	55 (27.2%)	15 (15.0%)	40 (39.2%)	
Low-Medium	147 (72.8%)	85 (85.0%)	62 (60.8%)	
LN				0.382
No	116 (57.4%)	61 (61.0%)	55 (53.9%)	
Yes	86 (42.6%)	39 (39.0%)	47 (46.1%)	
R0				<0.001*
No	43 (21.3%)	5 (5.00%)	38 (37.3%)	
Yes	159 (78.7%)	95 (95.0%)	64 (62.7%)	
TNM stages				0.129
1	26 (12.9%)	11 (11.0%)	15 (14.7%)	
2	29 (14.4%)	20 (20.0%)	9 (8.82%)	
3	116 (57.4%)	53 (53.0%)	63 (61.8%)	
4	31 (15.3%)	16 (16.0%)	15 (14.7%)	

Continuous variables are presented as mean (standard deviation), and categorical variables are presented as count (percentage)

*P value < 0.05

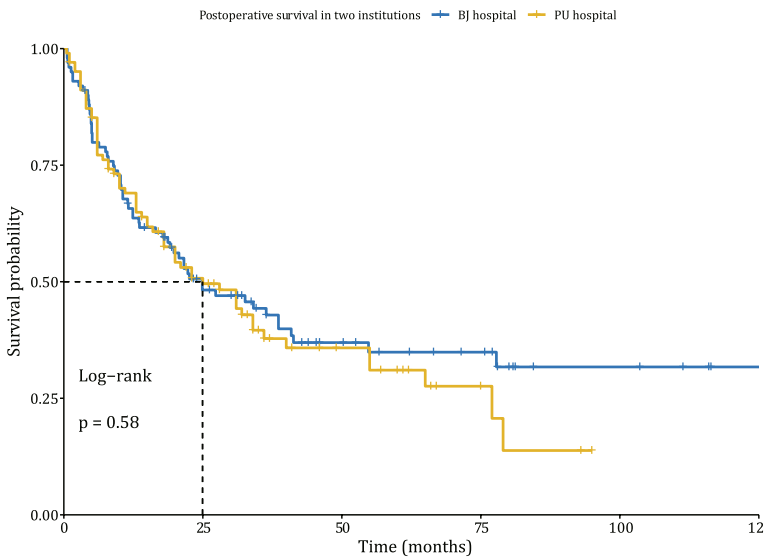

Fig. 1 Postoperative survival (months) in institutions PU and BJ. The median overall survival (95% CI) did not show a significant difference between the two institutions

in survival were observed between the two groups ($P<0.0001$). The high-risk group had a median survival of 7.5 months, whereas the low-risk group had a median survival of 38.6 months (Fig. 4A). Among late-stage patients with TNM stages of 3-4, 64 were classified as high-risk, while 83 were classified as low-risk. Kaplan-Meier curve revealed a median survival of 7.5 months in the high-risk group and 21.6 months in the low-risk group, with a *P*-value of <0.0001 (Fig. 4B). Accordingly, the scoring information of an exemplary patient is

Table 2 Univariate and stepwise multivariate Cox regression results

	Univariate Cox				Stepwise Multivariate Cox			
Characteristics	HR	CI 2.5	CI 97.5	P	HR	CI 2.5	CI 97.5	P
Age elder by 1 year	1.011	0.993	1.030	0.241				
Sex Female vs. Male	0.770	0.539	1.100	0.151				
Year of operation later by 1 year	0.948	0.896	1.002	0.058				
POD longer by 1 day	1.007	0.997	1.016	0.168				
BMI larger by 1 kg/m^2	0.927	0.880	0.977	0.005*	0.936	0.887	0.989	0.018*
GS Yes vs. No	1.200	0.825	1.744	0.340				
JAU Yes vs. No	0.937	0.574	1.530	0.796				
DM Yes vs. No	2.856	1.869	4.363	0.000*				
HTN Yes vs. No	0.877	0.564	1.363	0.559				
HD Yes vs. No	0.984	0.459	2.112	0.967				
aCCI higher by 1 score	1.026	1.009	1.043	0.003*	1.020	1.002	1.037	0.029*
Mono higher by 1×10^9/L	0.761	0.444	1.304	0.320				
NEU higher by 1×10^9/L	1.013	0.982	1.046	0.415				
LYM higher by 1×10^9/L	0.818	0.590	1.133	0.227				
PLT higher by 1×10^9/L	1.005	1.001	1.008	0.007*	0.996	0.993	1.000	0.052
TBIL higher by 1 μmol /L	1.004	1.002	1.005	0.000*				
ALB higher by 1 g/L	0.934	0.903	0.965	0.000*	0.949	0.911	0.988	0.011*
TC higher by 1 mmol/L	1.156	0.980	1.363	0.086				
FIN higher by 1 g/L	1.185	1.029	1.366	0.019*				
CEA higher by 1 μg/L	1.007	1.004	1.011	0.000*				
CA125 higher by 1 U/mL	1.013	1.009	1.017	0.000*	1.011	1.006	1.016	0.000*
CA199 higher by 1 U/mL	1.000	1.000	1.000	0.000*	1.000	1.000	1.000	0.005*
ASA levels				*				
2 vs. 1	1.539	1.063	2.227	0.022*				
3 vs. 1	1.529	0.723	3.234	0.266				
OD longer by 1 min	1.002	1.000	1.003	0.016*				
BLD larger by 1 mL	1.000	1.000	1.001	0.068				
POC Clavien-Dindo levels				*				
1 vs. 0	2.105	1.276	3.473	0.004*				
2 vs. 0	1.494	0.938	2.379	0.091				
3 vs. 0	6.090	0.830	44.669	0.076				
4 vs. 0	3.912	0.954	16.048	0.058				
5 vs. 0	6.289	1.943	20.351	0.002*				
TRF Yes vs. No	1.886	1.226	2.903	0.004*				
DF Low-Medium vs. High	2.426	1.515	3.886	0.000*				
LN Yes vs. No	2.705	1.883	3.886	0.000*				
R0 Yes vs. No	0.381	0.259	0.560	0.000*	0.485	0.325	0.723	0.000*
TNM				*				*
2 vs. 1	2.797	0.757	10.333	0.123	1.789	0.470	6.805	0.394
3 vs. 1	10.587	3.340	33.560	0.000*	7.063	2.204	22.639	0.001*
4 vs. 1	17.559	5.333	57.807	0.000*	9.613	2.838	32.559	0.000*

CI 2.5 and CI 97.5: The lower and upper limit of the 95% CI

*$P < 0.05$. HR: hazard ratio

plotted in Fig. 2 as a visualization of the cut-off value. When the composite score of these five factors was 257, the predicted risks of mortality at 1, 3, and 5 years postoperatively were 0.394, 0.760, and 0.751, respectively. Patients with a total score > 257 should be considered high-risk patients, while the others could be classified as low-risk patients. Decision curve analysis further indicated additional survival benefits of applying the new

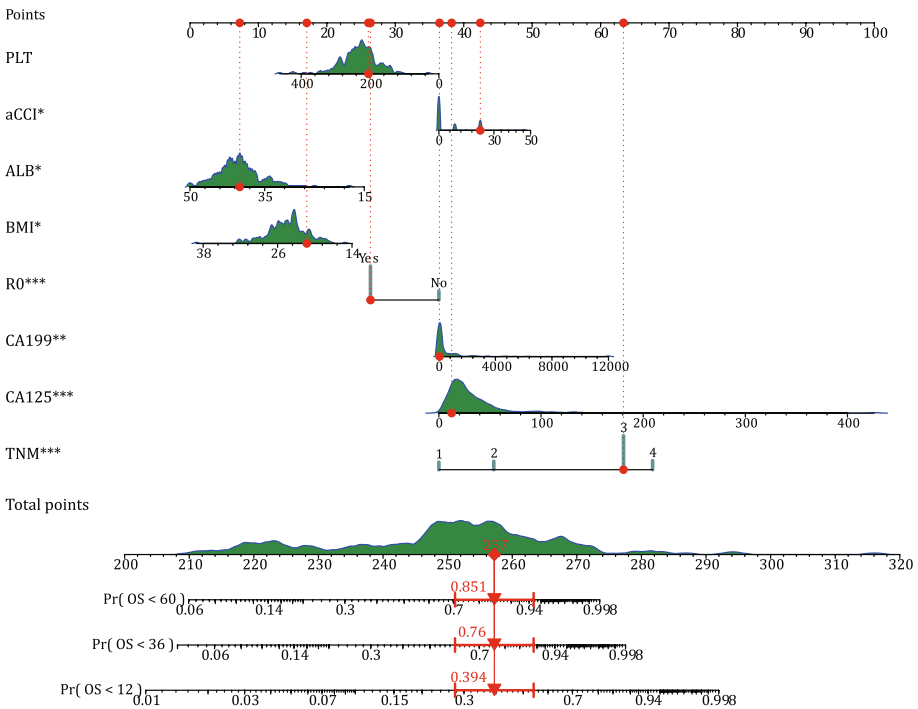

Fig. 2 Postoperative survival nomogram for GBC. The scoring items in the nomogram are arranged in reverse order based on their main effect sizes. The red line and arrows illustrate an exemplary patient's score and the corresponding predicted risk of death. The total score of the exemplary patient equals the cut-off value for stratifying high-risk and low-risk patients

Table 3 Discriminative ability (Harrell's C-index) of the novel nomogram for postoperative survival in comparison with traditional prognostic indicators

	Unadjusted C-index (95%CI)	Bias-adjusted C-index (95%CI)
Novel nomogram	0.770 (0.724–0.815)	0.757 (0.712–0.802)
TNM	0.677 (0.636–0.718)	0.673 (0.632–0.714)
CA199	0.639 (0.584–0.694)	0.639 (0.584–0.694)

nomogram for surgical decision-making compared with using TNM stages or CA199 levels (Fig. 5).

Validation of the nomogram

We utilized the PU cohort ($N=102$) for model training and fitting, and the BJ cohort ($N=100$) for internal validation. In the BJ dataset, the time-dependent C-index ranged from 0.6940 to 0.7751 (Fig. 6A), and the AUC of the time-dependent ROC at 1, 3, and 5 years were 75.10%, 72.36%, and 81.65%, respectively (Fig. 6B). Calibration curves revealed that the predicted 1-year, 3-year, and 5-year survival rates closely matched the actual survival rates (Fig. 6C). Using the same cut-off value from the model development process, the high-risk group in the BJ dataset showed significantly worse postoperative survival than the low-risk group (Fig. 6D).

The same statistical analyses were performed on the WC dataset. In this external cohort, the time-dependent C-index ranged from 0.7171 to 0.7514 (Fig. 7A). The AUC of time-dependent ROC at 1, 2, and 3 years were 82.81%, 85.57%, and 78.82%, respectively (Fig. 7B). Calibration curves indicated favorable consistency between the predicted and actual survival rates at 1, 3, and 5 years (Fig. 6C). Finally, the external cohort was stratified according to the predicted risk scores from the nomogram, demonstrating that a large proportion of high-risk patients (50 / 85), who had significantly worse postoperative survival than the low-risk group (Fig. 7D).

Discussion

This study aimed to explore the indicators of postoperative survival and construct a novel predictive model to assist surgical decision-making in GBC. Multifaceted data, including demographic data, comorbidities, laboratory results, perioperative variables, and clinicopathological parameters, were comprehensively analyzed. These findings demonstrated that a few factors were independently correlated with postoperative survival. A predictive nomogram incorporating these factors exhibited

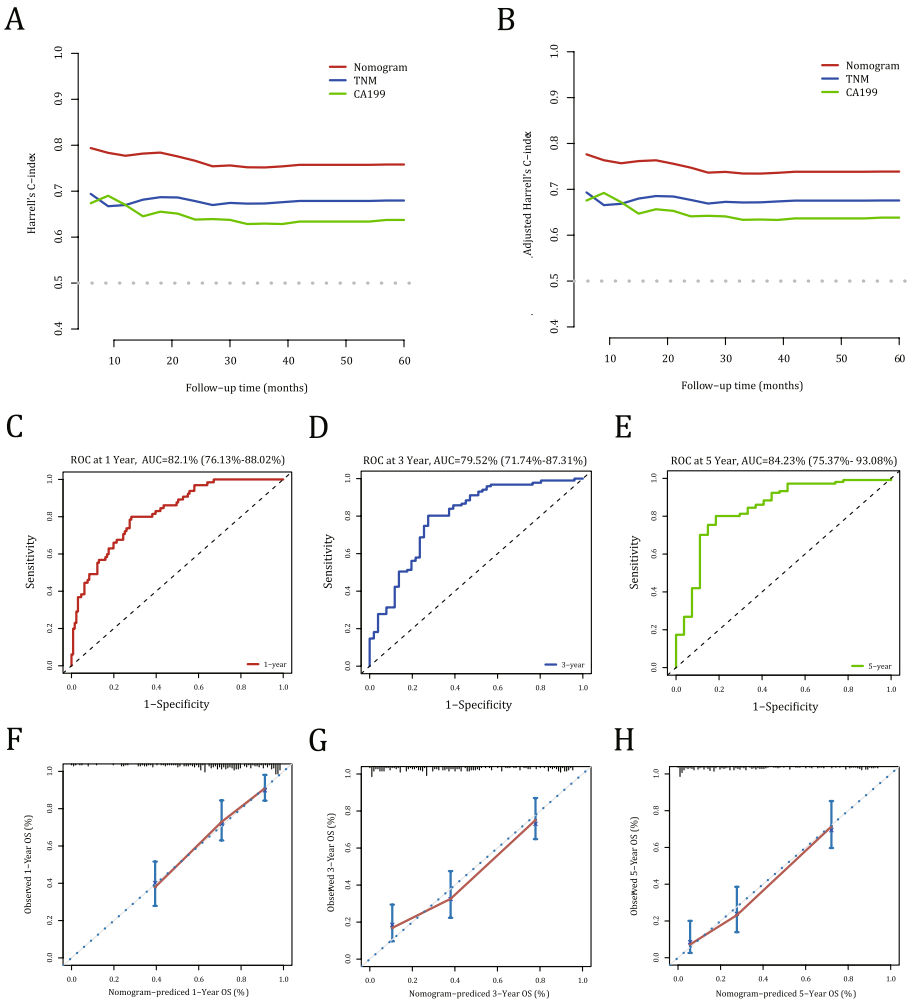

Fig. 3 Assessment of discriminative power and predictive accuracy of the nomogram. **A**-**B** The C-index of the nomogram during (**A**) the training phase and (**B**) bootstrap validation, compared with TNM staging and CA199 levels. **C**-**E** ROC curves of the nomogram for predicting (**C**) 1-year, (**D**) 3-year and (**E**) 5-year survival. **F**-**H** Calibration plots of the nomogram for predicting (**F**) 1-year, (**G**) 3-year, and (**H**) 5-year survival rates

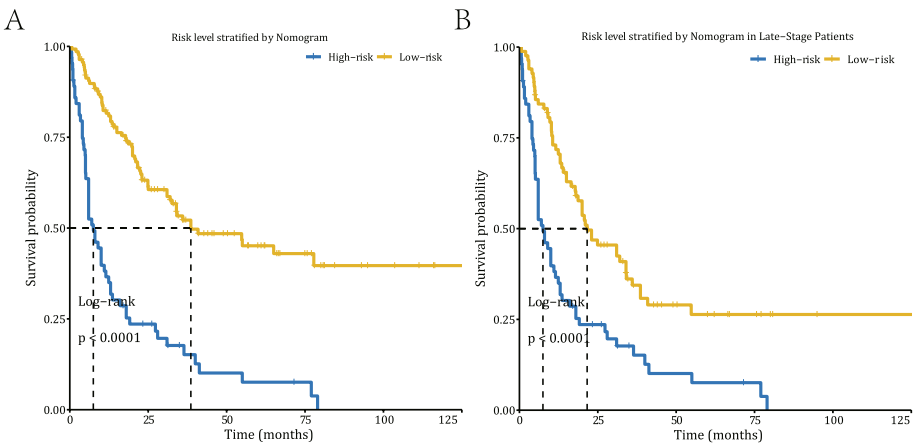

Fig. 4 In (**A**) the overall cohort and (**B**) late-stage subgroup with TNM stages 3-4 tumors, notable survival variations were identified between high-risk and low-risk groups according to the nomogram

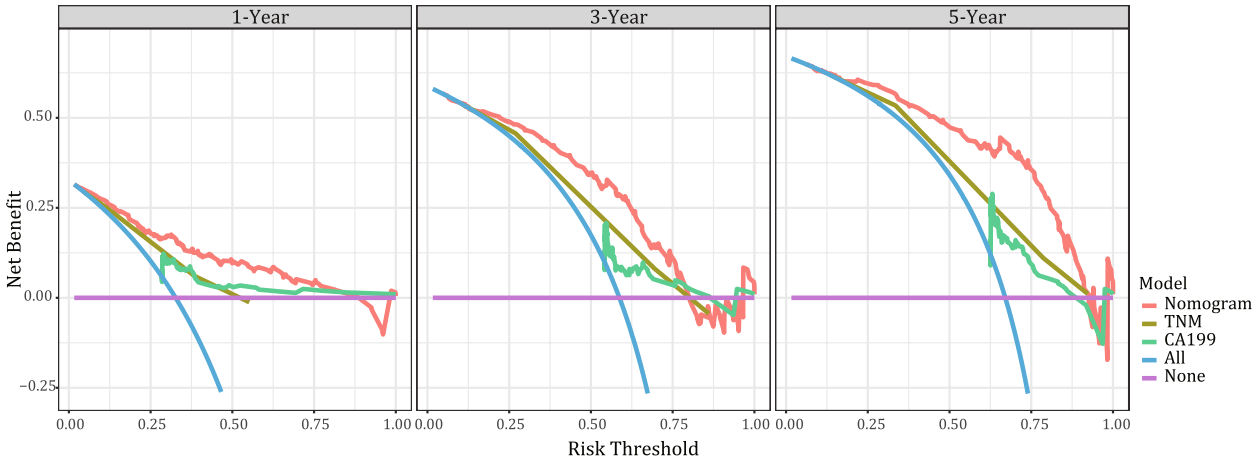

Fig. 5 Decision Curve Analysis comparing the nomogram model with TNM staging and CA199 levels, from left to right, the nomogram model exhibits superior clinical benefits in 1-year, 3-year, and 5-year postoperative survival

efficacy and clinical benefits surpassing traditional prognostic indicators.

In our study population for model development, the median postoperative survival was 25 months, with no significant difference between the PU and BJ institutions. The survival profiles were consistent with those of previous reports [6, 28]. Additionally, we retrieved and analyzed case listing data from the SEER database (8 registries, 1975–2020), including 1701 GBC cases that received surgical resection [29]. The median survival time of the SEER cohort was 21 months (Supplementary Fig. 4), further underscoring the representativeness of our cohort. Considering the congruence in baseline demographic characteristics and postoperative survival profiles between PU and BJ institutions, despite some clinical heterogeneity between cohorts, the combined analysis of the two cohorts was undertaken for feature selection and model development to ensure a large, representative, and possibly diverse data source.

From 2005 to 2019, the year of operation showed an insignificant protective effect on survival, favoring those who underwent operations in nearer years, which we assume might be associated with the advances in the comprehensive treatment of GBC, including systematic therapies, such as chemotherapy, targeted therapies, and immunotherapies. Moreover, this trend underscores the importance of incorporating the latest cases. In future studies, recent years' data will be included for analysis through further follow-up efforts, which may be compared with current findings to expand their generalizability.

Among all included factors, TNM stage emerged as the most influential risk factor in the nomogram, showing an escalating hazard ratio from stage 1 to stage 4. Previous studies [14, 30, 31] and our exploratory analysis of the SEER dataset (Supplementary Fig. 4) have demonstrated a significant correlation between TNM stages and postoperative survival in GBC. However, relying solely on the TNM staging system for surgical decision-making falls short of the precision required for optimal individualized management, with a C-index of <0.70, according to our statistics. In addition, in late-stage patients with TNM 3-4 tumors, the novel nomogram could further stratify patients into low- and high-risk groups, which demonstrated distinct survival outcomes. Hence, constructing a multifactorial model serves as a necessary complement to the traditional prognostic indicators. Similar to TNM stage, serum CA199 is another important variable in the nomogram, which is a classic diagnostic and prognostic biomarker for GBC. Wang et al. reported a significant correlation between serum CA199 and clinical staging of GBC, as well as an independent correlation between serum CA199 and postoperative survival [32]. In our analyses, the C-index of CA199 alone for distinguishing postoperative survival outcomes was close to that of TNM stage, which was far lower than that of the nomogram.

Another serum tumor marker, CA125, was the second most influential risk factor in the nomogram after TNM stage. To the best of our knowledge, this is the first study to report the independent risk effect of CA125 on postoperative survival in patients with GBC. Although CA125 is a specific marker for ovarian cancer, its prognostic significance has been reported in digestive system tumors such as hepatocellular carcinoma [33], hilar cholangiocarcinoma [34], etc. In Wang et al.'s research [32], both CA199 and CA125 were proven as diagnostic and prognostic indicators for GBC, and serum CA125 levels

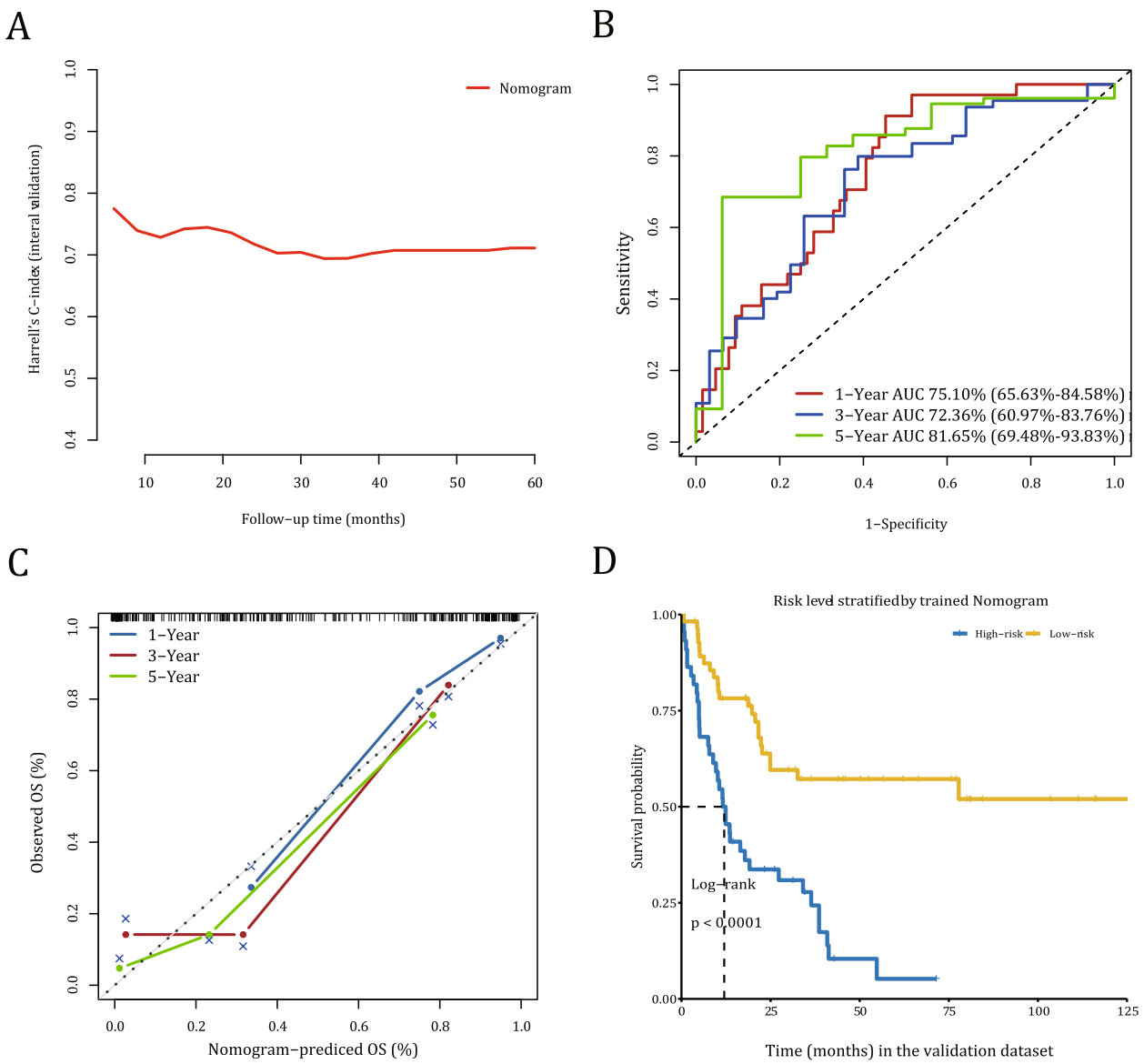

Fig. 6 Internal Validation of the Nomogram Efficacy in BJ Dataset, illustrated by (**A**) time-dependent C-index, (**B**) time-dependent ROC curves, (**C**) calibration curves, and (**D**) Kaplan-Meier curves

were positively correlated with lymph node metastasis and 1-year postoperative recurrence. Xu et al. demonstrated associations between preoperative CA125 levels and tumor size, pathological classification, microvascular invasion, and postoperative survival in hilar cholangiocarcinoma [34]. The specific mechanisms by which CA125 influences GBC prognosis of GBC are unclear. Studies on other cancers have suggested that CA125 may be associated with the invasive biological characteristics of cancer, predicting poorer postoperative survival [34–36]. Our results suggest that an elevated preoperative serum CA125 level is an independent adverse prognostic factor, which is independent of tumor TNM stages and traditional digestive tumor markers such as CA199 and CEA. This finding may have crucial implications for the clinical surgical management of GBC.

As a classic comorbidity scoring system that combines age with the severity of 16 common comorbidities [24], increased aCCI was significantly associated with adverse prognosis in our multivariate regression analysis. Previously, Tian et al. revealed a correlation between aCCI and in-hospital mortality after surgery in various digestive malignancies including GBC [37]. In this study, we found that aCCI was an important independent prognostic

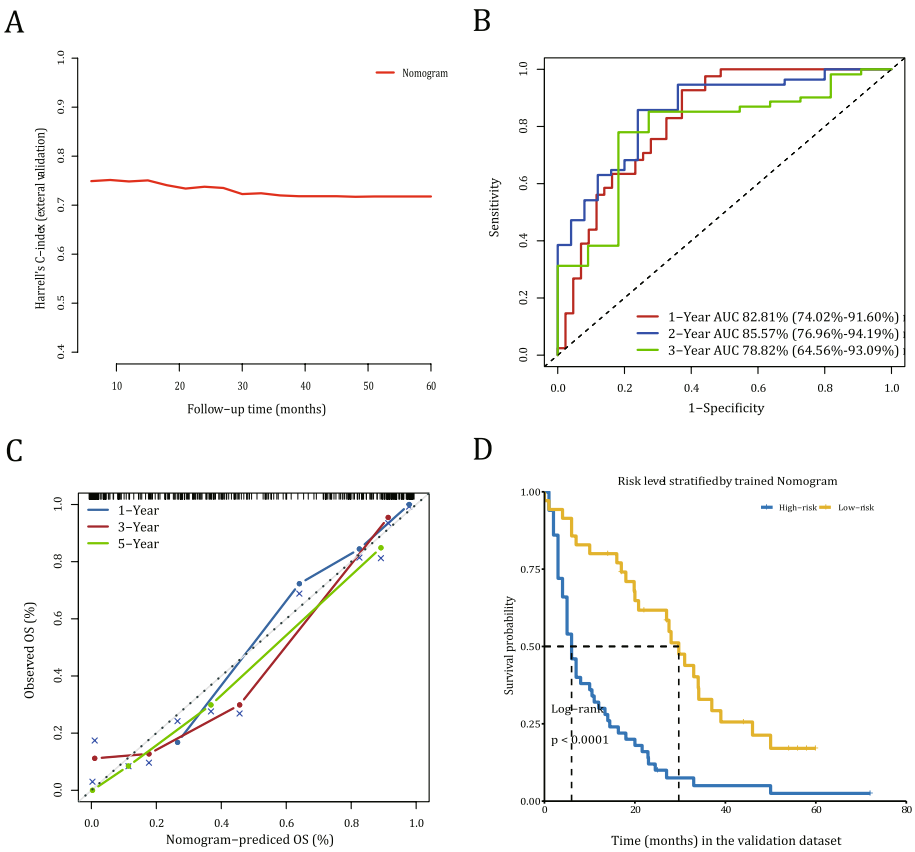

Fig. 7 External Validation of the Nomogram Efficacy in WC Dataset, illustrated by (**A**) time-dependent C-index, (**B**) time-dependent ROC curves, (**C**) calibration curves, and (**D**) Kaplan-Meier curves

indicator of long-term postoperative survival in patients with GBC. Besides aCCI, other comorbidities did not show a significant independent risk effect in the multivariate analysis. Although jaundice is usually recognized as an adverse prognostic factor and a relative contraindication for GBC surgery [30], a total of 49 patients (out of 287, 17.1%) in our study presenting with jaundice eventually underwent surgical treatment based on patients' willingness and response to bile drainage. In our study, jaundice did not show a significant association with postoperative overall survival, indicating that GBC patients with jaundice could also benefit from surgeries [30, 38].

Owing to the significant correlations and collinearities among the factors within the same category, we believe that the variables eliminated through stepwise multivariate Cox regression did not exert a significant independent impact on postoperative survival, although secondary effects caused by their correlations with major risk factors may exist. In addition to comorbidities, other variables also reflected this hypothesis. While BMI (associated with general nutritional status), ALB (associated with liver function), and PLT (associated with liver function) were selected using stepwise multivariate regression, other laboratory results were excluded. Of interest, PLT, as one of the hematologic indices, exhibits inconsistent hazard ratio directions in multivariate and univariate regressions. According to previous studies, the prognostic significance of preoperative PLT in GBC were also inconclusive [39, 40]. Instead of being used as a standalone indicator, PLT (P) is often combined and calculated with neutrophil count (N), lymphocyte count (L), etc., to reflect inflammation status. These hematologic biomarkers were also proved to be associated with survival in GBC [41]. We have further conducted supplementary correlation analyses, revealing significant positive correlations between the risk score and these hematologic indices (NLR, defined as the ratio of the peripheral blood absolute neutrophil count to the lymphocyte count, MLR, the monocyte-to-lymphocyte ratio, and PLR, the platelet-to-lymphocyte ratio), which were observed consistently in both the training and validation sets (Supplementary Fig. 5 and Supplementary Table 2). These findings align with conclusions from Velasco et al.'s meta-analysis [41].

R0 resection was another independent prognostic factor in the nomogram. R0 resection, compared with R1 resection, was demonstrated to be a protective factor. R0

resection has been widely acknowledged as a prognostic indicator for GBC and is considered the only potentially curative approach [42]. Based on this principle, tumors staged as T1b and above are amenable to similar surgical principles, including gallbladder resection combined with limited hepatectomy and portal lymph node dissection [43]. However, studies have suggested that the survival benefit of R0 resection over R1 resection may be significant only in T1b, T2, and certain T3 stage tumors [17, 44]. Extensive surgery is associated with an increased incidence of complications [45]. Therefore, in consideration of surgery and surgery-centric comprehensive treatment, a predictive nomogram involving other clinical factors is important to guide and individualize the decision-making process.

In this study, we developed, evaluated, and validated a novel prognostic nomogram for GBC. A series of statistical assessments indicated that the novel nomogram had fine discriminative capability, predictive accuracy, and risk-stratification function. The novel nomogram can provide personalized risk scoring and postoperative survival prediction for patients, with significantly higher accuracy than traditional prognostic markers such as TNM staging and serum CA199 levels. We stratified individuals into high-risk and low-risk groups based on the nomogram, with the latter experiencing significant surgical benefits. Kaplan-Meier analysis demonstrated that employing our novel nomograms could better identify suitable candidates for surgical intervention among late-stage patients. Conversely, for high-risk patients with risk scores exceeding 257 points, due to significantly poorer postoperative prognosis, consideration might lean towards comprehensive non-surgical treatments. Guiding surgical decisions with the novel nomograms yields significant additional benefits compared to sole reliance on TNM staging, as evidenced by the decision curve analysis. Furthermore, internal and external validations have corroborated the reliability of the nomogram's performance, indicating its potential for broader applicability.

Compared to previous nomogram models [18, 19, 46–48], this study brought forth significant innovations, including: (1) it is a multi-center retrospective study, allowing good representativeness and diversity of the data source; (2) the variables for model development are common and easy to collect, facilitating the application and generalization within healthcare institutions; (3) the nomogram incorporates multifaceted data including tumor staging, comorbidity scores, demographic information, preoperative laboratory results, and types of pathological margins, enhancing the interpretability of the nomogram; and (4) the independent impact of aCCI and preoperative CA125 levels on long-term postoperative survival was first reported.

Limitations and future perspectives

This study had certain limitations. Firstly, alterations in baseline characteristics, including the features incorporated into the nomogram, may influence the predictive efficacy of the nomogram via confounding associative effects. Therefore, larger and more heterogeneous cohorts including various regions, ethnic groups and nations, especially prospectively designed cohorts, are required to thoroughly validate the nomogram's effectiveness. We are going to conduct further studies in larger, multi-center, and prospective cohorts, with more patient-centered outcomes assessed over a longer period of follow-up. Additionally, biological and molecular factors, such as immunohistochemical, genomic, or transcriptomic data and tumor microenvironmental subtypes, were not incorporated in this nomogram. Future studies focusing on the biological correlations of this nomogram and combining them with molecular data would enhance the interpretability and reliability of our conclusions. Finally, the nomogram should be tested or modified in other settings, such as systematic and comprehensive treatments. Nonetheless, this study introduced and validated a novel, simple nomogram for predicting postoperative survival in patients with GBC, which showed promising performance and clinical benefits.

Conclusions

We established a novel predictive nomogram for postoperative survival in GBC patients. The model demonstrated superior discriminative and predictive efficacy compared to traditional prognostic factors including TNM stages and CA199 levels, as well as robust generalizability. The novel multifactor model is promising for assissting surgical decision-making and the comprehensive management of GBC.

Abbreviations

GBC	Gallbladder cancer
OS	Overall survival
SEER	Surveillance Epidemiology and End Results database
IBM	Incidence-based mortality
BMI	Body mass index
DM	Diabetes mellitus
GS	Gallstones
JAU	Jaundice
aCCI	Age-adjusted Charlson Comorbidity Index
NEU	Neutrophils
Mono	Monocytes
LYM	Lymphocytes
PLT	Platelet
TBIL	Total bilirubin
ALB	Albumin
TC	Total cholesterol
FIN	Fibrinogen
CEA	Carcinoembryonic antigen

CA199	Carbohydrate antigen 199
CA125	Carbohydrate antigen 125
ASA	American society of Anesthesiologists
OD	Operation duration
BLD	Blood loss
TRF	Transfusion
POD	Postoperative hospital days
POC	Postoperative complications
AJCC	American Joint Committee on Cancer
DF	Differentiation
LN	Lymph nodes
R0	Resection with pathologically negative surgical margins
CI	Confidence interval
AIC	Akaike information criterion
C-index	Concordance index
ROC	Receiver operating characteristic
AUC	Area under curve
DCA	Decision curve analysis
HR	Hazard ratio
TMB	Tumor mutation burden

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12957-024-03533-z.

Supplementary Material 1. Supplementary Figure 1. Conceptual Diagram of the Study Workflow.

Supplementary Material 2. Supplementary Figure 2. The Schoenfeld residual test for the nomogram shows adherence to the assumption of proportional hazards.

Supplementary Material 3. Supplementary Figure 3. The dfbetas residual test for the nomogram. The few outliers show symmetric impact on the model's performance.

Supplementary Material 4. Supplementary Figure 4. Postoperative survival data of gallbladder cancer cases from the SEER database. The postoperative survival results of the overall population, as well as that for patients in different TNM subgroups.

Supplementary Material 5. Supplementary Figure 5. Spearman's correlation coefficient between nomogram parameters, nomogram risk scores, and hematologic indices in (A) PU and BJ cohorts and (B) QD cohort, respectively.

Supplementary Material 6.

Supplementary Material 7.

Supplementary Material 8.

Provenance and peer review
Not commissioned, externally peer-reviewed.

Authors' contributions
Study conception and design (Kaige Deng, Jiali Xing, Gang Xu, Bao Jin), collected the original clinical data (Gang Xu, Zijian Leng, Xueshuai Wan, Jingyong Xu, Xiaolei Shi, Jiangchun Qiao, Ruixue Ma), drafted the first version of the manuscript (Kaige Deng, Jiali Xing), edited and revised the manuscript (Jinghai Song, Jiayin Yang, Yongchang Zheng, Xinting Sang, Shunda Du).

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Availability of data and materials
All data generated during the analysis in this study are included in the article and supplementary materials. Further enquiries can be directed to the corresponding author.

Declarations

Ethics approval and consent to participate
The Institutional Review Board of All institutions have approved this study. Informed consent was considered unnecessary due to the retrospective and observational design of the study. This study was performed in line with the ethical guidelines of the Declaration of Helsinki, and all clinical information was anonymized and deidentified prior to analysis.

Competing interest
The authors have no conflict of interest related to this publication.

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