

Original Article

Effects of combining durvalumab with chemotherapy in individuals suffering from advanced biliary tract cancer: an investigation into the prognostic nutritional index, systemic immune-inflammation index and patient survival outcomes

Xiaobin Zhang¹, Shangbo Jin¹, Jiaqi Han², Xiaozhi Zhao²

¹Department of Hepatobiliary and Pancreatic Surgery, Baoji People's Hospital, No. 24 Xinhua Lane, Weibin District, Baoji 721000, Shaanxi, China; ²Department of Hepatobiliary Surgery, Baoji High-tech Hospital, No. 19 Hexie Road, Weibin District, Baoji 721000, Shaanxi, China

Received April 22, 2026; Accepted July 6, 2026; Epub September 15, 2026; Published September 30, 2026

Abstract: Objective: To evaluate the dynamic effects of durvalumab plus chemotherapy on the prognostic nutritional index (PNI) and systemic immune-inflammation index (SII) in patients with advanced biliary tract cancer (BTC), and to develop a nomogram for individualized prognostic assessment. Methods: Clinical data from 417 patients with advanced BTC treated between October 2019 and October 2022 were retrospectively analyzed. Patients were assigned to a training cohort (n=271) and a validation cohort (n=146) based on treatment timeline. The study group received durvalumab combined with gemcitabine/cisplatin, while the control group received gemcitabine/cisplatin monotherapy. Alterations in PNI and SII were compared between the two groups. Short-term antitumor response was assessed according to the Response Evaluation Criteria in Solid Tumors version 1.1. Survival analysis was performed using the Kaplan-Meier method and Cox proportional hazards regression. A prognostic nomogram was constructed and validated via bootstrap resampling. Results: Post-treatment PNI was significantly higher, whereas post-treatment SII was markedly lower in the study group (both $P < 0.001$). The study group achieved a higher objective response rate ($P = 0.003$), with more prominent clinical benefits observed in patients with low post-treatment SII. Median overall survival (OS) was substantially prolonged in the study group (21.00 vs 13.00 months; hazard ratio (HR)=0.555, 95% confidence interval (CI): 0.408-0.755, $P < 0.001$). Independent prognostic factors for OS included treatment regimen, tumor stage, ECOG performance status (PS), pretreatment PNI, pretreatment SII, and carbohydrate antigen 19-9. The established nomogram exhibited favorable discriminative ability and satisfactory internal calibration in the training cohort, with a bias-corrected Harrell's concordance index (C-index) of 0.758 and a calibration slope of 0.917. In the validation cohort, acceptable discrimination was retained (C-index=0.711), whereas calibration efficacy declined, with a calibration slope of 0.677, suggesting overestimation of survival probability among high-risk patients. Conclusion: Compared with chemotherapy alone, the combined therapy ameliorated patients' nutritional status, mitigated systemic inflammatory response, and prolonged survival. The nomogram yielded acceptable discriminative power and favorable internal calibration but achieved suboptimal external calibration. Further model recalibration and prospective multicenter validation are warranted prior to its widespread clinical application.

Keywords: Biliary tract cancer, durvalumab, prognostic nutritional index, systemic immune-inflammation index, nomogram, overall survival, prediction model

Introduction

Biliary tract cancer (BTC) refers to a heterogeneous group of malignancies derived from biliary epithelial and gallbladder mucosal cells, and cholangiocarcinoma is subclassified into intrahepatic and extrahepatic subtypes [1]. The

global incidence of BTC has risen steadily in recent years, with disproportionately higher incidence and mortality rates in Asia relative to Western countries [2]. Due to non-specific early clinical manifestations, most patients are diagnosed with locally advanced or metastatic BTC, and less than 30% of cases are eligible for

curative resection. For advanced BTC, the median overall survival (OS) remains approximately 12 months, and the 5-year survival rate is below 10%, rendering BTC one of the most lethal gastrointestinal malignancies [3].

Gemcitabine plus cisplatin has long served as the standard first-line systemic therapy for advanced BTC. Nevertheless, no breakthroughs in systemic treatment emerged for nearly a decade after the regimen was validated [4]. Given its limited objective response rate (ORR) and dismal long-term survival outcomes, there is an urgent need to develop more efficacious therapeutic strategies.

Immune checkpoint inhibitors (ICIs) have revolutionized the therapeutic landscape of multiple solid tumors. Durvalumab, a programmed death-ligand 1 (PD-L1) monoclonal antibody, blocks the programmed death-1 (PD-1)/PD-L1 signaling axis, reverses T-cell exhaustion within the tumor microenvironment, and restores endogenous antitumor immune responses [5]. Yu et al. [6] delineated the immune microenvironment characteristics of cholangiocarcinoma, clarified the formation mechanism of an immunosuppressive tumor milieu, and highlighted the necessity of blocking the PD-1/PD-L1 pathway to reactivate effector T-cell function. The TOPAZ-1 trial was the first phase III randomized controlled trial validating the survival benefit of first-line ICI-combined chemotherapy for advanced BTC. Oh et al. [4, 7] demonstrated that durvalumab combined with gemcitabine/cisplatin yielded superior OS and progression-free survival (PFS) versus chemotherapy alone, establishing this combination regimen as a mainstream first-line treatment option. However, participants enrolled in clinical trials are often highly screened and do not represent real-world patient populations. Clinically, advanced BTC patients exhibit heterogeneous performance status, comorbidity burdens and tumor biological characteristics. Rimini et al. [8, 9] verified the efficacy of durvalumab-based combination therapy in multicenter real-world cohorts, emphasizing the clinical value of real-world data in identifying prognostic factors for this regimen.

Nutritional status and systemic inflammation jointly modulate tumor progression, treatment tolerance and therapeutic response in cancer patients. Prognostic nutritional index (PNI), cal-

culated based on serum albumin and peripheral lymphocyte counts, reflects systemic nutritional and basal immune status. Utsumi et al. [10] verified that PNI was an independent prognostic indicator for resected BTC, and a combined prognostic model incorporating PNI outperformed pathological staging alone. Yang et al. [11] reported that elevated pretreatment PNI independently predicted prolonged PFS and OS in metastatic BTC patients receiving ICIs, indicating that PNI could predict not only chemotherapy tolerance but also immunotherapeutic responsiveness. Systemic immune-inflammation index (SII), derived from peripheral platelet, neutrophil and lymphocyte counts, quantifies the crosstalk between systemic inflammation and host immunity. Li et al. [12] validated SII as an independent OS predictor after radical resection of intrahepatic cholangiocarcinoma. Huang et al. [13] and Zeng et al. [14] found that SII and PNI served as independent prognostic biomarkers for locally advanced intrahepatic cholangiocarcinoma patients undergoing R0 resection, and combined application of the two indices optimized patient risk stratification. Despite accumulating relevant evidence, real-world data regarding dynamic peri-treatment alterations in PNI and SII, as well as their correlation with durvalumab-combined chemotherapy efficacy in BTC treatment, remain scarce. Liu et al. [15] explored the predictive value of the combined SII-PNI score for cholangiocarcinoma PFS, yet comprehensive prognostic analyses integrating survival endpoints are still lacking.

Multiple clinical covariates determine advanced BTC prognosis, including treatment regimen, tumor stage, performance status, tumor subtype and serum tumor marker levels. Most existing prognostic tools rely on single biomarkers or conventional tumor staging systems, resulting in insufficient accuracy for individualized prognostic evaluation. As a visualized multivariable regression-based predictive tool, the prognostic nomogram integrates multiple independent prognostic factors into an intuitive scoring system, and has achieved satisfactory predictive performance across various malignancies. Imaoka et al. [16] constructed and validated a survival nomogram for chemotherapy-treated advanced BTC patients based on albumin and carbohydrate antigen 19-9 (CA19-9). Persano et al. [17] developed the MAGIC-D

index, which integrates inflammation- and nutrition-related indicators including neutrophil-to-lymphocyte ratio and albumin for clinical risk stratification. Collectively, a prognostic model integrating therapeutic regimens, nutritional and inflammatory biomarkers is expected to refine individualized prognostic prediction for advanced BTC.

Accordingly, we conducted a real-world retrospective cohort study enrolling advanced BTC patients administered with durvalumab-combined chemotherapy or single-agent chemotherapy. The overall cohort was split into training and validation cohorts chronologically. This study aimed to address three research objectives: (1) compare peri-treatment dynamic alterations in PNI and SII between the two treatment groups; (2) evaluate the predictive efficacy of PNI and SII for short-term treatment response and long-term OS; (3) construct and externally validate a novel nomogram integrating treatment regimen, tumor stage, Eastern Cooperative Oncology Group performance status (ECOG PS), PNI, SII and CA19-9, so as to facilitate individualized prognostic assessment and clinical decision-making for advanced BTC.

Materials and methods

Sample size calculation

Sample size was estimated using Schoenfeld's formula. Based on the hazard ratio reported in the TOPAZ-1 trial (hazard ratio (HR)=0.80, 95% confidence interval (CI): 0.66-0.97) [7], with a two-sided α of 0.05 ($Z_{\alpha/2}=1.960$) and statistical power of 80% ($Z_{\beta}=0.842$), the required endpoint event number was calculated as $d = (Z_{\alpha/2} + Z_{\beta})^2 / (\ln(HR))^2$, yielding 158 survival events. Assuming an approximate 70% event rate among advanced BTC patients, a minimum of 113 patients per group (226 cases in total) was required. A total of 417 patients were enrolled in this study (215 in the study group and 202 in the control group), which exceeded the sample size required to achieve over 90% statistical power (302 cases), confirming adequate statistical robustness of the cohort.

Study design and patient source

This was a single-center retrospective observational cohort study. Clinical data were retrieved from patients diagnosed with advanced BTC

who received standardized treatment at Baoji People's Hospital between October 2019 and October 2022. Patients in the study group received durvalumab (1,500 mg intravenously every 3 weeks, up to 8 cycles) combined with gemcitabine (1,000 mg/m²) and cisplatin (25 mg/m²). Upon completion of 8 combination cycles, eligible patients received durvalumab maintenance monotherapy (1,500 mg intravenously every 4 weeks) until disease progression or occurrence of intolerable adverse events. Patients in the control group received gemcitabine plus cisplatin chemotherapy without additional immunotherapy. The chemioimmunotherapy regimen strictly followed the published TOPAZ-1 protocol [7], and the control group adopted the standard first-line chemotherapy regimen recommended contemporarily. This study was approved by the Ethics Committee of Baoji People's Hospital.

Inclusion and exclusion criteria

Inclusion criteria: (1) histopathologically confirmed advanced BTC, including intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma and gallbladder carcinoma; (2) stage IIIB-IVB unresectable, locally advanced or metastatic disease; (3) ECOG PS score of 0-1 [18]; (4) at least one radiologically measurable lesion per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) criteria; (5) intact major organ function and tolerance to combined antitumor therapy; (6) complete baseline and follow-up clinical data.

Exclusion criteria: (1) concurrent or prior history of other primary malignant tumors; (2) previous systemic antitumor treatment for advanced BTC; (3) active uncontrolled autoimmune diseases or chronic inflammatory disorders; (4) ampullary carcinoma; (5) missing core clinical or laboratory data required for subsequent analysis.

Clinical data collection

Baseline and peri-treatment clinical data of all eligible patients were collected retrospectively: (1) demographic characteristics: sex, age, body mass index (BMI); (2) comorbidity burden: Charlson Comorbidity Index (CCI), with CCI ≤ 2 defined as low comorbidity and CCI > 2 as high comorbidity; (3) tumor-related indicators: pathological subtype, tumor stage (IIIB-IVB), distant

metastasis status, maximum tumor diameter; (4) treatment-related information: therapeutic grouping, prior biliary surgery history, preoperative or peri-treatment biliary drainage status; (5) hepatic reserve function: Child-Pugh classification (Grade A: 5-6 points; Grade B: 7-9 points); (6) serial laboratory parameters: pre-treatment and post-treatment CA19-9, serum albumin (ALB), peripheral lymphocyte, neutrophil and platelet counts; (7) composite immunonutritional indices calculated via validated formulas: $PNI = 10 \times ALB \text{ (g/dL)} + 0.005 \times \text{lymphocyte count } (/mm^3)$; $SII = (\text{platelet count } (\times 10^9/L) \times \text{neutrophil count } (\times 10^9/L)) / \text{lymphocyte count } (\times 10^9/L)$.

Measurement methods

Fasting peripheral venous blood samples were collected 1 to 3 days before treatment initiation and at the first efficacy evaluation (6 to 8 weeks after treatment commencement). All laboratory tests were completed by the hospital clinical laboratory department. Peripheral blood cell counts were detected using an automated hematology analyzer (Sysmex XN-9000, Japan) with matched supporting reagents. Serum albumin (ALB) level was measured via the bromocresol green method using an automatic biochemical analyzer (HITACHI 7600, Japan). Serum CA19-9 concentration was quantified using commercial enzyme-linked immunosorbent assay kits (Shanghai Enzyme-linked Biotechnology Co., Ltd.) at a detection wavelength of 450 nm, and all operations complied with manufacturer specifications. For radiological evaluation, contrast-enhanced computed tomography or abdominal magnetic resonance imaging was performed before treatment and every two treatment cycles thereafter. Two radiologists with over five years of abdominal imaging diagnostic experience independently measured the maximum tumor diameter, and the average value was adopted for statistical analysis; discrepancies were resolved through consultation with a senior attending radiologist.

Functional scoring

ECOG PS was assessed by attending oncologists at enrollment, with scores categorized as 0 (fully active without daily activity restriction) or 1 (restricted in strenuous physical activity but ambulatory) [18]. Child-Pugh classification was evaluated by specialized hepatologists

based on five indicators: ascites status, hepatic encephalopathy, serum bilirubin, serum albumin and prolonged prothrombin time. Child-Pugh Grade A (5-6 points) indicated favorable hepatic reserve, while Grade B (7-9 points) indicated moderately impaired hepatic reserve [19].

Study outcomes

The primary endpoint was OS, defined as the interval from treatment initiation to all-cause death or the last valid follow-up visit, calculated in months. Continuous follow-up was conducted until October 2025 via outpatient re-examination and standardized telephone follow-up. Secondary endpoints included: (1) short-term antitumor response assessed per RECIST 1.1, including complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD); ORR was defined as the proportion of patients achieving CR+PR, and disease control rate (DCR) as CR+PR+SD; (2) peri-treatment dynamic alterations in PNI and SII; (3) predictive model performance validated via Harrell's concordance index (C-index), bias-corrected calibration slope, inverse probability of censoring weighting (IPCW) Brier score and decision curve analysis (DCA).

Statistical analysis

All statistical analyses were performed using R software (version 4.5.2) and SPSS (version 28.0). A two-tailed $P < 0.05$ was considered statistically significant. The Shapiro-Wilk test was adopted to verify the normality of continuous variables. Normally distributed data were presented as mean $\pm$ standard deviation, while non-normal data were expressed as median (interquartile range, P25-P75). Categorical variables were summarized as case numbers and percentages. Between-group comparisons of continuous variables adopted the independent-samples t-test or Mann-Whitney U test as appropriate; paired t-test or Wilcoxon signed-rank test was used for intra-group peri-treatment comparison. Categorical variable comparisons were conducted via the chi-square test or Fisher's exact test when applicable.

Pearson correlation analysis was performed to evaluate pairwise correlations among candidate prognostic variables prior to multivariable regression analysis. Survival curves were plot-

ted via the Kaplan-Meier method, and inter-group survival differences were compared using the log-rank test. Univariable and multivariable Cox proportional hazards regression analyses were sequentially conducted to screen independent prognostic factors. The optimal cut-off values of pretreatment and post-treatment PNI and SII were determined via maximally selected log-rank statistics.

The proportional hazards (PH) assumption of Cox regression models was verified using Schoenfeld residuals. For variables violating the PH assumption, extended Cox models with time-varying coefficients were established by introducing log(time) interaction terms. To further quantify time-dependent treatment effects, an auxiliary sensitivity analysis was conducted using a flexible time-varying coefficient Cox model, wherein the interaction between treatment regimen and log(time) was fitted with natural cubic splines. A stratified Cox model with tumor stage as the stratification factor was additionally constructed to validate the robustness of treatment-related survival benefits.

Based on the finalized multivariable Cox model, a prognostic nomogram was established using the rms package to predict 1-year and 2-year OS probabilities. Model predictive performance was validated from three dimensions: (1) discriminative ability quantified by Harrell's C-index, with internal validation performed via 1,000-time bootstrap resampling to report apparent and bias-corrected C-indexes; (2) calibration capability evaluated by calibration plots and calibration slopes; the training cohort adopted bias-corrected slopes calculated via the rms::validate function, while the validation cohort calculated calibration slopes by fitting a Cox model with linear predictors as covariates; IPCW Brier scores were supplemented to quantify overall predictive error; (3) clinical practicality verified by time-dependent receiver operating characteristic (td-ROC) curves and corresponding area under the curve (AUC) values of 1-year and 2-year OS, as well as DCA across different threshold probabilities.

Results

Baseline characteristics of the training cohort

No significant inter-group differences were observed in baseline demographics, tumor

characteristics and laboratory indicators, including sex ($P=0.760$), age ($P=0.983$), BMI ($P=0.538$), CCI ($P=0.809$), tumor subtype ($P=0.433$), tumor stage ($P=0.803$), ECOG PS ($P=0.288$), distant metastasis ($P=0.898$), prior surgical history ($P=0.546$), biliary drainage status ($P=0.670$), Child-Pugh grade ($P=0.487$), maximum tumor diameter ($P=0.311$), serum CA19-9 ($P=0.093$), pretreatment PNI ($P=0.617$), or pretreatment SII ($P=0.992$), confirming balanced baseline characteristics between the two groups (**Table 1**).

Changes in PNI and SII before and after treatment

Consistent with baseline cohort balance, pretreatment PNI ($P=0.617$) and SII ($P=0.992$) were comparable between the two groups. Both groups presented significantly elevated post-treatment PNI and decreased post-treatment SII relative to baseline (all $P<0.001$). Post-treatment inter-group comparison demonstrated that the study group yielded remarkably higher PNI and lower SII than the control group (both $P<0.001$), indicating that durvalumab-combined chemotherapy exerted superior efficacy in improving host nutritional status and mitigating systemic inflammatory response (**Figure 1**).

Comparison of short-term response between groups

In the training cohort, the overall distribution of radiological treatment response differed significantly between the two groups ($P=0.018$). The study group achieved a markedly higher ORR ($P=0.003$), whereas DCR showed no statistical difference ($P=0.092$) (**Figure 2**).

Subgroup analysis of short-term response by post-treatment PNI and SII

The optimal post-treatment cut-off values calculated via maximally selected log-rank statistics were 46.89 for PNI and 778.81 for SII. Stratified by post-treatment PNI, neither low-PNI nor high-PNI subgroups exhibited significant inter-group differences in ORR ($P=0.123$ and $P=0.050$, respectively) or DCR ($P=0.750$ and $P=0.079$, respectively), suggesting that post-treatment PNI could not modify inter-group disparities in short-term therapeutic response.

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Table 1. Comparison of baseline clinical characteristics between the study group and the control group in the training cohort

Variable	Total	Study group (n=141)	Control group (n=130)	Statistic	P value
Sex				0.093	0.760
Male	161 (59.41%)	85 (60.28%)	76 (58.46%)		
Female	110 (40.59%)	56 (39.72%)	54 (41.54%)		
Age				<0.001	0.983
<65 years	152 (56.09%)	79 (56.03%)	73 (56.15%)		
≥65 years	119 (43.91%)	62 (43.97%)	57 (43.85%)		
BMI				0.38	0.538
<24 kg/m ²	170 (62.73%)	86 (60.99%)	84 (64.62%)		
≥24 kg/m ²	101 (37.27%)	55 (39.01%)	46 (35.38%)		
CCI				0.058	0.809
Low comorbidity (CCI ≤2)	175 (64.58%)	92 (65.25%)	83 (63.85%)		
High comorbidity (CCI >2)	96 (35.42%)	49 (34.75%)	47 (36.15%)		
Tumor type				1.673	0.433
Intrahepatic cholangiocarcinoma	125 (46.13%)	70 (49.65%)	55 (42.31%)		
Extrahepatic cholangiocarcinoma	83 (30.63%)	39 (27.66%)	44 (33.85%)		
Gallbladder cancer	63 (23.25%)	32 (22.70%)	31 (23.85%)		
Tumor stage				0.438	0.803
Stage IIIB	54 (19.93%)	26 (18.44%)	28 (21.54%)		
Stage IVA	112 (41.33%)	60 (42.55%)	52 (40.00%)		
Stage IVB	105 (38.75%)	55 (39.01%)	50 (38.46%)		
ECOG PS				1.127	0.288
0	141 (52.03%)	69 (48.94%)	72 (55.38%)		
1	130 (47.97%)	72 (51.06%)	58 (44.62%)		
Distant metastasis				0.017	0.898
Yes	99 (36.53%)	51 (36.17%)	48 (36.92%)		
No	172 (63.47%)	90 (63.83%)	82 (63.08%)		
Previous surgery				0.364	0.546
Yes	84 (31.00%)	46 (32.62%)	38 (29.23%)		
No	187 (69.00%)	95 (67.38%)	92 (70.77%)		
Biliary drainage				0.182	0.670
Yes	112 (41.33%)	60 (42.55%)	52 (40.00%)		
No	159 (58.67%)	81 (57.45%)	78 (60.00%)		
Child-Pugh class				0.483	0.487
Class A	227 (83.76%)	116 (82.27%)	111 (85.38%)		
Class B	44 (16.24%)	25 (17.73%)	19 (14.62%)		
Maximum tumor diameter	6.06 [4.02, 8.18]	6.51 [4.07, 8.48]	5.67 [3.91, 7.95]	1.014	0.311
CA19-9	405.68 ± 104.86	395.39 ± 103.05	416.84 ± 106.07	1.688	0.093
Pretreatment PNI	42.44 ± 5.27	42.59 ± 5.00	42.27 ± 5.56	-0.501	0.617
Pretreatment SII	856.71 ± 118.46	856.78 ± 119.63	856.63 ± 117.65	-0.011	0.992

Note: BMI, Body Mass Index; CCI, Charlson Comorbidity Index; ECOG PS, Eastern Cooperative Oncology Group performance status; CA19-9, carbohydrate antigen 19-9; PNI, Prognostic Nutritional Index; SII, Systemic Immune-Inflammation Index.

Stratified by post-treatment SII, patients in the low-SII subgroup obtained prominently higher ORR in the study group (P=0.003), with equivalent

DCR between groups (P=0.597). By contrast, no significant inter-group differences in ORR or DCR were observed in the high-SII sub-

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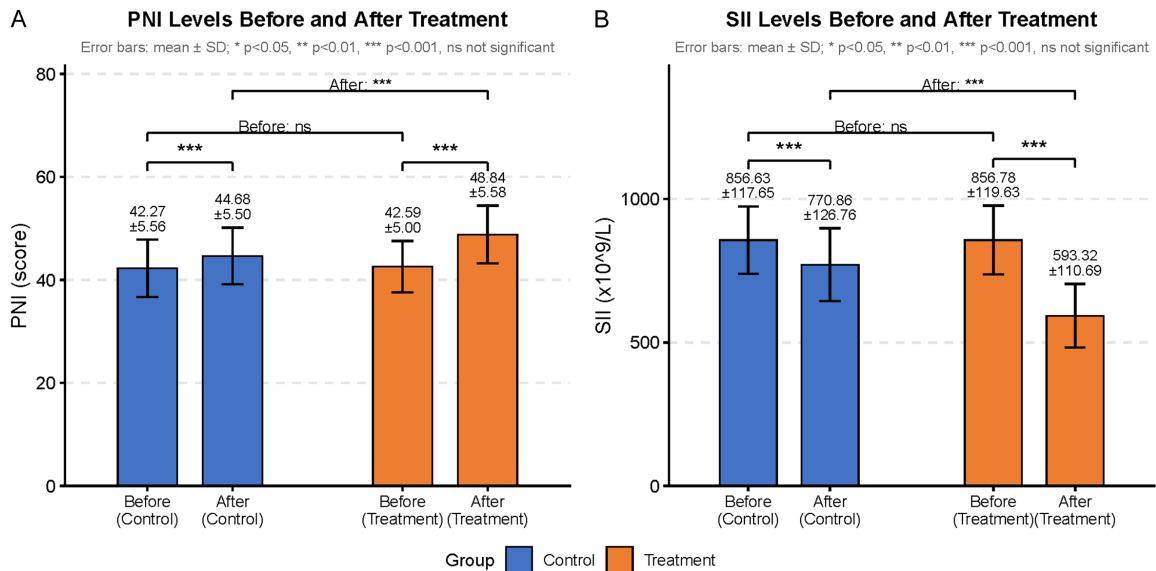


Figure 1. Comparison of PNI and SII levels before and after treatment between the study group and the control group in the training cohort. A: Within-group and between-group comparisons of PNI levels before and after treatment in the study group and the control group in the training cohort. B: Within-group and between-group comparisons of SII levels before and after treatment in the study group and the control group in the training cohort. Note: PNI, prognostic nutritional index; SII, systemic immune-inflammation index; SD, standard deviation. ns $P > 0.05$, *** $P < 0.001$.

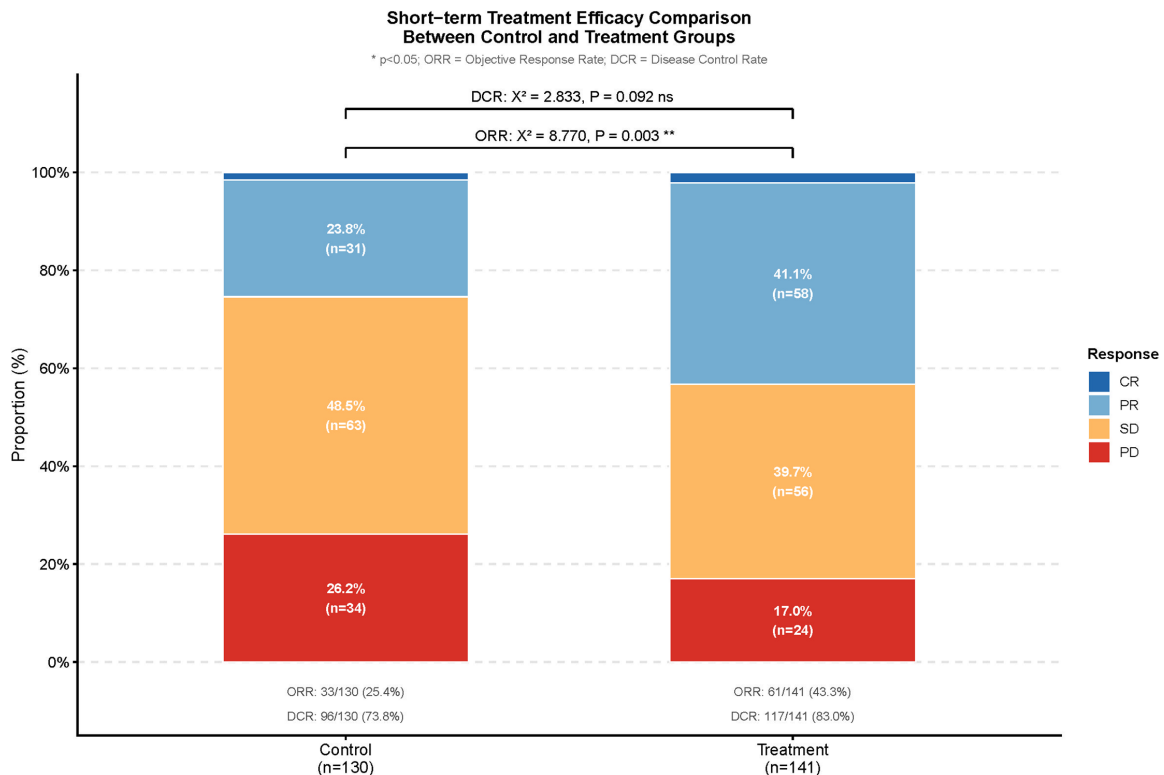


Figure 2. Comparison of short-term response distribution between the study group and the control group in the training cohort. Note: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate. ns $P > 0.05$, ** $P < 0.01$.

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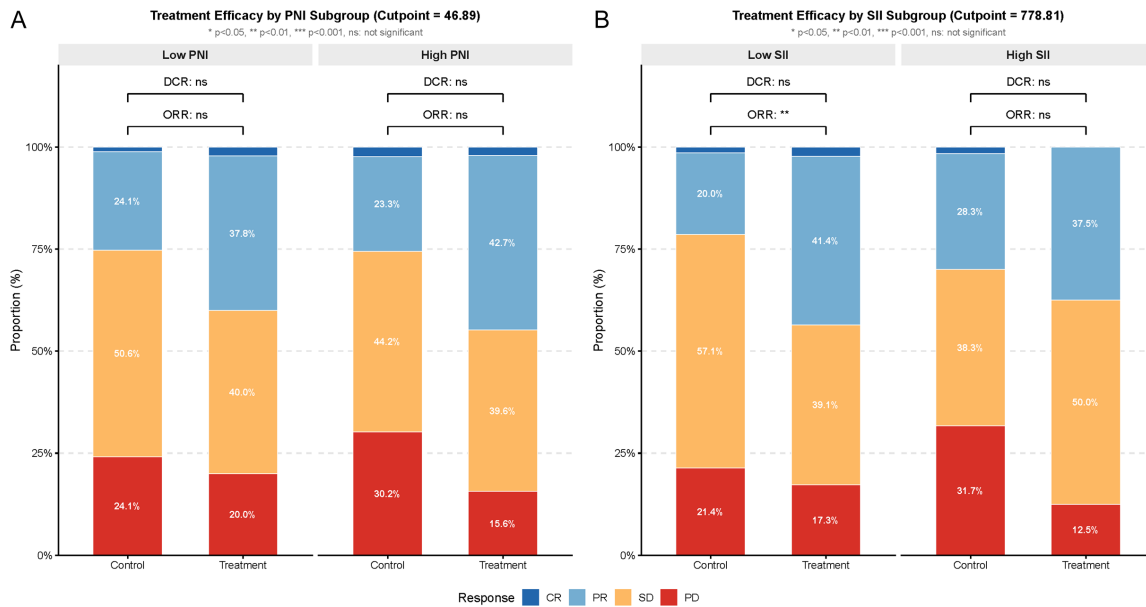


Figure 3. Comparison of short-term response distribution by post-treatment PNI and SII subgroups in the training cohort. A: Comparison of short-term response distribution, ORR, and DCR between the study group and the control group in the low-PNI and high-PNI subgroups, stratified by the post-treatment PNI cutoff value (46.89). B: Comparison of short-term response distribution, ORR, and DCR between the study group and the control group in the low-SII and high-SII subgroups, stratified by the post-treatment SII cutoff value (778.81). Note: PNI, prognostic nutritional index; SII, systemic immune-inflammation index; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate. ns $P>0.05$, ** $P<0.01$.

group ($P=0.695$ and $P=0.421$, respectively). These findings indicated that advanced BTC patients with low post-treatment SII could obtain more prominent objective tumor regression benefits from durvalumab-combined chemotherapy (Figure 3).

Overall survival in the training cohort

Among 271 patients in the training cohort, the median OS was 17.00 months (95% CI: 15.00-20.00), and 177 deaths occurred during follow-up (Figure 4A). The study group presented substantially prolonged median OS versus the control group (21.00 vs 13.00 months; log-rank $P<0.001$). Multivariable Cox regression further verified that durvalumab-combined chemotherapy independently reduced all-cause mortality risk (HR=0.555, 95% CI: 0.408-0.755), confirming robust survival superiority of the combination regimen (Figure 4B).

Correlation analysis among candidate variables

Pairwise correlation analysis of variables enrolled in univariable Cox regression identified five statistically significant correlations.

Treatment regimen was positively correlated with post-treatment PNI ($P<0.001$) and negatively correlated with post-treatment SII ($P<0.001$), corroborating enhanced nutritional improvement and inflammatory suppression in the chemoimmunotherapy group. Tumor stage was strongly correlated with distant metastasis ($P<0.001$), as advanced tumor stages were accompanied by higher distant metastasis risks. Maximum tumor diameter was negatively correlated with tumor subtype ($P<0.001$), which was attributed to inherent anatomical discrepancies in lesion expansion patterns across BTC subtypes. Post-treatment PNI was inversely correlated with post-treatment SII ($P=0.003$). In addition, post-treatment SII showed weak positive correlation with CA19-9 ($P=0.023$) and weak negative correlation with age ($P=0.044$). No significant correlation was detected among the remaining variables (all $P>0.05$), verifying negligible collinearity for subsequent multivariable regression (Figure 5).

Univariable Cox regression and multicollinearity assessment

Univariable Cox regression incorporating 15 candidate variables in the training cohort indi-

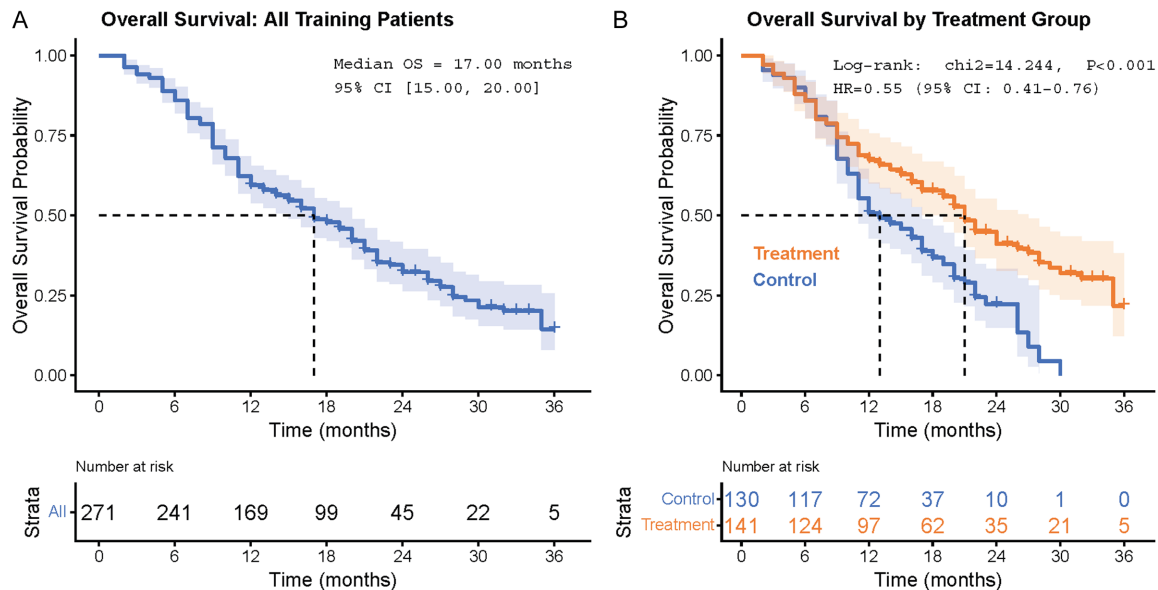


Figure 4. Overall survival curves in the training cohort and survival comparison between the study group and the control group. A: Kaplan-Meier curve for overall survival in the entire training cohort. The shaded area represents the 95% confidence interval. B: Kaplan-Meier comparison of overall survival between the study group and the control group in the training cohort. The shaded area represents the 95% confidence interval. Note: OS, overall survival; HR, hazard ratio; CI, confidence interval.

cated that tumor stage (IVA: $P=0.010$; IVB: $P<0.001$), ECOG PS ($P=0.005$), CA19-9 ($P<0.001$), pretreatment SII ($P<0.001$), pretreatment PNI ($P<0.001$), treatment regimen ($P<0.001$) and distant metastasis ($P<0.001$) were significantly associated with OS. Advanced tumor stage, poor ECOG PS, elevated CA19-9 and high pretreatment SII correlated with increased mortality risk; conversely, elevated pretreatment PNI, durvalumab-combined chemotherapy and absence of distant metastasis were protective prognostic factors. Age ($P=0.055$), tumor subtype ($P=0.399$; $P=0.725$), biliary drainage ($P=0.364$), prior surgery ($P=0.584$), maximum tumor diameter ($P=0.824$), CCI ($P=0.743$), sex ($P=0.478$) and BMI ($P=0.468$) exerted no significant prognostic effects (Figure 6A).

Variables with $P<0.1$ in univariable analysis were enrolled into the multivariable Cox model. Multicollinearity diagnosis revealed that except for distant metastasis (adjusted generalized variance inflation factor (GVIF)=3.1201, moderate collinearity), all remaining variables including treatment regimen, tumor stage, ECOG PS, pretreatment PNI, pretreatment SII and CA19-9 yielded adjusted GVIF values below 2.5. The overall collinearity was acceptable; therefore,

the six low-collinearity variables were finalized for multivariable Cox regression modeling (Figure 6B).

Proportional hazards assumption

Schoenfeld residuals were adopted to examine the PH assumption. The global test indicated violation of the overall model PH assumption ($P<0.001$). At the variable level, treatment regimen ($P=0.007$), tumor stage ($P=0.025$) and pretreatment SII ($P=0.011$) violated the PH assumption, implying potential time-varying prognostic effects. ECOG PS ($P=0.120$), pretreatment PNI ($P=0.098$) and CA19-9 ($P=0.747$) complied with the PH assumption (Figure 7).

Time-varying coefficient Cox model and stratified Cox sensitivity analysis

An extended time-varying Cox model was constructed via the `tt()` function by introducing variable $\times \log(\text{time})$ interaction terms. The interaction between treatment regimen and $\log(\text{time})$ reached statistical significance ($P=0.021$), confirming time-dependent antitumor efficacy of durvalumab-combined chemotherapy. The time-varying HRs of combination therapy versus single chemotherapy were 0.893, 0.612,

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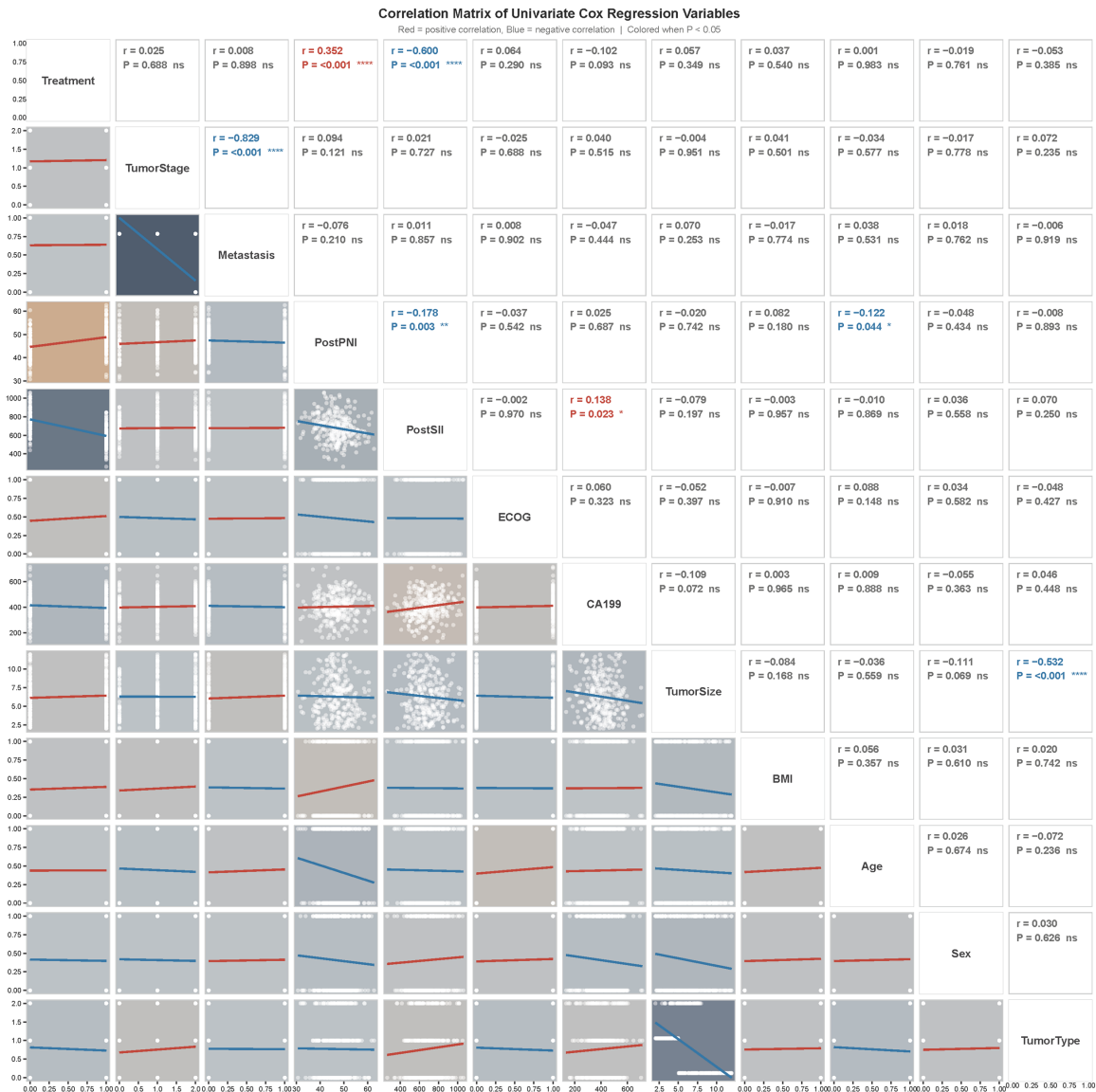


Figure 5. Correlation matrix of variables included in the univariable Cox regression analysis in the training cohort. Note: PNI, prognostic nutritional index; SII, systemic immune-inflammation index; CA19-9, carbohydrate antigen 19-9; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group performance status; ns, not significant.

0.419, 0.336 and 0.287 at 3, 6, 12, 18 and 24 months after treatment initiation, respectively, suggesting incremental survival benefits of chemioimmunotherapy with prolonged follow-up. For tumor stage, time-varying interaction was significant for stage IVB ($P=0.020$), and stage IVA presented marginal statistical significance ($P=0.099$), indicating attenuated prognostic predictive efficacy of tumor stage over time (**Figure 8A**).

An auxiliary flexible time-varying Cox model embedded with natural cubic splines was

established to further verify time-dependent treatment effects, and this model generated consistent HR trends: 0.840, 0.799, 0.370, 0.281 and 0.320 at 3, 6, 12, 18 and 24 months, respectively. Likelihood ratio test between the spline-based time-varying model and fixed-effect stratified Cox model showed marginal and non-significant improvement in model fitting ($\chi^2=6.541$, $df=3$, $P=0.088$). Accordingly, although time-varying analyses consistently demonstrated amplified chemioimmunotherapy benefits in late follow-up, this conclusion was interpreted as hypothesis-generating evidence

Nutrition and inflammation in biliary cancer survival

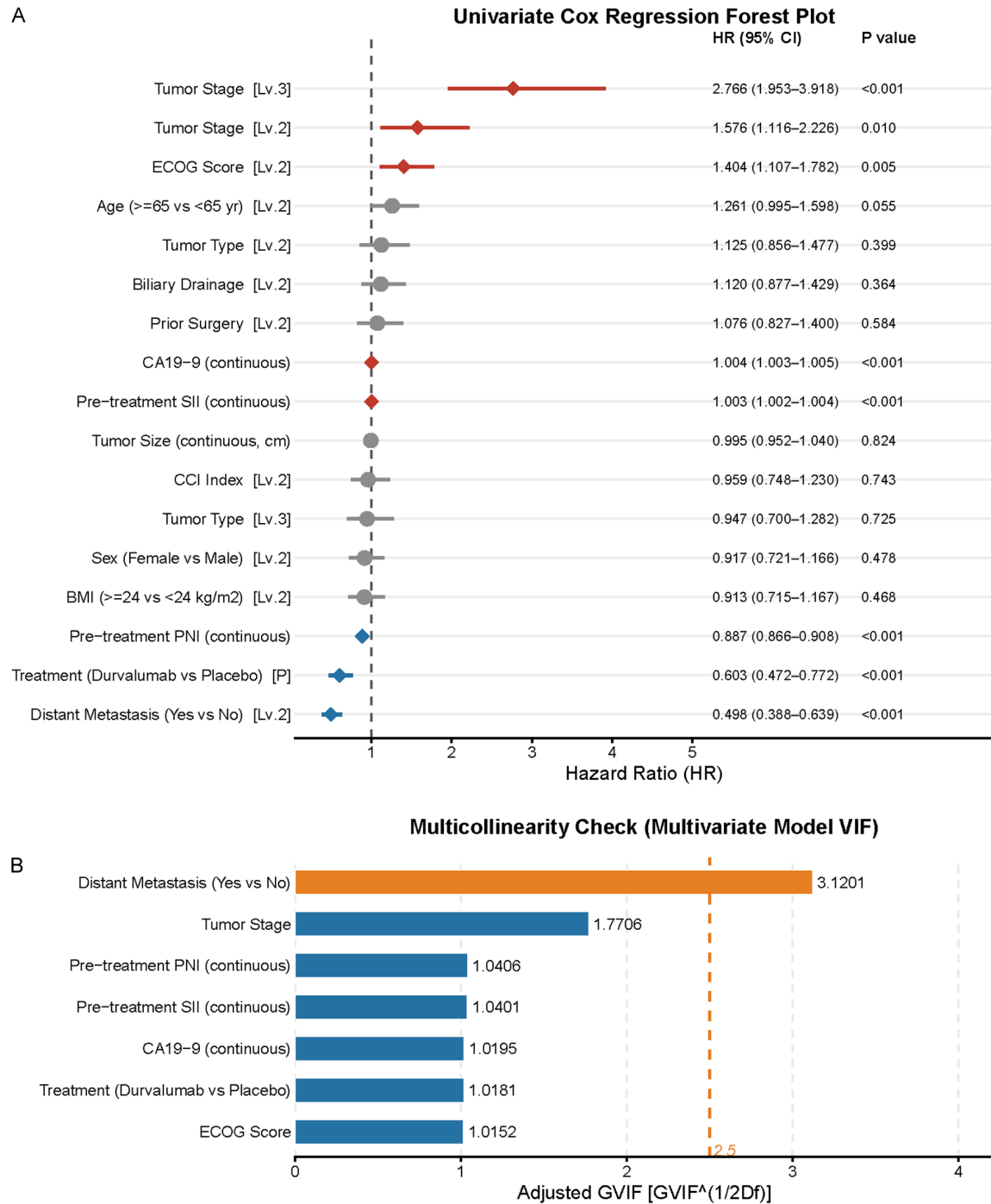


Figure 6. Forest plot of univariable Cox regression and multicollinearity assessment of the multivariable model in the training cohort. A: Forest plot of univariable Cox regression for candidate variables in the training cohort, showing hazard ratios and 95% confidence intervals. Diamond symbols indicate statistically significant associations, whereas circular symbols indicate nonsignificant associations. B: Multivariable Cox regression model including variables with $P < 0.1$ in univariable analysis. Adjusted generalized variance inflation factors were used to assess multicollinearity among variables. Blue indicates normal (<2.5), orange indicates moderate collinearity ($2.5\text{--}5.0$), and red indicates high collinearity (>5.0). Note: HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group performance status; CA19-9, carbohydrate antigen 19-9; PNI, prognostic nutritional index; SII, systemic immune-inflammation index; BMI, body mass index; CCI, Charlson Comorbidity Index; GVIF, generalized variance inflation factor.

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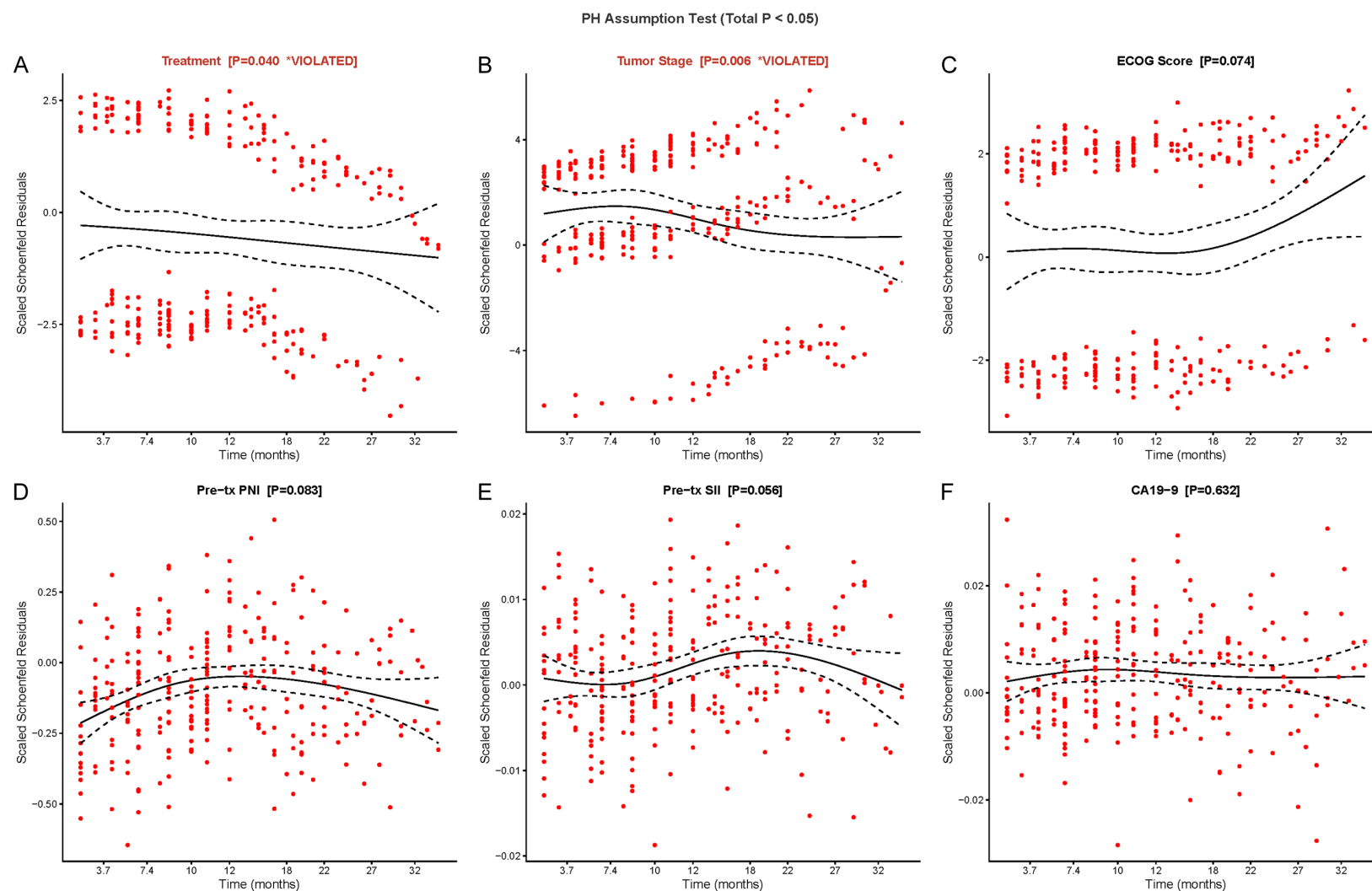


Figure 7. Schoenfeld residual tests for the proportional hazards assumption in the multivariable Cox regression model. A: Distribution of Schoenfeld residuals over time for treatment regimen (PH assumption violated, $P=0.040$). B: Distribution of Schoenfeld residuals over time for tumor stage (PH assumption violated, $P=0.006$). C: Distribution of Schoenfeld residuals over time for ECOG PS ($P=0.074$). D: Distribution of Schoenfeld residuals over time for pretreatment PNI ($P=0.083$). E: Distribution of Schoenfeld residuals over time for pretreatment SII ($P=0.056$). F: Distribution of Schoenfeld residuals over time for CA19-9 ($P=0.632$). Note: PH, proportional hazards; PNI, prognostic nutritional index; SII, systemic immune-inflammation index; CA19-9, carbohydrate antigen 19-9; ECOG, Eastern Cooperative Oncology Group performance status.

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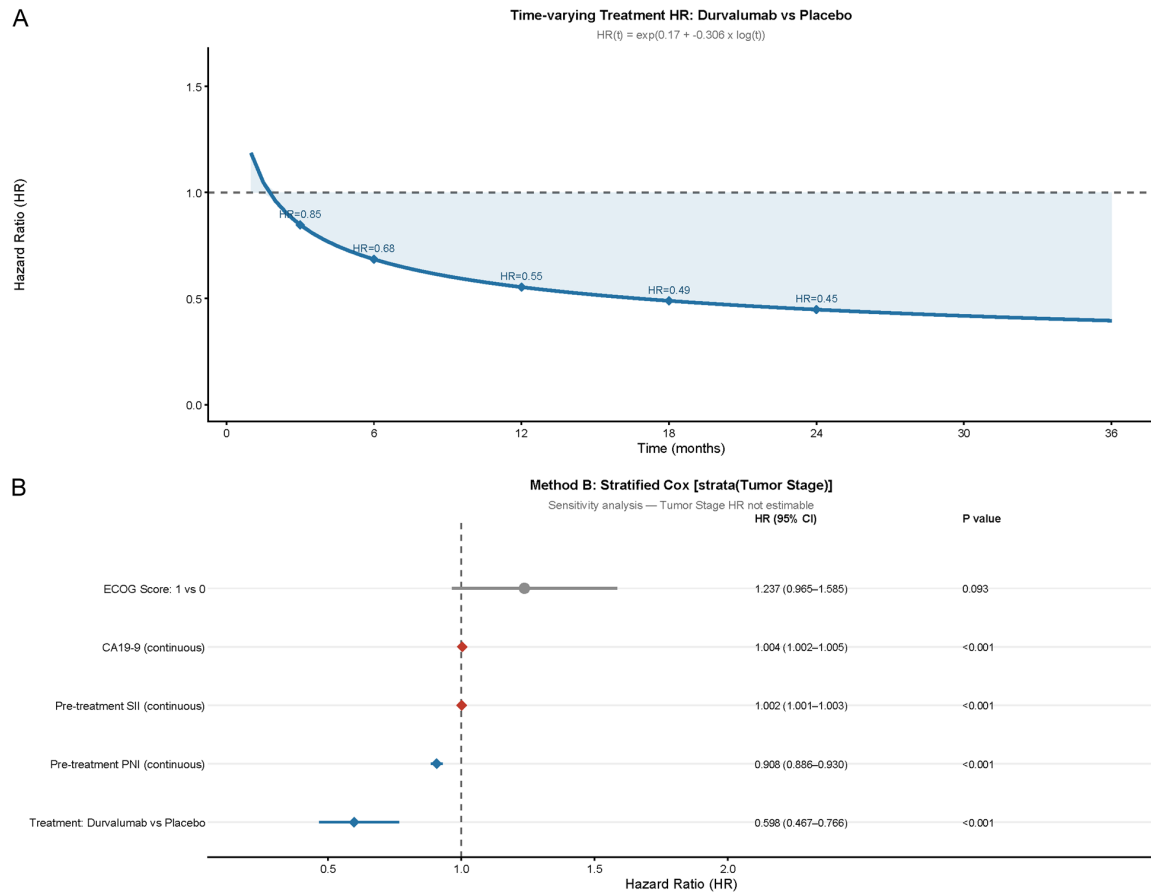


Figure 8. Time-varying coefficient extended Cox model and stratified Cox sensitivity analysis for variables violating the proportional hazards assumption. A: Time-varying hazard ratio curve for durvalumab plus chemotherapy versus chemotherapy alone estimated using an extended Cox model with a treatment $\times$ log(time) interaction. Diamond markers indicate the estimated hazard ratios at 3, 6, 12, 18, and 24 months. The treatment-by-log(time) interaction was statistically significant ($P=0.021$), and the estimated hazard ratios decreased numerically over follow-up. B: Forest plot of the stratified Cox sensitivity analysis with tumor stage included as the stratification factor. Because tumor stage was used for stratification, its hazard ratio was not estimated in this model. Treatment regimen remained significantly associated with improved overall survival. Note: HR, hazard ratio; CI, confidence interval; PNI, prognostic nutritional index; SII, systemic immune-inflammation index; CA19-9, carbohydrate antigen 19-9; ECOG, Eastern Cooperative Oncology Group performance status.

rather than definitive causal verification of non-linear time-varying treatment effects ([Supplementary Figure 1](#)).

The stratified Cox sensitivity analysis adopting tumor stage as the stratification factor validated that durvalumab-combined chemotherapy remained independently associated with favorable OS (HR=0.485, 95% CI: 0.350–0.672, $P<0.001$). Pretreatment PNI ($P<0.001$), pretreatment SII ($P<0.001$) and CA19-9 ($P<0.001$) retained independent prognostic value, while ECOG PS showed marginal significance ($P=0.052$). The above results consolidated the robustness of survival benefits brought by durvalumab-combined chemotherapy (**Figure 8B**).

Baseline comparison between training and validation cohorts

A total of 417 advanced BTC patients were chronologically divided into the training cohort ($n=271$) and temporal external validation cohort ($n=146$). Baseline demographics, tumor characteristics, treatment information and laboratory indicators were well-balanced between the two cohorts, including sex ($P=0.657$), age ($P=0.580$), BMI ($P=0.636$), CCI ($P=0.602$), tumor subtype ($P=0.985$), tumor stage ($P=0.807$), ECOG PS ($P=0.084$), distant metastasis ($P=0.613$), prior surgery ($P=0.225$), biliary drainage ($P=0.388$), Child-Pugh grade ($P=0.493$), radiological response distribution ($P=0.337$),

maximum tumor diameter ($P=0.846$), CA19-9 ($P=0.364$), pretreatment PNI ($P=0.771$) and pretreatment SII ($P=0.558$) (**Table 2**).

Nomogram construction

A visualized prognostic nomogram was established to quantify 1-year and 2-year OS probabilities based on six independent baseline prognostic factors: treatment regimen, tumor stage, ECOG PS, pretreatment PNI, pretreatment SII and CA19-9. Each clinical variable corresponds to a specific point value; the total score summed from individual indicators is mapped to the survival probability scale at the bottom to obtain individualized 1-year and 2-year OS risks (**Figure 9**).

Time-dependent ROC analysis

In the training cohort, the AUC values of the nomogram for predicting 1-year and 2-year OS were 0.853 (95% CI: 0.807-0.898) and 0.875 (95% CI: 0.810-0.939), respectively. In the validation cohort, the corresponding AUC values were 0.786 (95% CI: 0.706-0.866) and 0.722 (95% CI: 0.605-0.839), confirming acceptable external discriminative ability of the nomogram (**Figure 10**).

Calibration performance

In the training cohort, the apparent C-index was 0.767, the bias-corrected C-index was 0.758, and the IPCW Brier score was 0.1597. The bias-corrected calibration slope reached 0.917, close to the ideal value of 1, indicating favorable internal calibration. In the validation cohort, the C-index was 0.711 and the IPCW Brier score was 0.1994; nevertheless, the calibration slope decreased to 0.677 (95% CI: 0.492-0.863, $P<0.001$ versus ideal slope = 1), suggesting model over-dispersion and overestimation of survival probability among high-risk patients (**Figure 11**).

Decision curve analysis

DCA for 1-year OS prediction demonstrated that the established nomogram yielded higher net clinical benefits than both the “universal treatment” and “no treatment” strategies across wide threshold probability ranges in both training and validation cohorts, verifying reliable clinical applicability of the predictive model (**Figure 12**).

Risk-stratified survival analysis

According to the optimal linear predictor cut-off value of -0.262, all enrolled patients were categorized into high-risk and low-risk prognostic subgroups. In the training cohort, the low-risk subgroup obtained significantly superior OS ($P<0.001$; HR=0.085, 95% CI: 0.046-0.159). Consistent risk-stratification efficacy was validated in the external cohort ($P<0.001$; HR=0.373, 95% CI: 0.221-0.630), confirming stable risk-stratification performance of the nomogram (**Figure 13**).

Discussion

Based on real-world retrospective clinical data, this study evaluated the clinical value of durvalumab combined with gemcitabine/cisplatin chemotherapy in patients with advanced BTC, focusing on dynamic changes in PNI and SII, treatment response, OS, and individualized prognostic prediction. The main findings suggest that chemoimmunotherapy may improve host immune-nutritional status, attenuate systemic inflammation, and provide survival benefit compared with chemotherapy alone. In addition, pretreatment PNI and SII showed prognostic relevance and could be integrated with conventional clinical variables to support baseline risk stratification.

The clinical rationale for this regimen has been established by the TOPAZ-1 trial, which demonstrated the survival advantage of durvalumab plus gemcitabine/cisplatin over chemotherapy alone in advanced BTC [4]. From a biological perspective, durvalumab blocks the PD-1/PD-L1 pathway, reverses tumor microenvironment-mediated T-cell suppression, and promotes restoration of antitumor immune activity [6]. The updated TOPAZ-1 analysis further confirmed that this benefit could be maintained during extended follow-up, supporting the durable therapeutic potential of chemoimmunotherapy in this disease setting [7].

The post-treatment increases in PNI and decrease in SII observed in this study may partly reflect systemic improvement after tumor control. Effective antitumor therapy can reduce tumor-related inflammation, relieve biliary obstruction, improve appetite and nutritional intake, and stabilize hepatic function. These changes may improve albumin level and lym-

Table 2. Comparison of baseline clinical characteristics between the training cohort and the validation cohort

Variable	Total	Training cohort (n=271)	Validation cohort (n=146)	Statistic	P value
Sex				0.198	0.657
Male	251 (60.19%)	161 (59.41%)	90 (61.64%)		
Female	166 (39.81%)	110 (40.59%)	56 (38.36%)		
Age				0.307	0.580
<65 years	238 (57.07%)	152 (56.09%)	86 (58.90%)		
≥65 years	179 (42.93%)	119 (43.91%)	60 (41.10%)		
BMI				0.224	0.636
<24 kg/m ²	265 (63.55%)	170 (62.73%)	95 (65.07%)		
≥24 kg/m ²	152 (36.45%)	101 (37.27%)	51 (34.93%)		
CCI				0.272	0.602
Low comorbidity (CCI ≤2)	273 (65.47%)	175 (64.58%)	98 (67.12%)		
High comorbidity (CCI >2)	144 (34.53%)	96 (35.42%)	48 (32.88%)		
Tumor type				0.03	0.985
Intrahepatic cholangiocarcinoma	192 (46.04%)	125 (46.13%)	67 (45.89%)		
Extrahepatic cholangiocarcinoma	127 (30.46%)	83 (30.63%)	44 (30.14%)		
Gallbladder cancer	98 (23.50%)	63 (23.25%)	35 (23.97%)		
Tumor stage				0.428	0.807
Stage IIIB	83 (19.90%)	54 (19.93%)	29 (19.86%)		
Stage IVA	168 (40.29%)	112 (41.33%)	56 (38.36%)		
Stage IVB	166 (39.81%)	105 (38.75%)	61 (41.78%)		
ECOG PS				2.993	0.084
0	204 (48.92%)	141 (52.03%)	63 (43.15%)		
1	213 (51.08%)	130 (47.97%)	83 (56.85%)		
Distant metastasis				0.255	0.613
Yes	156 (37.41%)	99 (36.53%)	57 (39.04%)		
No	261 (62.59%)	172 (63.47%)	89 (60.96%)		
Previous surgery				1.473	0.225
Yes	121 (29.02%)	84 (31.00%)	37 (25.34%)		
No	296 (70.98%)	187 (69.00%)	109 (74.66%)		
Biliary drainage				0.747	0.388
Yes	166 (39.81%)	112 (41.33%)	54 (36.99%)		
No	251 (60.19%)	159 (58.67%)	92 (63.01%)		
Child-Pugh class				0.47	0.493
Class A	353 (84.65%)	227 (83.76%)	126 (86.30%)		
Class B	64 (15.35%)	44 (16.24%)	20 (13.70%)		
Treatment response				3.376	0.337
CR	10 (2.40%)	5 (1.85%)	5 (3.42%)		
PR	135 (32.37%)	89 (32.84%)	46 (31.51%)		
SD	174 (41.73%)	119 (43.91%)	55 (37.67%)		
PD	98 (23.50%)	58 (21.40%)	40 (27.40%)		
Maximum tumor diameter	6.03 [4.09, 8.20]	6.06 [4.02, 8.18]	5.96 [4.21, 8.23]	0.194	0.846
CA19-9	402.36 ± 101.66	405.68 ± 104.86	396.20 ± 95.47	0.908	0.364
Pretreatment PNI	42.50 ± 5.32	42.44 ± 5.27	42.60 ± 5.44	-0.291	0.771
Pretreatment SII	853.98 ± 129.23	856.71 ± 118.46	848.92 ± 147.46	0.587	0.558

Note: BMI, Body Mass Index; CCI, Charlson Comorbidity Index; ECOG PS, Eastern Cooperative Oncology Group performance status; CR, Complete Response; PR, Partial Response; SD, Stable Disease; PD, Progressive Disease; CA19-9, Carbohydrate Antigen 199; PNI, Prognostic Nutritional Index; SII, Systemic Immune-Inflammation Index.

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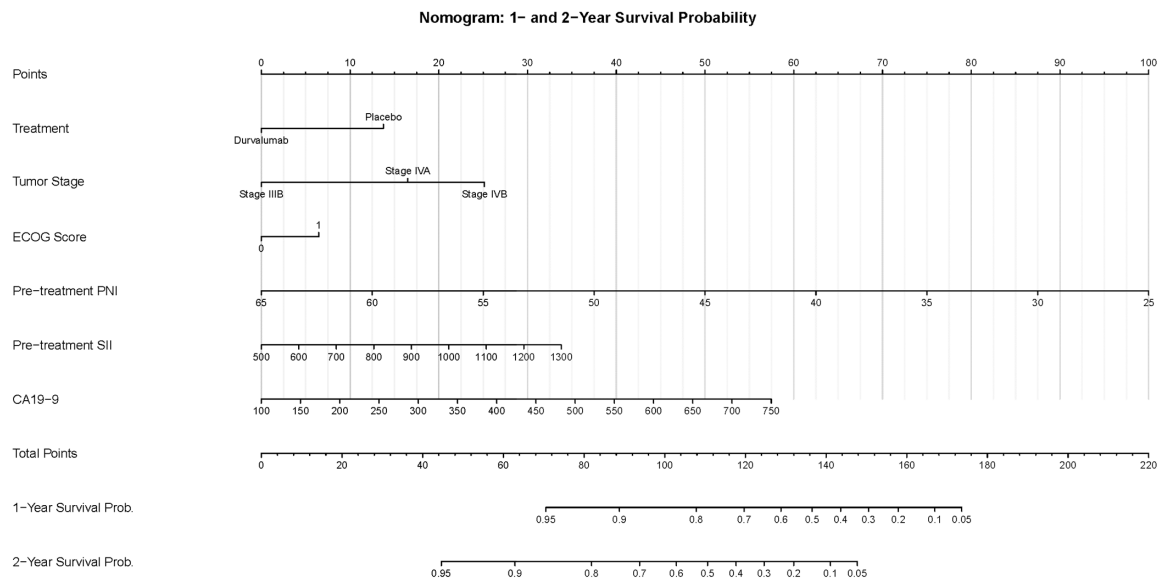


Figure 9. Nomogram for predicting 1-year and 2-year overall survival probabilities in patients with advanced biliary tract cancer. Note: PNI, prognostic nutritional index; SII, systemic immune-inflammation index; CA19-9, carbohydrate antigen 19-9; ECOG, Eastern Cooperative Oncology Group performance status.

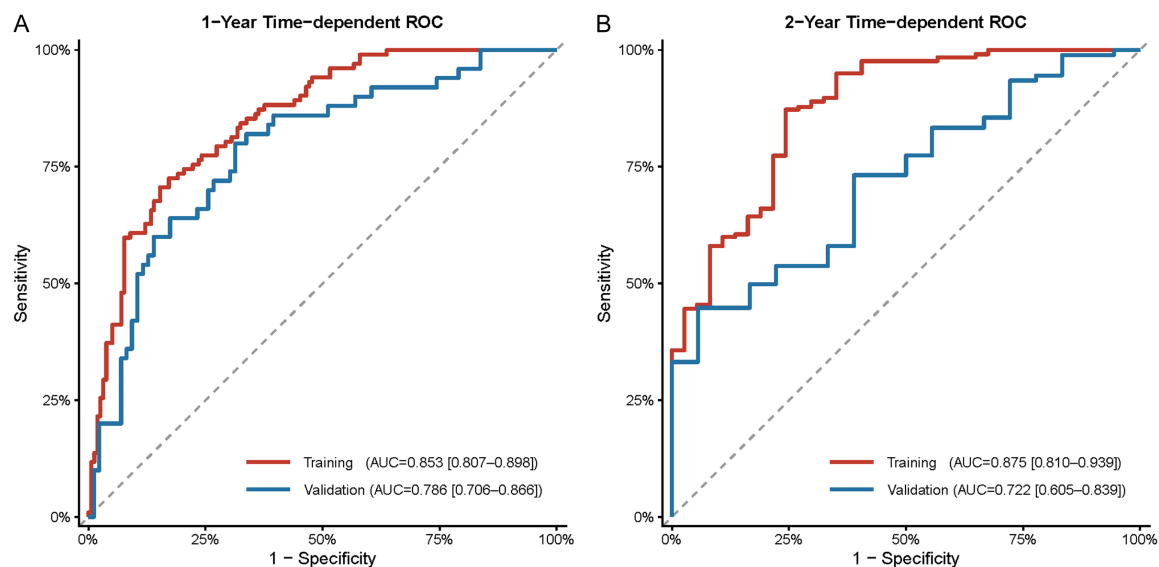


Figure 10. Time-dependent ROC curves of the prediction model for 1-year and 2-year survival in the training and validation cohorts. A: Comparison of time-dependent ROC curves for predicting 1-year overall survival in the training and validation cohorts. B: Comparison of time-dependent ROC curves for predicting 2-year overall survival in the training and validation cohorts. Note: ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval.

phocyte status while reducing inflammatory cell activation. Compared with chemotherapy alone, the more favorable biomarker changes in the durvalumab-combined group suggest an additional immunomodulatory effect, although this interpretation should remain cautious because PNI and SII are indirect composite

indicators rather than direct mechanistic markers.

The association between PNI/SII improvement and survival benefit should not be interpreted as definitive causality. Peri-treatment changes in these indices may reflect multiple overlap-

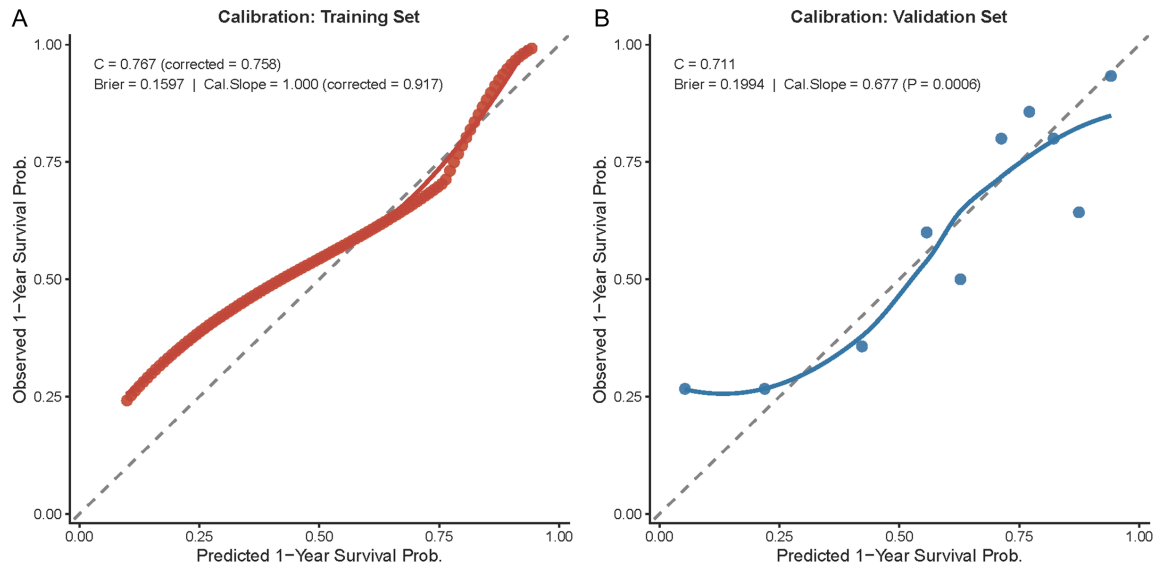


Figure 11. Calibration curves of the prediction model for 1-year survival probability in the training and validation cohorts. A: Calibration curve for the predicted 1-year survival probability in the training cohort, showing the agreement between bias-corrected predicted values and observed values. B: Calibration curve for the predicted 1-year survival probability in the validation cohort, showing the agreement between predicted values and grouped Kaplan-Meier estimates. Note: C-index, concordance index; Brier, Brier score; IPCW, inverse probability of censoring weighting; bootstrap (B=1000).

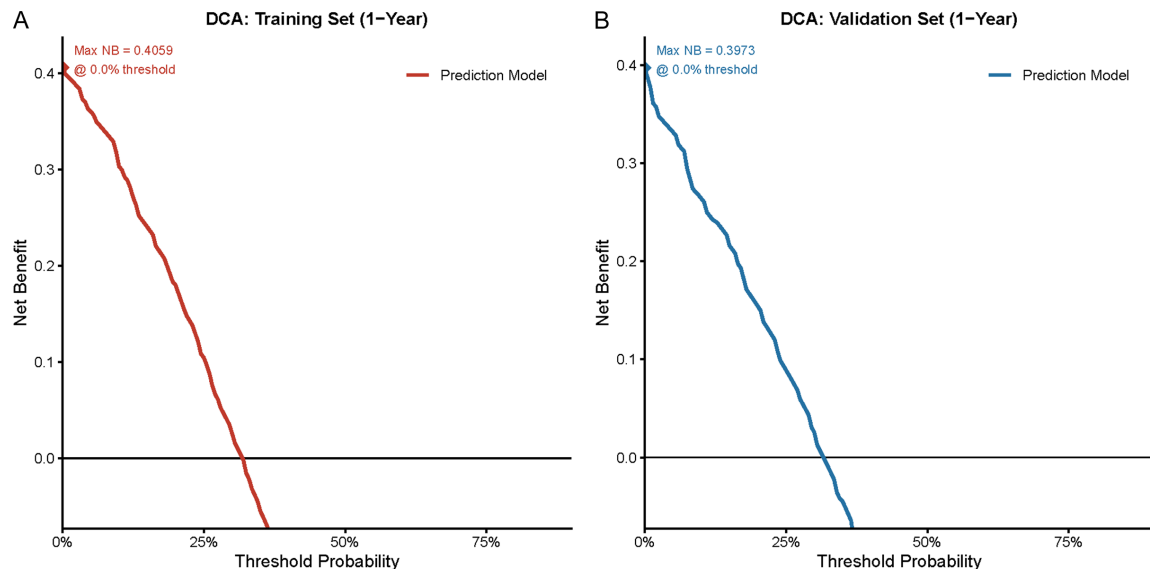


Figure 12. Decision curve analysis of the prediction model for 1-year overall survival in the training and validation cohorts. A: Decision curve for 1-year overall survival predicted by the model in the training cohort, compared with the “treat-all” and “treat-none” strategies. B: Decision curve for 1-year overall survival predicted by the model in the validation cohort, compared with the “treat-all” and “treat-none” strategies. Note: DCA, decision curve analysis; NB, net benefit.

ping factors, including tumor response, chemotherapy-induced myelosuppression, biliary drainage, infection control, nutritional intervention, and baseline host tolerance. Therefore,

improved PNI and reduced SII should be regarded primarily as prognostic or response-associated biomarkers. Previous research has shown that higher PNI is associated with better immu-

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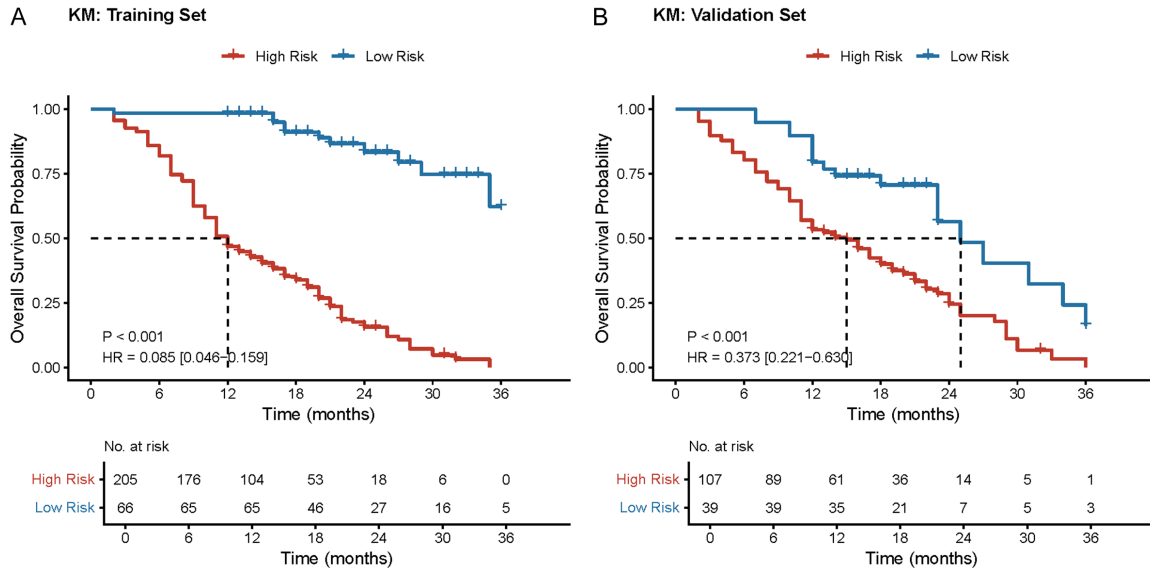


Figure 13. Kaplan-Meier survival curves for risk stratification in the training and validation cohorts based on the optimal cutoff of the linear predictor score. A: Kaplan-Meier comparison of overall survival between the high-risk and low-risk groups in the training cohort, stratified by the optimal LP cutoff value, with risk table. B: Kaplan-Meier comparison of overall survival between the high-risk and low-risk groups in the validation cohort, stratified by the same LP cutoff value, with risk table. Note: OS, overall survival; HR, hazard ratio; CI, confidence interval; LP, linear predictor score.

notherapy outcomes in metastatic BTC, supporting the value of nutritional and immune reserve in long-term treatment benefit [11]. Similarly, combined assessment of SII and PNI has been reported to improve prognostic evaluation in cholangiocarcinoma, suggesting that these two indices may provide complementary information [15].

A key methodological feature of this study was the inclusion of pretreatment rather than post-treatment PNI and SII in the final nomogram. This design is clinically appropriate because the model was intended for baseline prognostic assessment before treatment initiation. Post-treatment biomarkers can only be obtained after early treatment exposure and may be affected by treatment toxicity, supportive care, infection, biliary drainage, or early disease progression. Incorporating post-baseline variables into a baseline prediction model may introduce immortal-time bias, guarantee-time bias, and collider bias. Thus, dynamic PNI/SII changes were used to explore treatment-response associations, whereas pretreatment indices were retained to preserve the clinical applicability of the nomogram.

The constructed nomogram incorporated treatment regimen, tumor stage, ECOG PS, pretreat-

ment PNI, pretreatment SII, and CA19-9, all of which are readily available in routine practice. Compared with models based only on tumor stage or single biomarkers, this multivariable tool reflects both tumor burden and host systemic condition. Imaoka et al. previously developed a prognostic nomogram for advanced BTC and emphasized the role of clinical and laboratory indicators in survival prediction [16]. The MAGIC-D index also highlighted the importance of inflammation- and nutrition-related variables in patients receiving durvalumab-based chemioimmunotherapy [18]. Our model is consistent with this direction while additionally incorporating treatment regimen and tumor marker information.

The subgroup findings suggest that SII may be more sensitive than PNI in reflecting early treatment responsiveness. PNI mainly represents nutritional reserve and basal immune competence, which may be more closely related to long-term treatment tolerance and survival than to immediate tumor shrinkage. In contrast, SII integrates neutrophil, platelet, and lymphocyte counts and therefore captures the balance between systemic inflammation, pro-tumor immune suppression, and host antitumor immunity. Yang et al. reported that improvement in inflammation-based scores was asso-

ciated with favorable immunotherapy response in intrahepatic cholangiocarcinoma, supporting the relevance of inflammatory status to treatment sensitivity [20]. Wang et al. also found that SII had prognostic value in advanced BTC patients receiving immunotherapy [21]. In addition, Mii et al. showed that elevated neutrophil-to-lymphocyte ratio, a core component of SII, was associated with unfavorable outcomes in real-world BTC patients treated with gemcitabine, cisplatin, and durvalumab [22]. Pan et al. further demonstrated that lower inflammatory burden was associated with better outcomes in BTC patients receiving anti-PD-1 therapy [23].

The survival pattern observed in this study is generally consistent with long-term evidence from TOPAZ-1, in which durable benefit became more apparent with extended follow-up [24]. Real-world evidence has further supported the feasibility and effectiveness of durvalumab plus gemcitabine/cisplatin beyond highly selected clinical trial populations. Rimini et al. reported encouraging outcomes in a large international real-world cohort [25], and subsequent multicenter data from the same research network further confirmed the clinical value of this regimen [26]. Regional cohorts from Taiwan and Germany also reported consistent effectiveness and safety profiles in routine clinical practice [27, 28]. These findings collectively support the generalizability of durvalumab-based chemoimmunotherapy, while also emphasizing the need for prognostic tools that account for patient heterogeneity. In this context, the observation that favorable baseline inflammatory status may facilitate sustained treatment, along with durvalumab maintenance treatment, indirectly explains amplified late-phase survival benefits. However, spline-based sensitivity analysis only yielded marginal non-significant model optimization, reminding researchers to prudently interpret time-varying treatment effects. Notably, the stratified Cox model eliminating tumor stage confounding still validated stable survival benefits of combination therapy, proving the reliability of our core clinical conclusion provides a clinically meaningful explanation for why some patients obtain more durable benefit [29].

Although the nomogram showed acceptable discrimination and risk stratification, reduced calibration in the validation cohort indicates

that it may overestimate survival probability in high-risk patients. This limitation is common in survival prediction models and may be related to differences in patient composition, treatment sequence, supportive care, follow-up duration, and unmeasured molecular characteristics. Previous BTC prognostic models have also faced challenges in maintaining stable performance across cohorts, reflecting the biological and clinical heterogeneity of this disease [30]. More recent modeling strategies, including penalized regression and variable selection approaches, may help improve prediction, but cross-cohort generalizability remains a major challenge [31]. Therefore, recalibration of the baseline hazard, flexible modeling of continuous variables, and prospective multicenter validation are needed before broad clinical implementation.

This study has several limitations. First, the retrospective single-center design inevitably introduced selection bias and residual confounding despite multivariable adjustment and temporal validation. Second, the validation cohort was derived from the same institution, limiting geographic and practice-pattern generalizability. Third, molecular alterations such as IDH1 mutation, FGFR2 fusion, HER2 amplification, and microsatellite instability were not routinely available and could not be incorporated into the model. Fourth, post-treatment PNI and SII were not included in the baseline nomogram to avoid time-dependent bias. Finally, this study focused on clinical associations, and mechanistic experiments were not performed to verify the biological pathways linking durvalumab, immune-nutritional modulation, and survival improvement.

Conclusion

In summary, durvalumab combined with gemcitabine/cisplatin chemotherapy was associated with improved immune-nutritional status, reduced systemic inflammatory burden, better treatment response, and prolonged OS in patients with advanced BTC. PNI and SII provided complementary prognostic information: pretreatment values supported baseline risk stratification, whereas post-treatment SII showed potential value for identifying patients more likely to benefit from chemoimmunotherapy. The six-variable nomogram demonstrated acceptable discrimination and risk-stratifica-

tion performance, but its external calibration remained suboptimal. Further recalibration and prospective multicenter validation are required before broad clinical application.

Disclosure of conflict of interest

None.

Address correspondence to: Xiaozhi Zhao, Department of Hepatobiliary Surgery, Baoji High-tech Hospital, No. 19 Hexie Road, Weibin District, Baoji 721000, Shaanxi, China. E-mail: zhaoxiaozhi198-306@163.com

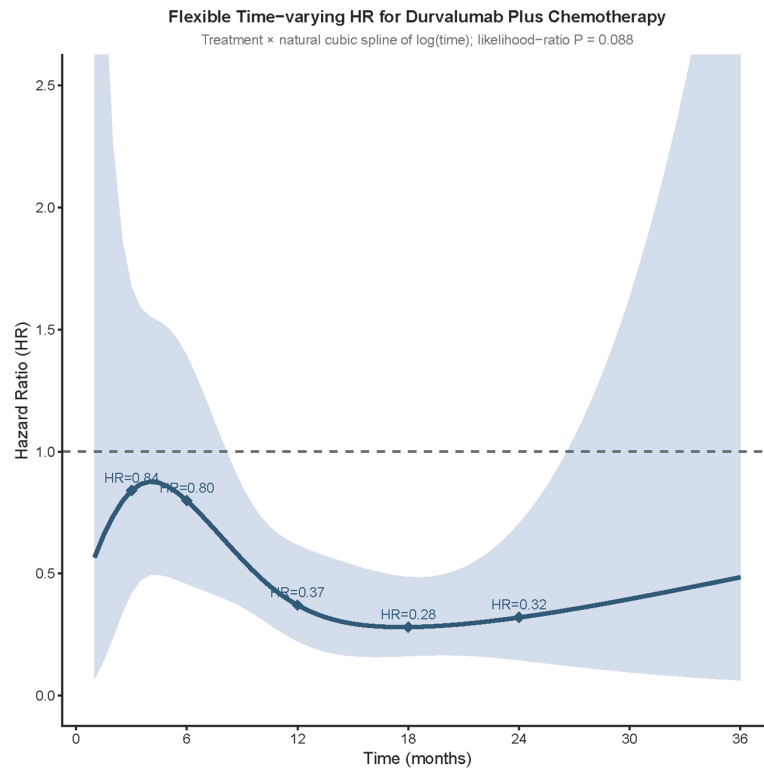
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Supplementary Figure 1. Flexible time-varying hazard ratio for durvalumab plus chemotherapy versus chemotherapy alone. The treatment effect was modeled using a natural cubic spline interaction with log(time) in a flexible time-varying coefficient Cox model. Tumor stage was included as a stratification factor because it violated the proportional hazards assumption. The solid line represents the estimated time-varying hazard ratio, and the shaded area represents the 95% confidence interval. The spline-based model showed lower estimated hazard ratios at later follow-up, but the likelihood-ratio test comparing the flexible time-varying model with the fixed-effect stratified Cox model showed only borderline, non-significant improvement in model fit ($\chi^2=6.541$, $df=3$, $P=0.088$). Therefore, this analysis was interpreted as supportive sensitivity evidence rather than definitive proof of a non-linear time-varying treatment effect.