

C-reactive Protein-to-Albumin Ratio as a Superior Inflammatory Marker in Resected Biliary Tract Cancer: Development of a Prognostic Nomogram Complementary to TNM Staging

SHINICHI IKUTA, TSUKASA AIHARA, TAKAYOSHI NAKAJIMA, MASATAKA FUJIKAWA and NAOKI YAMANAKA

Department of Surgery, Meiwa Hospital, Hyogo, Japan

Abstract

Background/Aim: Consensus on the most informative inflammatory marker for prognosis in biliary tract cancer (BTC) is lacking. The aim of this study was to comprehensively evaluate preoperative inflammatory indices and develop a prognostic nomogram complementary to TNM staging.

Patients and Methods: A total of 247 patients with resected BTC were retrospectively analyzed. Eight inflammatory indices, including prognostic nutritional index (PNI) and C-reactive protein-to-albumin ratio (CAR), were assessed alongside non-TNM clinicopathological variables. Least absolute shrinkage and selection operator (LASSO) regression identified overall survival-associated variables for multivariable Cox regression and nomogram construction. Model performance was evaluated using Kaplan–Meier analysis, concordance (C-) index, time-dependent area under the curve (tdAUC), decision curve analysis (DCA), and calibration plots, with bootstrap validation.

Results: LASSO selected PNI and CAR; CAR remained independently significant. The nomogram incorporated CAR and five clinicopathological factors: body mass index ≥ 25 kg/m², carbohydrate antigen 19-9 > 37 U/ml, moderate/poor differentiation, perineural invasion, and residual tumor status. Patients were stratified by nomogram score into four risk groups showing distinct survival differences. Notably, 50.6% of TNM Stage I-II were reclassified as higher risk, 16.1% of Stage III-IV as lower risk. The nomogram achieved C-index 0.722 versus 0.659 for TNM ($p=0.022$), with superior tdAUCs, clinical benefit on DCA, and good calibration. Consistent prognostic performance was observed across BTC subtypes and TNM stages.

Conclusion: CAR demonstrated superiority over other inflammatory indices in resected BTC. This CAR-based nomogram complements TNM staging, offering enhanced prognostic stratification for patients with heterogeneous outcomes within the same anatomical stage.

Keywords: Biliary tract cancer, prognostic nomogram, inflammatory indices, C-reactive protein-to-albumin ratio, TNM staging.



Shinichi Ikuta, Department of Surgery, Meiwa Hospital, 4-31 Agenaruo, Nishinomiya, Hyogo 663-8186, Japan. Tel: +81 798471767, Fax: +81 798477613, e-mail: g2s1002@gmail.com

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Introduction

Biliary tract cancer (BTC), encompassing intrahepatic cholangiocarcinoma (ICC), extrahepatic cholangiocarcinoma (ECC), gallbladder cancer (GBC), and ampullary carcinoma (AC), represents the second most common hepatobiliary malignancy, accounting for approximately 3% of all gastrointestinal cancers (1, 2). Despite its relative rarity, BTC is characterized by aggressive behavior and poor prognosis, often diagnosed at advanced stages that limit therapeutic efficacy (3). Although surgical resection remains the only potentially curative treatment and recent advances in chemotherapy have improved outcomes, high rates of recurrence and metastasis continue to challenge long-term survival, underscoring the urgent need for improved prognostic tools (2, 4, 5).

The Tumor-Node-Metastasis (TNM) staging system serves as the cornerstone for evaluating disease extent and guiding treatment decisions in BTC (6). However, its reliance solely on anatomical features fails to capture critical biological and host-related factors that significantly influence clinical outcomes. Patients with identical TNM stages frequently exhibit divergent survival trajectories, suggesting that tumor biology and systemic responses play pivotal roles in BTC progression (7). This limitation highlights the inadequacy of TNM staging as a standalone prognostic tool, particularly in this heterogeneous and aggressive malignancy.

Mounting evidence indicates that the tumor microenvironment's inflammatory response plays a crucial role in the development, progression, and metastasis of solid tumors, including BTC (8). Multiple pretreatment inflammation-based indices, such as the neutrophil-to-lymphocyte ratio (NLR), prognostic nutritional index (PNI), and C-reactive protein-to-albumin ratio (CAR), have been proposed as prognostic markers in BTC (9-11). However, their individual prognostic value remains inconsistent across studies, and consensus on the most informative marker for risk stratification is lacking (12). This knowledge gap underscores the need for evaluation of multiple inflammatory indices in the same

cohort to objectively identify the optimal prognostic marker in BTC.

To address these challenges, this study aimed to comprehensively evaluate eight preoperative inflammatory indices and develop a prognostic nomogram incorporating the most informative marker alongside clinicopathological factors in patients with BTC undergoing resection. By deliberately excluding TNM components, we sought to capture biological and host-related prognostic factors orthogonal to anatomical staging, thereby providing a complementary tool to enhance postoperative risk stratification for overall survival (OS) and improve clinical decision-making in this aggressive malignancy.

Patients and Methods

Patients and data collection. This retrospective cohort study included 286 consecutive patients with histologically confirmed BTC who underwent surgical resection at our institution between January 2010 and September 2024. Exclusion criteria were palliative-intent surgery (n=25), incomplete clinicopathological or laboratory data (n=11), and non-adenocarcinoma histology (n=5; *e.g.*, neuroendocrine carcinoma), with some overlap among excluded cases, yielding 247 patients: 53 with ICC, 120 with ECC, 33 with GBC, and 41 with AC. Clinical and demographic data – age, sex, American Society of Anesthesiologists Physical Status (ASA-PS), body mass index (BMI), and surgical procedure – were extracted from electronic medical records. Of these, 149 (60.3%) had biliary obstruction and underwent preoperative stenting or drainage to relieve jaundice. Serum carbohydrate antigen (CA) 19-9 levels were measured within one month before surgery, post-stenting/drainage, using chemiluminescent enzyme immunoassay (Fujirebio, Tokyo, Japan). Histopathological assessment included TNM staging (7th edition, Union for International Cancer Control) (6), tumor differentiation (well, moderate, or poor), perineural invasion, and resection margin status (R0: no residual tumor; R1: microscopic; R2: macroscopic). The 7th edition was used

throughout, as the 8th requires invasion depth for T classification, often unavailable due to incomplete records. Eleven patients without lymphadenectomy – eight after transduodenal ampullectomy for AC and three after simple cholecystectomy for GBC – were classified as N0 based on preoperative imaging and intraoperative findings. During surgery, 19 patients (7.7%) had resectable limited metastases (liver, n=8; para-aortic lymph nodes, n=6; peritoneum, n=5) and underwent simultaneous resection of primary and metastatic lesions. Adjuvant chemotherapy (*e.g.*, S-1) was given at physician discretion, typically for N1 disease or R1/R2 resection without contraindications. Follow-up duration was estimated using the reverse Kaplan–Meier (KM) method (13). OS, the primary endpoint, was defined from surgery to last follow-up or death from any cause. Blood samples for inflammation-based indices were collected a median of two days (range=0-7 days) before surgery, with no active infection or systemic inflammation per clinical assessment. The following inflammation-based indices were calculated per established methods: NLR: Neutrophil count (/mm³)/lymphocyte count (/mm³); Platelet-to-lymphocyte ratio (PLR): Platelet count (/mm³)/lymphocyte count (/mm³); Lymphocyte-to-monocyte ratio (LMR): Lymphocyte count (/mm³)/monocyte count (/mm³); PNI: 10 × serum albumin (g/dl) + 0.005 × lymphocyte count (/mm³); Modified Glasgow prognostic score (mGPS) 0: Albumin ≥3.5 g/dl and C-reactive protein (CRP) ≤1.0 mg/dl; 1: Either albumin <3.5 g/dl or CRP >1.0 mg/dl; 2: Albumin <3.5 g/dl and CRP >1.0 mg/dl.; CAR: CRP (mg/dl)/albumin (g/dl); Systemic-immune-inflammation index (SII): Platelet count (/mm³) × neutrophil count (/mm³)/lymphocyte count (/mm³); Systemic-inflammation-response index (SIRI): Neutrophil count (/mm³) × monocyte count (/mm³)/lymphocyte count (/mm³).

Ethical approval. This study was approved by the Institutional Ethics Committee (approval no.: 2025-40) and adhered to the Declaration of Helsinki. Patient consent was waived due to the retrospective design and use of de-identified data.

Statistical analysis. Inflammation-based indices were dichotomized using optimal cutoffs from maximally selected rank statistics to maximize log-rank differences in KM curves. The same method stratified patients by nomogram score into four risk groups. Univariate Cox regression identified OS-associated factors. To address multicollinearity and select variables for the nomogram, Least Absolute Shrinkage and Selection Operator (LASSO) regression was applied, explicitly excluding TNM components (T stage, N stage, M stage, TNM stage), with λ optimized by 10-fold cross-validation. Selected variables entered multivariable Cox regression for hazard ratios and nomogram construction. Model performance was evaluated *via* KM analysis, Harrell's concordance (C-) index, time-dependent area under the receiver operating characteristic curve (tdAUC), decision curve analysis (DCA), and calibration plots for 1-, 3-, and 5-year OS. Internal validation used 1,000 bootstrap resamples to estimate 95% confidence intervals (CIs) and assess overfitting. All analyses used R (v4.4.1), with significance at $p < 0.05$ (two-tailed).

Results

Patient characteristics and univariate analysis. Table I summarizes the baseline characteristics of 247 patients. The median follow-up was 63.8 months (95%CI=53.7-74.9 months). Factors significantly associated with OS included biliary drainage, CA19-9 >37 U/ml, advanced T stage, N1 status, M1 status, higher TNM stage, moderate/poor tumor differentiation, perineural invasion, R1/R2 resection, and adjuvant chemotherapy. Among the inflammation-based indices, all except PLR showed significant associations with OS: NLR >4.5, LMR ≤2.5, PNI ≤40.4, mGPS 1 and 2, CAR >0.18, SII >547, and SIRI >2.15.

Variable selection and multivariate analysis. LASSO regression, applied to 20 variables from Table I excluding T stage, N stage, M stage, and TNM stage, selected seven OS predictors: CA19-9 >37 U/ml, CAR >0.18, PNI ≤40.4, BMI ≥25 kg/m², moderate/poor tumor differentiation,

Table I. Patient characteristics and univariate analysis for overall survival.

Characteristics	No. of patients (%)	HR	95%CI	p-Value
Age, years (median, range)	72 (39-88)			
<65	59 (23.9)	1.000		
≥65	188 (76.1)	1.120	0.730-1.718	0.604
Sex				
Female	109 (44.1)	1.000		
Male	138 (55.9)	0.986	0.682-1.427	0.942
ASA-PS				
1-2	80 (32.4)	1.000		
≥3	167 (67.6)	1.130	0.767-1.665	0.537
Body mass index, kg/m ²				
<25	202 (81.8)	1.000		
≥25	45 (18.2)	1.329	0.834-2.118	0.231
Type of BTC				
ICC	53 (21.5)	1.000		
ECC	120 (48.6)	1.115	0.692-1.796	0.655
GBC	33 (13.4)	0.884	0.448-1.747	0.723
AC	41 (16.6)	0.693	0.357-1.348	0.280
Biliary drainage				
No	98 (39.7)	1.000		
Yes	149 (60.3)	1.649	1.100-2.472	0.016
CA19-9, U/ml				
≤37	101 (40.9)	1.000		
>37	146 (59.1)	2.638	1.734-4.012	<0.001
Surgical procedure (Radical)				
Cholecystectomy	23 (9.3)	1.000		
Liver resection	40 (16.2)	1.254	0.541-2.909	0.598
Liver resection with BDR	77 (31.2)	1.319	0.619-2.811	0.473
Pancreaticoduodenectomy	99 (40.1)	1.138	0.536-2.417	0.736
Ampullectomy	8 (3.2)	0.180	0.023-1.446	0.107
T stage				
T1/T2	126 (51.0)	1.000		
T3/T4	121 (49.0)	2.155	1.479-3.139	<0.001
N stage				
N0	133 (53.8)	1.000		
N1	114 (46.2)	2.671	1.819-3.921	<0.001
M stage				
M0	228 (92.3)	1.000		
M1	19 (7.7)	2.455	1.312-4.596	0.005
TNM stage				
I	42 (17.0)	1.000		
II	112 (45.3)	4.483	1.922-10.450	<0.001
III	46 (18.6)	7.931	3.283-19.160	<0.001
IV	47 (19.0)	8.358	3.452-20.240	<0.001
Tumor differentiation				
Well	96 (38.9)	1.000		
Moderate/Poor	151 (61.1)	2.159	1.437-3.244	<0.001
Perineural invasion				
No	101 (40.9)	1.000		
Yes	146 (59.1)	2.589	1.714-3.911	<0.001
Residual tumor				
R0	217 (87.9)	1.000		
R1/R2	30 (12.1)	2.575	1.596-4.155	<0.001

Table I. Continued

Table I. *Continued*

Characteristics	No. of patients (%)	HR	95%CI	p-Value
Adjuvant chemotherapy				
No	86 (34.8)	1.000		
Yes	161 (65.2)	1.542	1.020-2.331	0.040
NLR				
≤4.5	220 (89.1)	1.000		
>4.5	27 (10.9)	1.841	1.096-3.094	0.021
PLR				
≤214.8	197 (79.8)	1.000		
>214.8	50 (20.2)	1.392	0.908-2.132	0.129
LMR				
>2.5	211 (85.4)	1.000		
≤2.5	36 (14.6)	1.846	1.148-2.968	0.011
PNI				
>40.4	190 (76.9)	1.000		
≤40.4	57 (23.1)	1.976	1.311-2.979	0.001
mGPS				
0	137 (55.5)	1.000		
1	69 (27.9)	2.217	1.459-3.370	<0.001
2	41 (16.6)	2.319	1.426-3.770	<0.001
CAR				
≤0.18	178 (72.1)	1.000		
>0.18	69 (27.9)	2.225	1.531-3.233	<0.001
SII				
≤547	140 (56.7)	1.000		
>547	107 (43.3)	1.486	1.029-2.146	0.035
SIRI				
≤2.15	217 (87.9)	1.000		
>2.15	30 (12.1)	1.974	1.205-3.233	0.007

HR: Hazard ratio; CI: confidence interval; ASA-PS: American society of anesthesiologists physical status; BTC: biliary tract cancer; CA19-9: carbohydrate antigen 19-9; BDR: bile duct resection; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; LMR: lymphocyte-to-monocyte ratio; PNI: prognostic nutritional index; mGPS: modified Glasgow prognostic score; CAR: C-reactive protein-to-albumin ratio; SII: systemic-immune-inflammation index; SIRI: systemic-inflammation-response index.

perineural invasion, and R1/R2 resection (Figure 1A-C). Multivariable Cox regression retained six independent prognostic factors: BMI ≥ 25 kg/m², CA19-9 >37 U/ml, moderate/poor tumor differentiation, perineural invasion, R1/R2 resection, and CAR >0.18. PNI was not an independent predictor in the final model ($p=0.067$) (Table II).

Nomogram development and survival analysis. A nomogram incorporating the six prognostic factors was developed (Figure 2). KM analysis stratified patients into four distinct risk groups (Low, Medium-low, Medium-high, High) based on optimal nomogram score cutoffs ($p<0.001$, Figure 3A). TNM stage-based stratification showed less distinct separation, particularly between

Stages III and IV (Figure 3B). Notably, nomogram-based reclassification assigned 50.6% (78/154) of TNM Stage I-II patients to Medium-high or High-risk groups, while 16.1% (15/93) of Stage III-IV patients were categorized as Low or Medium-low risk.

Discrimination and calibration of the nomogram. The nomogram achieved a C-index of 0.722 (95%CI=0.676-0.768) versus 0.659 (95%CI=0.608-0.706; $p=0.022$) for TNM staging. tdAUCs were consistently higher for the nomogram across all evaluated time points (Figure 4A). DCA demonstrated slightly higher net benefit for the nomogram versus TNM staging across a range of threshold probabilities (Figure 4B). Calibration plots

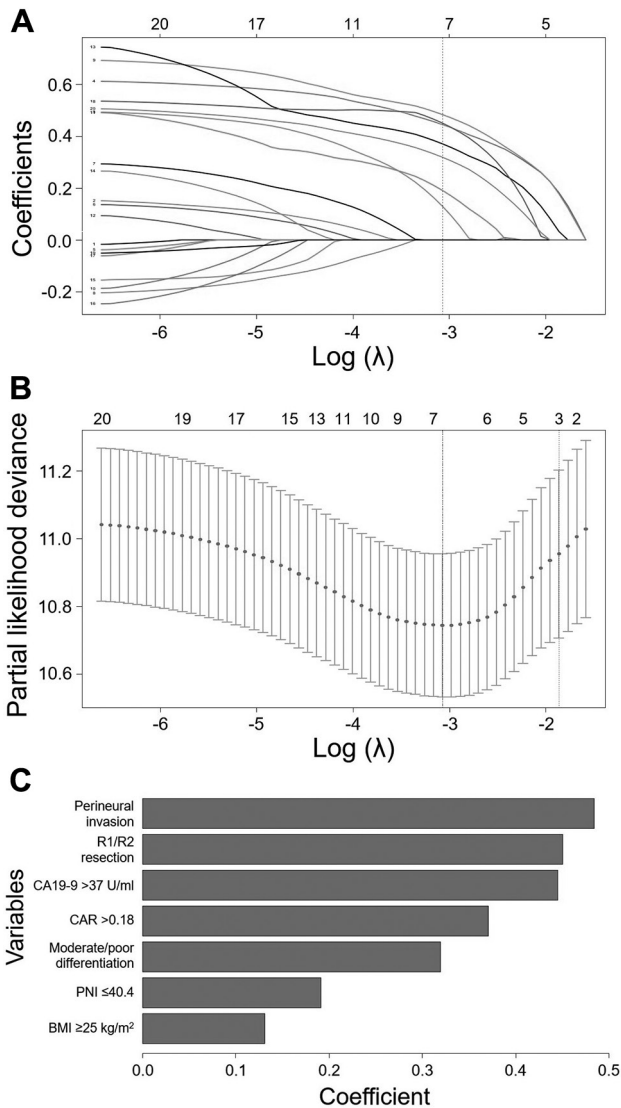


Figure 1. Least absolute shrinkage and selection operator (LASSO) regression for variable selection. (A) LASSO coefficient path as a function of $\log(\lambda)$, with a vertical line marking the optimal λ . (B) Cross-validation curve of deviance versus $\log(\lambda)$, with error bars and a vertical line marking the optimal λ . (C) Coefficients of variables selected by LASSO, with bar lengths representing absolute values.

confirmed reliable OS prediction at one, three, and five years (Figure 5).

Subgroup analysis of nomogram score prognostic impact. Stratified analysis by BTC subtype and TNM stage evaluated the nomogram's prognostic consistency across

Table II. Multivariate analysis of prognostic factors for overall survival.

Variables	HR (95%CI)	p-Value
BMI ≥25 kg/m ² (vs. <25 kg/m ²)	1.653 (1.001-2.730)	0.049
CA19-9 >37 U/ml (vs. ≤37 U/ml)	1.810 (1.162-2.819)	0.009
Tumor differentiation moderate/poor (vs. well)	1.612 (1.040-2.500)	0.033
Perineural invasion yes (vs. no)	1.877 (1.207-2.920)	0.005
Residual tumor R1/R2 (vs. R0)	1.835 (1.125-2.994)	0.015
PNI ≤40.4 (vs. >40.4)	1.517 (0.972-2.369)	0.067
CAR >0.18 (vs. ≤0.18)	1.691 (1.130-2.532)	0.011

HR: Hazard ratio; CI: confidence interval; BMI: body mass index; CA19-9: carbohydrate antigen 19-9; PNI: prognostic nutritional index; CAR: C-reactive protein-to-albumin ratio.

subgroups (Figure 6). The nomogram score demonstrated consistent association with OS across all subgroups, with no significant interaction (p for interaction=0.913 and 0.266 for tumor location and TNM stage, respectively).

Discussion

In this study, we developed a prognostic nomogram for patients with resected BTC, incorporating CAR selected from eight inflammation-based indices. The nomogram demonstrated acceptable discrimination, clinical utility, and good calibration. Subgroup analysis showed consistent prognostic performance across BTC subtypes and TNM stages without significant interactions, suggesting broad applicability.

The role of inflammation and nutritional status in cancer progression has been increasingly recognized, particularly through effects on the tumor microenvironment and systemic cytokine dynamics (8, 14). Chronic inflammation promotes tumor proliferation and metastasis via mediators such as interleukin-6, which activates STAT3 signaling, and tumor necrosis factor-alpha, which drives matrix remodeling (8, 15). These mechanisms are reflected in systemic inflammation-based indices (16). Numerous studies have examined the prognostic value of such indices in BTC, often focusing on specific subtypes. For instance, in ICC, a meta-analysis by Cui *et al.* reported NLR to be associated with worse prognosis, and other studies

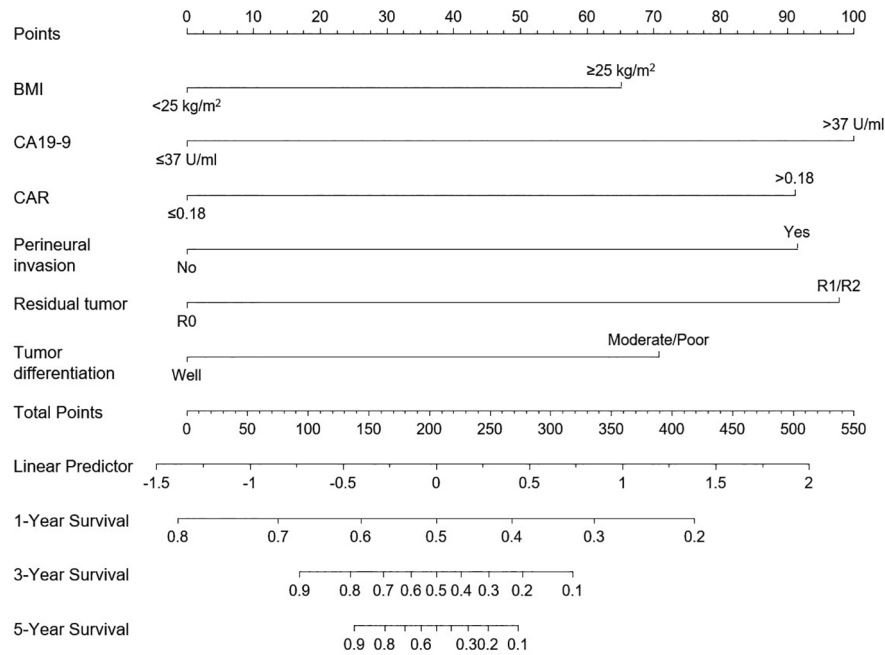


Figure 2. Prognostic nomogram.

identified SII as significant (17-19). In ECC, Miyahara *et al.* assessed NLR and LMR as potential prognostic markers (20). In GBC, several studies investigated NLR, SII, SIRI, and CAR for their prognostic relevance (21-24). Additionally, meta-analyses support SII, mGPS, PNI, and CAR as prognostic across BTC types (10, 11, 25, 26). However, studies systematically comparing a broad set of indices to identify the most informative remain scarce.

Among inflammation-based indices, CAR integrates CRP, a marker of systemic inflammation, and albumin, an indicator of nutritional status. This dual profile may enhance its prognostic value compared to inflammation-only indices like NLR or SII. CAR has shown prognostic relevance across various solid tumors (27, 28). Systemic inflammation, reflected by elevated CRP, contributes to tumor progression through cytokine-mediated pathways. Low albumin, indicating malnutrition, further impairs immune function and worsens outcomes, making CAR a strong prognostic marker in BTC. In our LASSO regression, CAR and PNI – both including albumin – were selected, emphasizing albumin's role in capturing nutritional

decline. PNI was excluded in multivariable Cox analysis, likely due to redundancy with CAR, which had greater prognostic strength. Unlike mGPS, which uses categorical thresholds, or PNI, which reflects nutrition alone, CAR's continuous scale and dual nature improve prognostic precision. Though we dichotomized CAR at >0.18 for survival stratification, its continuous structure distinguishes it from mGPS's fixed categories. This combination of nuance and practicality may explain CAR's advantage in our analysis.

Other nomogram components hold prognostic value. Elevated CA19-9 signals tumor burden and aggressiveness (29). Clinicopathological factors – tumor differentiation, perineural invasion, and residual tumor status – reflect disease aggressiveness (30-32). Notably, BMI ≥ 25 kg/m² independently predicted poor prognosis despite univariable insignificance, retained by LASSO for multivariable contribution. Obesity may promote tumor progression locally *via* adipose inflammation and microenvironment changes, and systemically through metabolic and inflammatory mediators (33). However, its

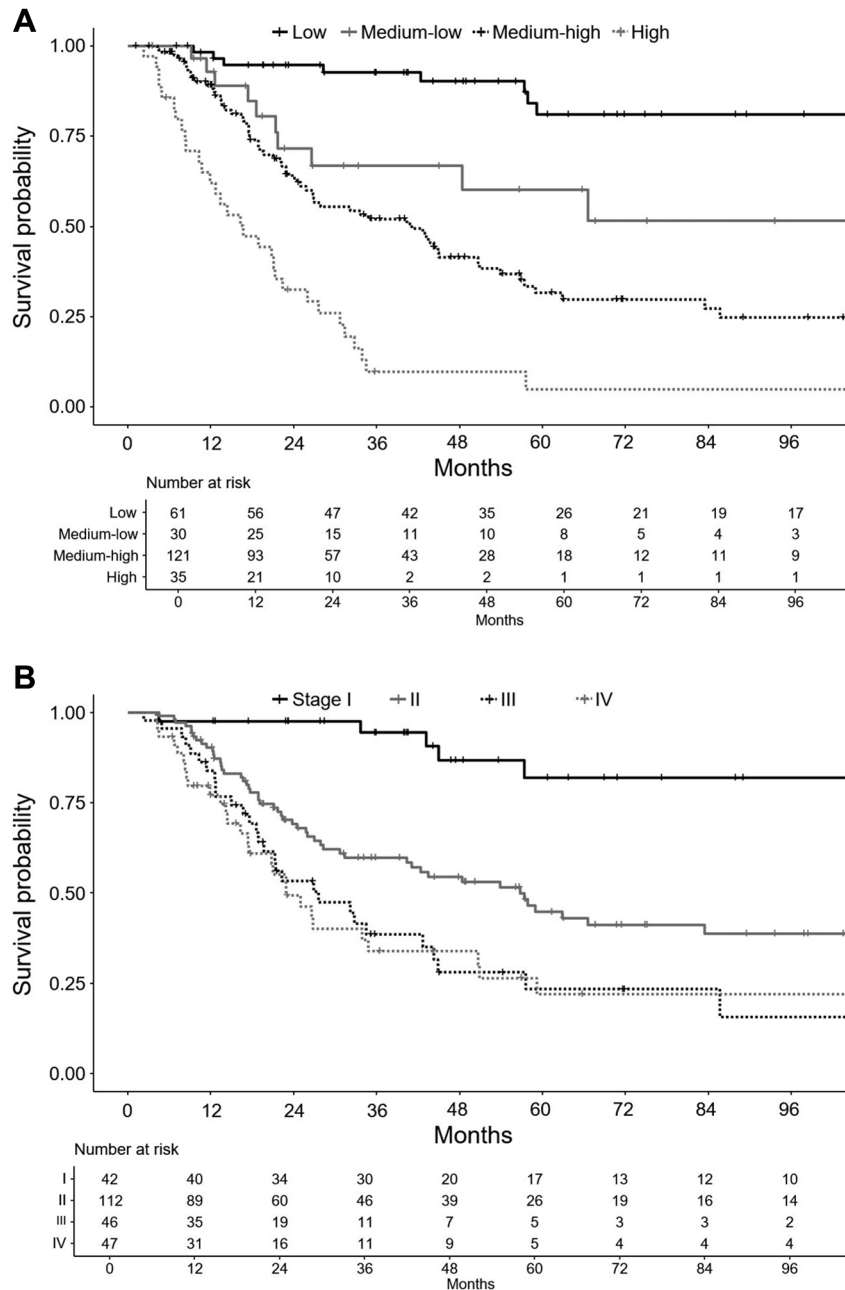


Figure 3. Kaplan-Meier survival curves stratified by (A) nomogram score and (B) TNM stage.

prognostic role in BTC remains unclear: some studies link obesity to higher mortality, while others suggest survival benefit in advanced cases treated with chemotherapy (34, 35). These inconsistencies warrant further exploration of

metabolic factors and body composition in BTC progression and treatment response.

Several nomograms incorporating inflammatory indices for resected BTC exist. Sun *et al*. proposed a

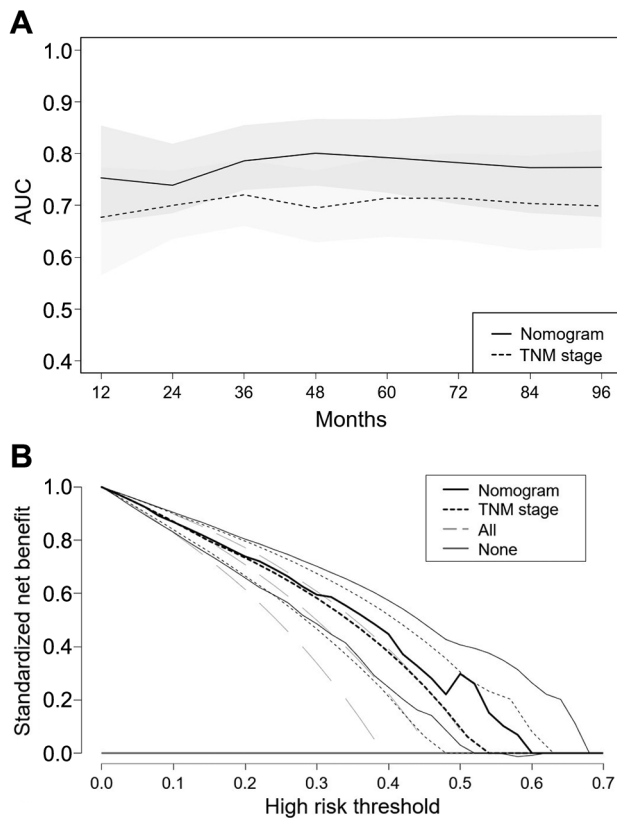


Figure 4. Performance evaluation of the nomogram and TNM stage: (A) *tdAUCs* and (B) decision curves.

GBC model combining SII, CA19-9, and TNM stage; Zhu *et al.* developed an ICC model integrating PIIN score (based on ALBI grade, NLR, PNI, and SII) with N stage and tumor number (22, 36). Though outperforming TNM alone, their TNM reliance limits capturing heterogeneity beyond anatomy. Our nomogram excludes TNM, using CAR and clinicopathological factors for biologically driven, complementary postoperative stratification – useful when TNM is uncertain (*e.g.*, incomplete lymph node assessment or unclear invasion depth). Like TNM models, it is postoperative-only due to variables like perineural invasion and residual status. Yet preoperative CAR, BMI, and CA19-9 enable preliminary estimates, with the full nomogram refining prognosis post-resection to guide follow-up and adjuvant therapy.

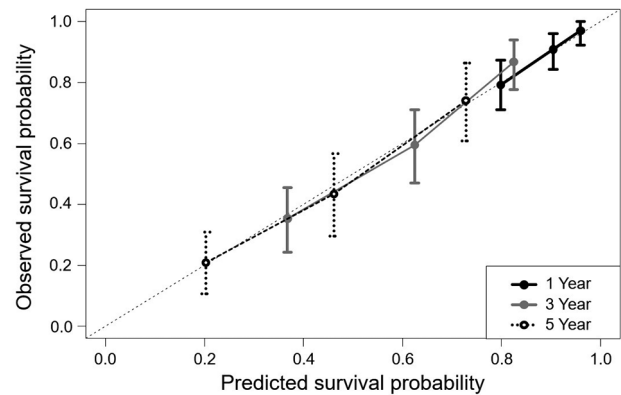


Figure 5. Calibration plots of the nomogram for survival prediction at 1, 3, and 5 years.

Study limitations. First, its retrospective, single-center design and small sample size risk selection bias and residual confounding. Second, and most critically, despite bootstrap internal validation, lack of external validation limits model robustness and generalizability – future studies must address this. Third, inflammatory indices could be affected by preoperative biliary drainage (common here), despite sampling without active inflammation. Fourth, BTC anatomical diversity and surgical invasiveness – including complications like liver failure after major resection – may confound OS. Fifth, classifying 11 patients without full lymphadenectomy as N0 constrains precise N staging. Yet, since the nomogram excludes TNM by design, this imprecision does not impair performance and highlights its utility when conventional staging is unreliable. Sixth, including limited metastatic disease adds prognostic heterogeneity but reflects real-world BTC surgery and aligns with the model's TNM-independent goal. Lastly, evolving surgical techniques, care, and therapies over the study period risk time-related bias, reducing applicability to current practice.

Conclusion

In conclusion, CAR was the most informative inflammatory marker for prognosis in resected BTC. This prognostic nomogram, integrating CAR with key

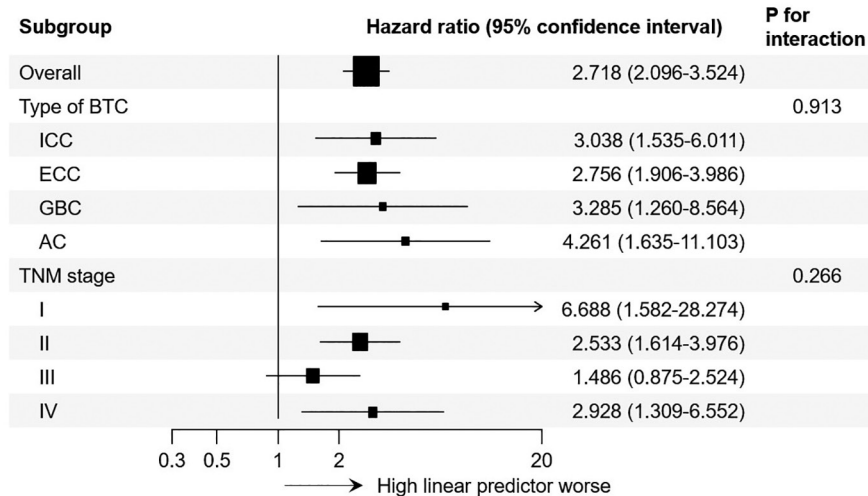


Figure 6. Prognostic impact of nomogram score across subgroups by type of BTC and TNM stage.

clinicopathological factors while excluding TNM components, complements TNM staging by enhancing prognostic stratification, especially for patients with heterogeneous outcomes within the same anatomical stage. However, external validation is required to confirm its clinical utility.

Conflicts of Interest

All Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

Shinichi Ikuta: Conceptualization, Methodology, Writing – original draft; Tsukasa Aihara and Takayoshi Nakajima: Data curation, Investigation; Masataka Fujikawa: Formal analysis, Visualization; Naoki Yamanaka: Supervision, Project administration, Writing – review and editing.

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Artificial Intelligence (AI) Disclosure

AI tools were used solely to assist with statistical coding and English text proofreading. The AI did not contribute to the study design, data collection, data interpretation, or the conclusions of the research.

References

- 1 Valle JW, Kelley RK, Nervi B, Oh D, Zhu AX: Biliary tract cancer. *Lancet* 397(10272): 428-444, 2021. DOI: 10.1016/S0140-6736(21)00153-7
- 2 Siegel RL, Miller KD, Fuchs HE, Jemal A: Cancer statistics, 2022. *CA Cancer J Clin* 72(1): 7-33, 2022. DOI: 10.3322/caac.21708
- 3 Ilyas SI, Khan SA, Hallemeier CL, Kelley RK, Gores GJ: Cholangiocarcinoma - evolving concepts and therapeutic strategies. *Nat Rev Clin Oncol* 15(2): 95-111, 2018. DOI: 10.1038/nrclinonc.2017.157
- 4 Oh DY, He AR, Bouattour M, Okusaka T, Qin S, Chen LT, Kitano M, Lee CK, Kim JW, Chen MH, Suksombooncharoen T, Ikeda

- M, Lee MA, Chen JS, Potemski P, Burris HA 3rd, Ostwal V, Tanasanvimon S, Morizane C, Zaucha RE, McNamara MG, Avallone A, Cundom JE, Breder V, Tan B, Shimizu S, Tougeron D, Evesque L, Petrova M, Zhen DB, Gillmore R, Gupta VG, Dayyani F, Park JO, Buchschacher GL Jr, Rey F, Kim H, Wang J, Morgan C, Rokutanda N, Żotkiewicz M, Vogel A, Valle JW: Durvalumab or placebo plus gemcitabine and cisplatin in participants with advanced biliary tract cancer (TOPAZ-1): updated overall survival from a randomised phase 3 study. *Lancet Gastroenterol Hepatol* 9(8): 694-704, 2024. DOI: 10.1016/S2468-1253(24)00095-5
- 5 Banales JM, Marin JGG, Lamarca A, Rodrigues PM, Khan SA, Roberts LR, Cardinale V, Carpino G, Andersen JB, Braconi C, Calvisi DF, Perugorria MJ, Fabris L, Boulter L, Macias RIR, Gaudio E, Alvaro D, Gradilone SA, Strazzabosco M, Marzioni M, Coulouarn C, Fouassier L, Raggi C, Invernizzi P, Mertens JC, Moncsek A, Ilyas SI, Heimbach J, Koerkamp BG, Bruix J, Forner A, Bridgewater J, Valle JW, Gores GJ: Cholangiocarcinoma 2020: the next horizon in mechanisms and management. *Nat Rev Gastroenterol Hepatol* 17(9): 557-588, 2020. DOI: 10.1038/s41575-020-0310-z
- 6 Wiltberger G, Krenzien F, Benzing C, Atanasov G, Klein F, Hau HM, Feldbrügge L, Pratschke J, Schmelzle M, Jonas S: Prognostic accuracy of the seventh edition of the TNM Classification compared with the fifth and sixth edition for distal cholangiocarcinoma. *Ann Surg Oncol* 23(4): 1320-1326, 2016. DOI: 10.1245/s10434-015-4999-9
- 7 Zhang XF, Beal EW, Bagante F, Chakedis J, Weiss M, Popescu I, Marques HP, Aldrighetti L, Maithel SK, Pulitano C, Bauer TW, Shen F, Poultsides GA, Soubrane O, Martel G, Koerkamp BG, Itaru E, Pawlik TM: Early *versus* late recurrence of intrahepatic cholangiocarcinoma after resection with curative intent. *Br J Surg* 105(7): 848-856, 2018. DOI: 10.1002/bjs.10676
- 8 Greten FR, Grivennikov SI: Inflammation and Cancer: Triggers, Mechanisms, and Consequences. *Immunity* 51(1): 27-41, 2019. DOI: 10.1016/j.immuni.2019.06.025
- 9 McNamara MG, Templeton AJ, Maganti M, Walter T, Horgan AM, McKeever L, Min T, Amir E, Knox JJ: Neutrophil/lymphocyte ratio as a prognostic factor in biliary tract cancer. *Eur J Cancer* 50(9): 1581-1589, 2014. DOI: 10.1016/j.ejca.2014.02.015
- 10 Lv X, Zhang Z, Yuan W: Pretreatment Prognostic Nutritional Index (PNI) as a prognostic factor in patients with biliary tract cancer: a meta-analysis. *Nutr Cancer* 73(10): 1872-1881, 2021. DOI: 10.1080/01635581.2020.1817955
- 11 Utsumi M, Inagaki M, Kitada K, Tokunaga N, Kondo M, Yunoki K, Sakurai Y, Hamano R, Miyasou H, Tsunemitsu Y, Otsuka S: Preoperative C-reactive protein-to-albumin ratio as a prognostic factor in biliary tract cancer: A systematic review and meta-analysis. *Medicine (Baltimore)* 102(22): e33656, 2023. DOI: 10.1097/MD.00000000000033656
- 12 Cho KM, Park H, Oh DY, Kim TY, Lee KH, Han SW, Im SA, Kim TY, Bang YJ: Neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and their dynamic changes during chemotherapy is useful to predict a more accurate prognosis of advanced biliary tract cancer. *Oncotarget* 8(2): 2329-2341, 2017. DOI: 10.18632/oncotarget.13731
- 13 Schemper M, Smith TL: A note on quantifying follow-up in studies of failure time. *Control Clin Trials* 17(4): 343-346, 1996. DOI: 10.1016/0197-2456(96)00075-X
- 14 Mantovani A, Allavena P, Sica A, Balkwill F: Cancer-related inflammation. *Nature* 454(7203): 436-444, 2008. DOI: 10.1038/nature07205
- 15 Kumari N, Dwarakanath BS, Das A, Bhatt AN: Role of interleukin-6 in cancer progression and therapeutic resistance. *Tumour Biol* 37(9): 11553-11572, 2016. DOI: 10.1007/s13277-016-5098-7
- 16 McMillan DC: Systemic inflammation, nutritional status and survival in patients with cancer. *Curr Opin Clin Nutr Metab Care* 12(3): 223-226, 2009. DOI: 10.1097/MCO.0b013e32832a7902
- 17 Cui H, Li Y, Li S, Liu G: Prognostic utility of preoperative inflammatory markers in patients with intrahepatic cholangiocarcinoma after hepatic resection: A systematic review and meta-analysis. *Cancer Med* 12(1): 99-110, 2023. DOI: 10.1002/cam4.4935
- 18 Tsilimigras DI, Moris D, Mehta R, Paredes AZ, Sahara K, Guglielmi A, Aldrighetti L, Weiss M, Bauer TW, Alexandrescu S, Poultsides GA, Maithel SK, Marques HP, Martel G, Pulitano C, Shen F, Soubrane O, Koerkamp BG, Endo I, Pawlik TM: The systemic immune-inflammation index predicts prognosis in intrahepatic cholangiocarcinoma: an international multi-institutional analysis. *HPB* 22(12): 1667-1674, 2020. DOI: 10.1016/j.hpb.2020.03.011
- 19 Zhang Z, Zhou Y, Hu K, Huang Y: Investigating effects of preoperative inflammatory biomarkers on predicting survival outcomes of intrahepatic cholangiocarcinoma after curative resection. *World J Surg Oncol* 18(1): 272, 2020. DOI: 10.1186/s12957-020-02053-w
- 20 Miyahara Y, Takashi S, Shimizu Y, Ohtsuka M: The prognostic impact of neutrophil-to-lymphocyte ratio (NLR) and lymphocyte-to-monocyte ratio (LMR) in patients with distal bile duct cancer. *World J Surg Oncol* 18(1): 78, 2020. DOI: 10.1186/s12957-020-01847-2
- 21 Mady M, Prasai K, Tella SH, Yadav S, Hallemeier CL, Rakshit S, Roberts L, Borad M, Mahipal A: Neutrophil to lymphocyte ratio as a prognostic marker in metastatic gallbladder cancer. *HPB* 22(10): 1490-1495, 2020. DOI: 10.1016/j.hpb.2020.02.002
- 22 Sun L, Jin Y, Hu W, Zhang M, Jin B, Xu H, Du S, Xu Y, Zhao H, Lu X, Sang X, Zhong S, Yang H, Mao Y: The impacts of systemic immune-inflammation index on clinical outcomes in gallbladder carcinoma. *Front Oncol* 10: 554521, 2020. DOI: 10.3389/fonc.2020.554521
- 23 Sun L, Hu W, Liu M, Chen Y, Jin B, Xu H, Du S, Xu Y, Zhao H, Lu X, Sang X, Zhong S, Yang H, Mao Y: High Systemic Inflammation Response Index (SIRI) indicates poor outcome in gallbladder cancer patients with surgical resection: a single institution

- experience in China. *Cancer Res Treat* 52(4): 1199-1210, 2020. DOI: 10.4143/crt.2020.303
- 24 Bao Y, Yang J, Duan Y, Chen Y, Chen W, Sun D: The C-reactive protein to albumin ratio is an excellent prognostic predictor for gallbladder cancer. *Biosci Trends* 14(6): 428-435, 2020. DOI: 10.5582/bst.2020.03326
 - 25 Peng X, Wang X, Hua L, Yang R: Prognostic and clinical value of the systemic immune-inflammation index in biliary tract cancer: a meta-analysis. *J Immunol Res* 2022: 6988489, 2022. DOI: 10.1155/2022/6988489
 - 26 Zhou Y, Liu Z, Cheng Y, Li J, Fu W: Prognostic value of the modified Glasgow prognostic score in biliary tract cancer patients: a systematic review and meta-analysis. *J Gastrointest Surg* 28(4): 559-565, 2024. DOI: 10.1016/j.gassur.2024.01.023
 - 27 Aoyama T, Maezawa Y, Hashimoto I, Kazama K, Uchiyama M, Hara K, Suematsu H, Cho H, Tamagawa A, Saito A, Yukawa N: The C-reactive protein to albumin ratio (CAR) is an independent prognostic factor for recurrence in patients with esophageal cancer after esophagectomy. *Anticancer Res* 45(8): 3365-3372, 2025. DOI: 10.21873/anticancer.17697
 - 28 Asaka S, Shimakawa T, Nishiguchi R, Yamaguchi K, Murayama M, Usui T, Yokomizo H, Shiozawa S: Preoperative and postoperative C-reactive protein to albumin ratio (CAR) as a prognostic marker for survival of esophageal squamous cell carcinoma patients after surgery. *Anticancer Res* 43(11): 5139-5147, 2023. DOI: 10.21873/anticancer.16714
 - 29 Harder J, Kummer O, Olschewski M, Otto F, Blum HE, Opitz O: Prognostic relevance of carbohydrate antigen 19-9 levels in patients with advanced biliary tract cancer. *Cancer Epidemiol Biomarkers Prev* 16(10): 2097-2100, 2007. DOI: 10.1158/1055-9965.EPI-07-0155
 - 30 Kawamata H, Yamashita K, Nakamura K, Katagiri H, Ishii K, Takahashi Y, Furuta K, Kumamoto Y, Watanabe M: Perineural invasion and preoperative serum CA19-9 as predictors of survival in biliary tract cancer. *Anticancer Res* 33(2): 583-594, 2013.
 - 31 Utsumi M, Kitada K, Tokunaga N, Kato T, Narusaka T, Hamano R, Miyasou H, Tsunemitsu Y, Otsuka S, Inagaki M: A combined prediction model for biliary tract cancer using the prognostic nutritional index and pathological findings: a single-center retrospective study. *BMC Gastroenterol* 21(1): 375, 2021. DOI: 10.1186/s12876-021-01957-5
 - 32 Yanagimoto H, Nakachi K, Ikeda M, Konishi M, Ogawa G, Sano Y, Nomura T, Yanagibashi H, Shibuya K, Shirakawa H, Takahashi A, Sakamoto Y, Makino I, Hatano E, Gotohda N, Ozaka M, Terashima T, Okusaka T, Furuse J, Ueno M: Risk factors for early relapse in patients with biliary tract cancers who underwent curative resection: An exploratory subgroup analysis of JCOG1202. *J Clin Oncol* 41(4_suppl): 541-541, 2023. DOI: 10.1200/JCO.2023.41.4_suppl.541
 - 33 Iyengar NM, Gucalp A, Dannenberg AJ, Hudis CA: Obesity and cancer mechanisms: tumor microenvironment and inflammation. *J Clin Oncol* 34(35): 4270-4276, 2016. DOI: 10.1200/JCO.2016.67.4283
 - 34 Oze I, Ito H, Koyanagi YN, Abe SK, Rahman MS, Islam MR, Saito E, Gupta PC, Sawada N, Tamakoshi A, Shu XO, Sakata R, Malekzadeh R, Tsuji I, Kim J, Nagata C, You SL, Park SK, Yuan JM, Shin MH, Kweon SS, Pednekar MS, Tsugane S, Kimura T, Gao YT, Cai H, Pourshams A, Lu Y, Kanemura S, Wada K, Sugawara Y, Chen CJ, Chen Y, Shin A, Wang R, Ahn YO, Shin MH, Ahsan H, Boffetta P, Chia KS, Qiao YL, Rothman N, Zheng W, Inoue M, Kang D, Matsuo K: Obesity is associated with biliary tract cancer mortality and incidence: A pooled analysis of 21 cohort studies in the Asia Cohort Consortium. *Int J Cancer* 154(7): 1174-1190, 2024. DOI: 10.1002/ijc.34794
 - 35 Kang J, Lee SH, Son JH, Lee JW, Choi YH, Choi JH, Paik WH, Ryu JK, Kim YT: Body mass index and weight change during initial period of chemotherapy affect survival outcome in advanced biliary tract cancer patients. *PLoS One* 13(4): e0195118, 2018. DOI: 10.1371/journal.pone.0195118
 - 36 Zhu J, Wang D, Liu C, Huang R, Gao F, Feng X, Lan T, Li H, Wu H: Development and validation of a new prognostic immune-inflammatory-nutritional score for predicting outcomes after curative resection for intrahepatic cholangiocarcinoma: A multicenter study. *Front Immunol* 14: 1165510, 2023. DOI: 10.3389/fimmu.2023.1165510