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Prognostic Value of Inflammation-based Biomarkers in Patients with *De Novo* Metastatic Biliary Tract Cancer

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ABSTRACT

Objective: Biliary tract cancers (BTCs) are highly aggressive malignancies associated with poor clinical outcomes; metastatic disease is already present at diagnosis in many patients. We investigated whether baseline inflammation-based biomarkers could provide prognostic information in patients with *de novo* metastatic BTC.

Material and Methods: This retrospective study included 70 patients with BTC who were treated with initial chemotherapy for *de novo* metastatic disease between January 2013 and December 2024. Clinical features and laboratory parameters at the time of metastatic diagnosis were obtained. Inflammation-based biomarkers, namely neutrophil-to-lymphocyte ratio, systemic immune-inflammation index, hemoglobin-albumin-lymphocyte-platelet (HALP) score, lactate dehydrogenase, and C-reactive protein (CRP), were evaluated. Overall survival (OS) was used as the primary outcome to evaluate the prognostic significance of baseline inflammation-based biomarkers.

Results: The cohort was followed for a median of 10.8 months, during which the median progression-free survival was 6.6 months [95% confidence interval (CI): 5.1-8.1] and the median OS was 10.8 months (95% CI: 7.4-14.1). In multivariable analysis, elevated CRP [hazard ratio (HR): 9.187; p<0.001], Eastern Cooperative Oncology Group performance status (ECOG-PS) 2 (HR: 2.439; p=0.022), and low HALP score (HR: 3.091; p<0.001) were independently associated with worse OS. Stratification by HALP score demonstrated a significant difference in survival, with median OS of 18.6 months among patients with high HALP, compared with 5.9 months among those with low HALP.

Conclusion: Poor ECOG-PS, elevated CRP, and low HALP score were independently related to worse survival in *de novo* metastatic BTC. These widely accessible and inexpensive parameters may provide a practical approach for identifying high-risk patients at baseline and improving prognostic stratification in routine clinical practice.

Keywords: Biliary tract cancer; prognosis; inflammation-based biomarkers; HALP score; C-reactive protein; overall survival

INTRODUCTION

Biliary tract cancers (BTCs), primarily cholangiocarcinoma and gallbladder carcinoma, are relatively rare malignancies associated with poor clinical outcomes. Although BTC is relatively uncommon, the incidence of this disease, particularly intrahepatic cholangiocarcinoma, has increased over time. Because early-stage BTC often progresses with subtle and non-specific clinical manifestations, many patients are diagnosed with metastatic disease at presentation, rendering curative treatment infeasible.[1,2]

For patients diagnosed with *de novo* metastatic BTC, systemic chemotherapy remains the cornerstone of therapeutic management. For patients with advanced BTC, gemcitabine-based platinum combinations have remained the cornerstone of first-line systemic treatment for many years. More recently, the incorporation of immunotherapy into frontline treatment has led to incremental improvements in survival outcomes. Despite these therapeutic advances, the prognosis remains poor, with median overall survival (OS) rarely exceeding one year in real-world settings. Given the substantial clinical heterogeneity among patients, identifying readily available

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prognostic biomarkers may improve baseline risk assessment and help identify those with an unfavorable prognosis.[3,4]

Accumulating evidence indicates that the crosstalk between tumor cells and the host inflammatory environment contributes to tumor growth, angiogenesis, and metastatic dissemination. In addition, systemic inflammatory responses contribute to immune dysregulation, malnutrition, and cancer cachexia, all of which may adversely affect treatment tolerance and survival outcomes. Over the past decade, readily available laboratory-derived inflammatory markers have increasingly been investigated as inexpensive tools for prognostic assessment in multiple solid tumors. The neutrophil-to-lymphocyte ratio (NLR), systemic immune-inflammation index (SII), hemoglobin-albumin-lymphocyte-platelet (HALP) score, C-reactive protein (CRP), and lactate dehydrogenase (LDH) are all easily obtainable and may provide clinically relevant prognostic information.[4-7]

Inflammatory biomarkers are correlated with unfavorable survival across various gastrointestinal malignancies, particularly pancreatic, colorectal, and hepatobiliary cancers.[7,8] In BTC, the prognostic significance of inflammation-based biomarkers remains limited and heterogeneous, particularly in real-world cohorts comprising patients with newly diagnosed metastatic BTC who started systemic treatment in the first-line setting. Although interest in these biomarkers has increased in recent years, their prognostic role in this particular clinical context has not been fully established.[5,9-11]

We assessed, in patients with *de novo* metastatic BTC who initiated first-line systemic chemotherapy, the prognostic utility of baseline inflammation-based biomarkers, including NLR, SII, HALP, CRP, and LDH, measured at the time of metastatic diagnosis, with respect to OS.

MATERIAL AND METHODS

Study Cohort

The retrospective analysis included patients with *de novo* metastatic BTC who received first-line systemic chemotherapy between January 2013 and December 2024. Baseline demographic, clinical, and laboratory data at the time of metastatic diagnosis were extracted from institutional medical records.

The study included adults (≥18 years) with histologically confirmed BTC, including cholangiocarcinoma and gallbladder carcinoma, who had radiologically confirmed *de novo* metastatic disease at initial diagnosis and initiated first-line chemotherapy.

Patients with recurrent metastatic disease following prior curative-intent treatment, non-metastatic disease, active systemic infection at baseline, or patients with an Eastern Cooperative Oncology Group performance status (ECOG-PS) ≥3 were considered ineligible. Tumor burden was assessed radiologically at baseline and during follow-up by serial computed tomography (CT) or positron emission tomography/CT examinations. Tumor response was evaluated using RECIST v1.1.

OS was the primary study endpoint, defined as the time from the date of metastatic diagnosis to death from any cause or to last follow-up. Progression-free survival (PFS) was defined as the time from initiation of first-line systemic treatment to the date of radiological or clinical disease progression, death from any cause, or the final follow-up, whichever came first. The study was conducted in accordance with the Declaration of Helsinki and was approved by the University of Health Sciences Türkiye, Haydarpaşa Numune Research and Training Hospital Non-Interventional Clinical Research Ethics Committee (approval number: HNEAH-GOEAK/KK/2026/97, date: 28.04.2026).

Inflammation-based Biomarkers

Baseline laboratory parameters obtained within 30 days before the initiation of first-line chemotherapy were used to calculate inflammation-based biomarkers. When multiple measurements were available within this period, the measurement closest to treatment initiation was selected. NLR was determined as the absolute neutrophil count divided by the absolute lymphocyte count. SII was derived as platelet count × neutrophil count / lymphocyte count, whereas HALP was calculated as hemoglobin × albumin × lymphocyte count / platelet count. Baseline CRP (mg/L) and LDH (U/L) levels were also analyzed as individual inflammatory biomarkers. Lymphocyte, neutrophil, and platelet counts were expressed as $\times 10^3/\mu L$, whereas hemoglobin and albumin levels were reported in g/dL.

Statistical Analysis

Data analyses were conducted using the IBM SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Categorical variables were presented as frequencies and percentages, whereas continuous variables were summarized as mean ± standard deviation or median (range), as appropriate. Data distribution was assessed using the Kolmogorov-Smirnov test. Comparisons between categorical variables were performed using the Pearson's chi-square (χ^2) test. Continuous laboratory variables, including NLR, SII, HALP, CRP, and LDH, were dichotomized at their median values. Carcinoembryonic antigen and carbohydrate antigen 19-9 were categorized as normal or abnormal based on institutional laboratory reference ranges. OS was estimated using the Kaplan-Meier

method and compared between groups using the log-rank test. Factors associated with OS were evaluated using univariate and multivariable Cox proportional hazards regression models. Variables with p<0.10 in univariate analysis were added to the multivariable model. A two-sided p-value <0.05 was considered significant.

RESULTS

The cohort included 70 patients with *de novo* metastatic BTC. The median follow-up duration was 10.8 months (5.8-19.1 months). Men accounted for 52.9% of the study population, whereas women comprised 47.1%, with a mean age of 61.9±9.9 years. The majority of tumors were cholangiocarcinomas (80%), while gallbladder carcinomas accounted for 20% of cases. A favorable performance status was observed in most patients: 70% had an ECOG-PS of 0-1, and 30% had an ECOG-PS of 2. The highest frequency of metastatic involvement was observed in the liver (70%), followed by peritoneal metastases (22.9%), bone metastases (22.9%), and lung metastases (18.6%). Most patients (60%) had metastatic involvement of a single organ, whereas 40% had metastases involving more than one organ. Regarding treatment for metastatic disease, cisplatin plus gemcitabine was the most frequently administered first-line regimen (58.6%), whereas 41.4% of patients received other chemotherapy regimens [gemcitabine 18 patients (25.7%), carboplatin + gemcitabine 3 patients (4.3%), capecitabine 3 patients (4.3%), FOLFOX (leucovorin, 5-fluorouracil, and oxaliplatin) 2 patients (2.9%), gemcitabine + capecitabine 1 patient (1.4%), and gemcitabine + oxaliplatin 2 patients (2.9%)]. Table 1 presents the baseline clinicopathological data.

Partial responses were identified in 15 patients (21.4%), stable disease was observed in 27 patients (38.5%), and progressive disease was observed in 28 patients (40.0%); no complete responses were recorded in first-line treatment. The objective response rate and disease control rate were 21.4% and 59.9%, respectively. Median PFS was 6.6 months [95% confidence interval (CI): 5.1-8.1], with 6- and 12-month PFS estimates of 58.6% and 17.1%, respectively. Median OS was 10.8 months (95% CI: 7.4-14.1); estimated OS at 6, 12, and 24 months was 72.2%, 46.5%, and 16.7%, respectively. Severe treatment-related toxicities (grade ≥3) during first-line therapy were observed in 8 patients (11.4%). Of the study population, 29 patients (41.4%) received second-line systemic treatment, whereas only 13 (18.6%) received third-line therapy. In addition, 32 patients (45.7%) underwent palliative radiotherapy at any time during the disease course for symptom control or management of metastatic complications.

Baseline laboratory parameters and inflammation-based biomarkers at the time of metastatic diagnosis are summarized in Table 2. In univariate Cox regression analysis, cholangiocarcinoma histology, ECOG-PS 2, presence of liver metastases, low HALP score (≤ 22.2), high SII (> 1060), high NLR (> 3.9), and elevated CRP (> 25 mg/L) were significantly associated with worse OS (Table 3). ECOG-PS 2 [hazard ratio (HR): 2.439; p=0.022], low HALP score (HR: 3.091; p<0.001), elevated CRP (HR: 9.187; p<0.001) remained independent predictors of worse OS in multivariable analysis (Table 3).

Using the median HALP score (22.2) as the cut-off value, 35 patients (50%) were stratified into the low HALP group (≤22.2),

TABLE 1: Baseline patient characteristics.

Age (years, mean ± SD)	61.94±9.91
Age	
≥65	34 (48.6%)
<65	36 (51.4%)
Sex	
Male	37 (52.9%)
Female	33 (47.1%)
BMI (kg/m^2, mean ± SD)	27.37±5.48
Primary site	
Cholangiocarcinoma	56 (80%)
Gallbladder	14 (20%)
ECOG-PS	
0-1	49 (70%)
2	21 (30%)
Liver metastases	
Yes	49 (70%)
No	21 (30%)
Lung metastases	
Yes	13 (18.6%)
No	57 (81.4%)
Bone metastases	
Yes	16 (22.9%)
No	54 (77.1%)
Peritoneal metastases	
Yes	16 (23%)
No	54 (77%)
Metastatic organ site	
1	42 (60%)
>1	28 (40%)
First line treatment regimen	
Cisplatin + gemsitabine	41 (58.6%)
Others	29 (41.4%)

ECOG PS: Eastern Cooperative Oncology Group performance status; SD: Standard deviation; BMI: Body mass index.

while the remaining 35 patients (50%) were categorized as the high HALP group (>22.2). Median OS was markedly longer in the high HALP cohort than in the low HALP cohort. Median OS was 18.6 months (95% CI: 12.9-24.3) in the high HALP cohort versus 5.9 months (95% CI: 3.9-8.0) in the low HALP cohort (p<0.001). One- and two-year OS estimates in the high HALP cohort were 77.2% and 30%, respectively; in the low HALP cohort they were 15% and 3%. Figure 1 shows the Kaplan-Meier survival curves.

TABLE 2: Laboratory parameters and inflammation-based biomarkers at metastatic diagnosis.

Variables (unit)	Median	Minimum	Maximum
CEA (ng/mL)	4	1	1573
CA 19-9 (U/mL)	65	2	160500
LDH (U/L)	281	120	1639
CRP (mg/L)	25.5	1	139
Neutrophil ($10^3/\mu L$)	5580	1100	33000
Hemoglobin (g/dL)	11.75	7.30	16
Albumin (g/dL)	3.60	2.00	5.00
Lymphocyte ($10^3/\mu L$)	1550	410	5800
Platelet ($10^3/\mu L$)	270000	97000	841000
NLR	3.90	0.74	19.41
SII	1059	123.9	11619.08
HALP score	22.17	2.33	120.93

CRP: C-reactive protein; CEA: Carcinoembryonic antigen; LDH: Lactate dehydrogenase.; CA 19-9: Cancer antigen 19-9; NLR: Neutrophil-to-lymphocyte ratio; HALP: Hemoglobin-albumin-lymphocyte-platelet; SII: Systemic immune-inflammation index.

TABLE 3: Univariate and multivariate Cox proportional analyses for overall survival.

Variables	Univariable analysis	p-value	Multivariable analysis	p-value
	HR (95% CI)		HR (95% CI)	
Male gender	1.238 (0.759-2.021)	p=0.391	-	-
Age	1.016 (0.991- 1.041)	p=0.209	-	-
Age ≥65 years	1.499 (0.916-2.454)	p=0.107	-	-
ECOG-PS 2	**9.145 (4.524-18.485)**	**p<0.001**	**2.439 (1.068-5.574)**	**p=0.022**
BMI ≥25 kg/m^2	1.458 (0.868-2.448)	p=0.154	-	-
Cholangiocarcinoma	**1.920 (1.008-3.660)**	**p=0.047**	1.213 (0.578-2.546)	p=0.667
Liver metastases	**2.468 (1.348-4.518)**	**p<0.001**	1.318 (0.691-2.472)	p=0.415
Lung metastases	1.430 (0.749-2.730)	p=0.279	-	-
Peritoneum metastases	1.141 (0.626-2.080)	p=0.666	-	-
Bone metastases	1.183 (0.651-2.150)	p=0.580	-	-
Metastatic organ site >1	1.378 (0.813-2.336)	p=0.234	-	-
First line treatment regimen others	1.148 (0.681-1.935)	p=0.603	-	-
CEA (abnormal)	1.446 (0.871-2.400)	p=0.152	-	-
CA 19-9 (abnormal)	1.479 (0.884- 2.476)	p=0.136	-	-
HALP score ≤22.2	**3.862 (2.289-6.515)**	**p<0.001**	**3.091 (1.723-5.542)**	**p<0.001**
SII >1060	**1.896 (1.155-3.111)**	**p=0.011**	1.298 (0.743-2.265)	p=0.359
NLR >3.9	**2.525 (1.369-3.700)**	**p=0.001**	0.814 (0.407-1.601)	p=0.714
CRP >25	**14.92 (6.01-37.07)**	**p<0.001**	**9.187 (3.358-25.135)**	**p<0.001**
LDH >281	1.543 (0.940-2.532)	p=0.087	1.062 (0.602-1.876)	p=0.956

Statistically significant p-values are shown in bold.
BMI: Body mass index; ECOG-PS: Eastern Cooperative Oncology Group performance status CRP: C-reactive protein; CEA: Carcinoembryonic antigen; LDH: Lactate dehydrogenase; CA 19-9: Cancer antigen 19-9; NLR: Neutrophil-to-lymphocyte ratio; HALP: Hemoglobin-albumin-lymphocyte-platelet; SII: Systemic immune-inflammation index.
CEA levels ≤5 ng/mL and CA 19-9 levels ≤37 U/mL were considered normal; values above these cut-offs were considered abnormal.

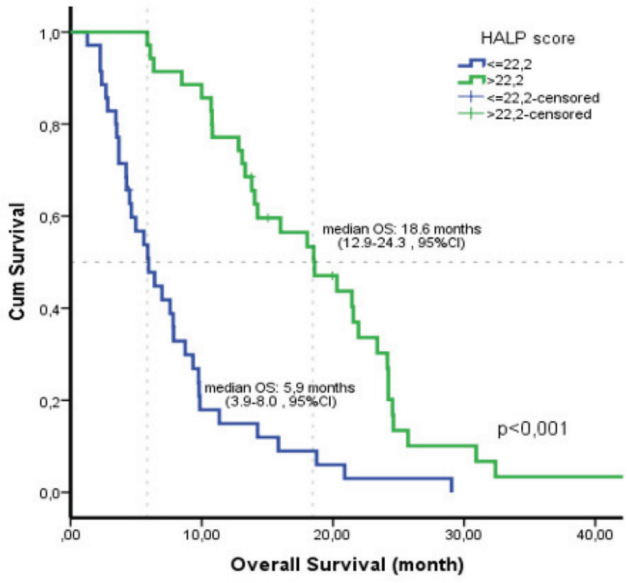

FIGURE 1: Kaplan-Meier analysis of overall survival stratified by baseline HALP score (≤22.2 vs. >22.2).

HALP: Hemoglobin-albumin-lymphocyte-platelet; OS: Overall survival; CI: Confidence interval

DISCUSSION

This retrospective study identified baseline inflammation-based biomarkers and clinical characteristics as predictors of OS among patients with *de novo* metastatic BTC. Poor ECOG-PS, elevated CRP levels, and a low HALP score independently predicted poorer OS.

The survival outcomes observed in our cohort were comparable to those reported in previous real-world studies and landmark clinical trials**.** Median OS and PFS of 10.8 and 6.6 months closely resembled those reported in the landmark ABC-02 trial[12], in which first-line gemcitabine plus cisplatin resulted in median survival times of 11.7 months for OS and 8.0 months for PFS in patients with advanced BTC. More recently, the TOPAZ-1 trial[13] showed that the addition of durvalumab to gemcitabine-cisplatin modestly improved survival, establishing chemoimmunotherapy as the preferred first-line treatment. Despite these therapeutic advances, survival outcomes remain poor and highly heterogeneous, highlighting the need for readily available prognostic biomarkers to improve baseline risk stratification.

Performance status is one of the most well-established prognostic factors in advanced BTC. In the present study, an ECOG-PS of 2 was associated with more than twice the risk of death compared with ECOG-PS 0-1 patients (HR: 2.44; p=0.022) and remained independently associated with worse OS in the multivariable model. Similar observations have been noted by Kim et al.[14], Bridgewater et al.[15], and Valle et al.[12], all of which demonstrated the adverse prognostic impact of poor performance status in advanced BTC.

Among inflammation-based biomarkers, CRP was the most robust independent prognostic factor in the study population, and remained independently associated with worse OS after multivariable adjustment (HR: 9.19; 95% CI: 3.36-25.14; p<0.001). CRP is a well-established marker of systemic inflammation and reflects tumor-associated cytokine activation, particularly interleukin-6-mediated signaling, which has been implicated in tumor progression, cancer cachexia, and immune dysregulation. Previous studies in gastrointestinal malignancies have consistently demonstrated the adverse prognostic impact of elevated CRP, and our findings further support its prognostic value in patients with *de novo* metastatic BTC.[8,16,17]

The HALP score demonstrated meaningful prognostic utility in our cohort. Patients with a low HALP score experienced markedly worse OS than those with a high HALP score, with an approximately threefold higher risk of death in the multivariable analysis. As a composite index integrating nutritional and inflammatory status, the HALP score reflects several biological processes associated with cancer progression. Its individual components—including anemia, hypoalbuminemia, lymphopenia, and thrombocytosis—have each been associated with impaired nutritional status, systemic inflammation, immune dysfunction, and tumor progression. The combined assessment of these parameters may therefore explain the strong prognostic discrimination observed in our cohort. Although evidence in BTC remains limited, previous studies in gastric, colorectal, pancreatic, and hepatocellular cancers have also demonstrated the prognostic utility of the HALP score.[18-21]

While NLR and SII were significant predictors in univariate analysis, their association with survival did not persist after multivariable adjustment**.** This finding suggests that their prognostic value may not be independent of other established clinical and inflammation-based prognostic factors. Similar inconsistencies have been described in previous BTC studies, where the prognostic impact of NLR and SII varied according to patient population, disease stage, and treatment setting.[4,9,11,22,23] Our findings further support the notion that these biomarkers should be interpreted in conjunction with other established prognostic factors rather than in isolation.

Study Limitations

Several methodological limitations should be acknowledged. The retrospective nature of the analysis and the modest number of included patients may restrict the broader applicability of the results. Although most patients received

first-line cisplatin plus gemcitabine, heterogeneity in treatment regimens among the remaining patients may have influenced survival outcomes. Moreover, no patients received immune checkpoint inhibitors because these agents were not reimbursed during the study period; therefore, our findings primarily reflect the pre-immunotherapy era. Accordingly, the generalizability of our findings to current clinical practice, where chemoimmunotherapy is increasingly used in the first-line setting, may be limited and should be interpreted with caution. Finally, longitudinal changes in inflammation-based biomarkers during treatment were not evaluated; these changes may provide additional prognostic information. Prospective studies are warranted to validate these findings. Nevertheless, the present findings support the prognostic relevance of clinical and inflammatory parameters in *de novo* metastatic BTC. As readily available, inexpensive biomarkers, CRP, HALP, and ECOG-PS may facilitate baseline risk stratification and identify patients at higher risk in routine clinical practice. Prospective studies should evaluate whether these parameters can be integrated into routine clinical practice to support individualized treatment decisions.

CONCLUSION

Our findings suggest that poor ECOG performance status, elevated CRP, and a low HALP score are independent predictors of adverse survival in *de novo* metastatic BTC. Because these parameters are inexpensive and routinely available, they may serve as practical tools for baseline risk assessment and prognostic stratification in clinical practice. Prospective validations in larger cohorts are needed before their widespread clinical implementation.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Türkiye, Haydarpaşa Numune Research and Training Hospital Non-Interventional Clinical Research Ethics Committee (approval number: HNEAH-GOEAK/KK/2026/97, date: 28.04.2026).

Informed Consent: Due to the retrospective nature of the study, the requirement for informed consent was waived.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Z.A.T., S.D., Concept: Z.A.T., M.B., Design: Z.A.T., M.B., Data Collection or Processing: Z.A.T., S.D., Analysis or Interpretation: Z.A.T., S.D., M.B., Literature Search: Z.A.T., Writing: Z.A.T., S.D.

Conflict of Interest: No conflict of interest was declared by the authors.

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