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Prognostic impact of neutrophil-to-lymphocyte ratio (NLR) in patients with unresectable biliary tract cancer treated with gemcitabine, cisplatin, and durvalumab

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Abstract

Background Biliary tract cancer (BTC) is a type of malignancy that is challenging to manage. Further, advanced-stage BTC has poor prognosis. Based on the recent TOPAZ-1 trial, adding durvalumab to gemcitabine and cisplatin significantly improves survival in unresectable BTC, thereby making it the new standard first-line treatment. However, real-world data are essential to validate its efficacy and safety in routine clinical settings, which often involve older patients and those with comorbidities or previous therapies. This study aimed to evaluate the outcomes of combination chemotherapy with gemcitabine, cisplatin, and durvalumab (GCD) in a real-world cohort with BTC.

Methods This retrospective analysis included patients with unresectable advanced-stage BTC treated with GCD between December 2022 and April 2024 at three institutions. GCD was administered for up to eight cycles, followed by durvalumab monotherapy. Clinical data, including the characteristics of the patients, adverse events, and treatment responses, were collected. The Kaplan–Meier method and the Cox proportional hazards model were used to assess progression-free survival (PFS), overall survival (OS), and other factors affecting outcomes.

Results The current study included 54 patients with a median age of 72 years. Half of the patients had recurrence post-surgery, and many of them had previously received chemotherapy. The median PFS and OS rates were 4.1 and 8.0 months, respectively. Adverse events (AEs) were frequently observed, with 42.1% of patients presenting with grade 3 or higher AEs. However, immune-related AEs were rare and mild. Dose adjustments, which are often caused by renal impairment or fatigue, were common (66.7%). Multivariate analysis revealed that older age, a lower performance status score, and a high neutrophil-to-lymphocyte ratio (NLR) were significant predictors of a shorter PFS. Further, a lower performance status score, and a high NLR were associated with a low OS.

Conclusions GCD combination chemotherapy is a viable treatment option for advanced-stage BTC in a real-world setting where dose modifications can improve tolerability among elderly patients. Neutrophil-to-lymphocyte ratio can be a prognostic biomarker of OS in patients with BTC receiving immune checkpoint inhibitors. This finding

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highlights the potential of individualized treatment strategies. Nevertheless, further research should be performed to validate these results in larger cohorts.

Keywords Biliary tract cancer, Durvalumab, Neutrophil-to-lymphocyte ratio

Background

Biliary tract cancer (BTC) is a heterogeneous group of malignancies that originate from the biliary tract that includes intrahepatic and extrahepatic cholangiocarcinoma, gallbladder cancer, and ampulla of Vater cancer [1]. The early diagnosis of BTC is still challenging. Due to the absence of comprehensive screening methods, patients with BTC are often diagnosed with advanced-stage disease and poor prognosis [1–10]. Early-stage BTC can be cured with surgery. However, this treatment option is only limited to some patients [11–14]. Since many patients with BTC present with either distant metastasis or locally advanced at the time of diagnosis, systemic and palliative therapies are the primary feasible treatment options [14, 15]. Even with surgical resection, the 3-year recurrence rate reaches up to 80% [16]. The prognosis of patients with advanced-stage BTC is poor, with only 2–5% surviving 5 years after diagnosis [17]. Over the past decade, owing to the significant therapeutic potential shown in the ABC-02 and BT-22 trials, the standard first-line treatment for advanced-stage BTC is combined cisplatin and gemcitabine [4, 15, 18, 19]. In the ABC-02 trial, the median progression-free survival (PFS) and the median overall survival (OS) of patients with advanced-stage BTC ($n = 410$) were 8.0 and 11.7 months, respectively. These outcomes were considered promising at the time. Similarly, in the BT-22 trial, the median PFS and median OS of the patients were 5.8 and 11.2 months, respectively. Thus, gemcitabine and cisplatin have since been established as the first-line treatment for advanced-stage BTC [18, 19]. In 2022, the phase III TOPAZ-1 trial, which included 685 patients with unresectable or metastatic BTC, showed that adding the anti-programmed death-ligand 1 antibody durvalumab to gemcitabine and cisplatin therapy significantly improved patient survival. Thus, this combination has been established as the novel standard of care for first-line treatment [2–4]. The survival outcomes in the TOPAZ-1 trial are impressive. However, the outcomes observed in various trials and those in routine clinical practice still differ. Participants who have a favorable general health and organ function are typically selected for clinical trials, which may not reflect the broader patient population. Thus, it is essential to validate the efficacy of chemotherapy in real-world clinical settings. However, this gap can be addressed by real-world data (RWD), which include the health status and treatment outcomes of patients based on standardized information such as electronic medical records and hospitalization data. RWD can offer valuable insights into the differences between clinical research and everyday medical practice, and recent cohort studies utilizing large databases have become a prominent approach to bridging this gap [7]. This study used a cohort design using RWD to evaluate the efficacy and tolerability of GCD combination chemotherapy for unresectable advanced-stage BTC. In addition to examining the characteristics of RWD, the applicability of clinical trial findings to real-world clinical practice was assessed. Further, the prognostic factors influencing treatment outcomes and OS were investigated.

Methods

Study population

The cohort included patients aged ≥ 18 years who received combination chemotherapy with gemcitabine, cisplatin, durvalumab (GCD) for unresectable advanced-stage BTC between December 2022 and April 2024 at three Fujita Health University hospitals (Fujita Health University Hospital, Fujita Health University Bantane Hospital, and Fujita Health University Okazaki Medical Center). GCD combination chemotherapy was administered up to 8 cycles according to the regimen used in the TOPAZ1 study [2]. After 8 cycles of combination chemotherapy, durvalumab monotherapy was administered once in 4 weeks until evident disease worsening or unacceptable toxicity.

Assessments

The clinical data were collected from an electronic medical record. The information included the characteristics of the patients (such as age, sex, body mass index, Eastern Cooperative Oncology Group performance status [ECOG-PS] score, platelet count, aspartate aminotransferase level, alanine aminotransferase level, neutrophil-to-lymphocyte ratio [NLR], carcinoembryonic antigen level, carbohydrate antigen 19 – 9 level, primary tumor type [intrahepatic cholangiocarcinoma, perihilar cholangiocarcinoma, gallbladder cancer, ampulla of Vater cancer, and distal bile duct cancer], disease status [locally advanced or metastatic], and previous treatment [surgery, adjuvant chemotherapy]. Body mass index, platelet count, aspartate aminotransferase level, alanine aminotransferase level, NLR, carcinoembryonic antigen level, and carbohydrate antigen 19 – 9 level were treated as ordinal variables, classified according to whether they were above the reference value, rather than as continuous variables based on the report of Rimini et al. [3]. Adverse events (AEs) were reported according to the US National

Cancer Institute's common terminology criteria for AEs version 5.0 (CTCAE ver. 5.0). If a patient experienced multiple AEs, all such events were reported. Tumor assessments were performed according to RECIST version 1.1 [20] using images obtained via computed tomography scan or magnetic resonance imaging of the chest, abdomen, and pelvis approximately 6 weeks after the initial administration of GCD combination chemotherapy.

Table 1 Baseline characteristics of the patients

		N **= 54**
Age, median, range		72 [51–86]
Sex, n (%)	Male	27 (50)
	Female	27 (50)
BMI, n (%)	Underweight	26 (48.1)
	Normal	11 (20.4)
	Overweight	17 (31.5)
ECOG-PS score, n (%)	0	44 (81.5)
	1	9 (16.7)
	2	1 (1.9)
Platelet count, n (%)	< 100,000/μL	5 (9.3)
	≥ 100,000/μL	49 (90.7)
AST level, n (%)	Within normal levels	37 (68.5)
	Above normal levels	17 (31.5)
ALT level, n (%)	Within normal levels	39 (72.2)
	Above normal levels	15 (27.8)
NLR, n (%)	< 3	29 (53.7)
	≥ 3	25 (46.3)
CEA level, n (%)	Within normal levels	22 (40.7)
	Normal levels	26 (48.1)
	Not reported	6 (11.1)
CA19-9 level, n (%)	Within normal levels	16 (29.6)
	Normal levels	32 (59.3)
	Not reported	6 (11.1)
Primary tumor site, n (%)	Intrahepatic cholangiocarcinoma	20 (37)
	Perihilar cholangiocarcinoma	11 (20.4)
	Gallbladder cancer	16 (29.6)
	ampulla of Vater cancer	5 (9.3)
	Distal bile duct cancer	2 (3.7)
Disease status, n (%)	Locally advanced	13 (24.1)
	Metastatic	41 (75.9)
Previous surgery, n (%)	No	27 (50)
	Yes	27 (50)
*Previous chemotherapy, n (%)	No	19 (35.2)
	Yes	35 (64.8)
GCD dose reduction, n (%)	No	18 (33.3)
	Yes	36 (66.7)

Abbreviations: BMI, body mass index; ECOG-PS, Eastern Cooperative Oncology Group performance status; AST, aspartate aminotransferase; ALT, alanine transaminase; NLR, neutrophil-to-lymphocyte ratio; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19 – 9

*: The breakdown of the 35 patients who previously received chemotherapy is as follows: $n = 14$, GC therapy; $n = 5$, GCS therapy; $n = 1$, S-1 therapy; $n = 6$, adjuvant chemotherapy; and $n = 9$, multiple types of chemotherapy. Among these nine patients, seven received GC therapy. Among these seven patients, two also received GCS therapy

Statistical analysis

PFS was measured from the start of treatment until disease progression, death, or last follow-up, whichever came first. OS was assessed from the start of treatment until death. The safety of this combination chemotherapy was assessed according to CTCAE ver5.0. Survival curves were estimated using the Kaplan–Meier curve. The role of stratification factors was analyzed with the log-rank tests. Unadjusted and adjusted hazard ratios (HRs) based on baseline characteristics were calculated using the Cox proportional hazards model. To identify independent prognostic factors associated with OS and PFS, a multivariate Cox proportional hazards regression model was constructed. All variables with a p-value < 0.2 in the univariate analysis were included in the initial model. A stepwise selection method was applied using the Wald test with a removal criterion of $p > 0.2$. The final models retained only variables with statistical significance ($p < 0.05$). To evaluate multicollinearity among covariates, variance inflation factors (VIFs) were calculated. The VIF values for the explanatory variables in the OS model were 1.11 for Age, 1.04 for ECOG-PS, and 1.07 for NLR, while those in the PFS model were 1.002 for ECOG-PS and 1.002 for NLR.

Since all VIF values were < 5, no significant multicollinearity was observed. Categorical variables were compared using the Fisher's exact test. A p value of < 0.05 was considered statistically significant. R version 4.3.1 (The R Project for Statistical Computing, www.r-project.org) and EZR version 1.52 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) were used to perform statistical analyses. EZR is a graphical user interface for R version 4.02 (The R Foundation for Statistical Computing, Vienna, Austria) and is a modified version of R commander that was designed to add statistical functions frequently used in biostatistics [21].

Ethics

Informed consent was obtained in the form of opt-out on the website. Patients who rejected were excluded from the analysis. This study was approved by the ethics committee of Fujita Health University (ethical permit number: HM24-011). Moreover, it complied with the provisions of the Good Clinical Practice guidelines and the 1975 Declaration of the Helsinki.

Results

Characteristics of the patients

This study enrolled 54 patients. Table 1 shows the baseline characteristics of the patients. The median age was 72 years old. Among them, 27 were men and 27 women.

The ECOG-PS scores were 0 in 44 (81.5%) patients, 1 in 9 (16.7%), and 2 in 1 (1.9%). The neutrophil-to-lymphocyte ratios (NLR) of 29 (53.7%) and 25 (46.3%) patients were < 3 and ≥ 3, respectively. The types of primary tumor site were as follows: intrahepatic cholangiocarcinoma ($n = 20$ [37%]), perihilar cholangiocarcinoma ($n = 11$ [20.4%]), gallbladder cancer ($n = 16$ [29.6%]), ampulla of Vater cancer ($n = 5$ [9.3%]), and distal bile duct cancer ($n = 2$ [3.7%]). In terms of disease status, 13 (24.1%) patients presented with locally advanced disease and 41 (75.9%) with metastatic disease. In total, 27 (50%) patients exhibited recurrence after surgery. In total, 35 (64.8%) patients were treated with other chemotherapeutic agents before the administration of GCD combination chemotherapy. The chemotherapy regimens before GCD therapy were as follows: GC combination therapy ($n = 14$), gemcitabine, cisplatin, and S-1 therapy ($n = 5$), S-1 therapy ($n = 1$), and multiple types of chemotherapy ($n = 9$). In addition, six patients exhibited recurrence after adjuvant chemotherapy.

Treatment efficacy and response rate

Figure 1 shows the PFS and OS of the patients. The median PFS was 4.1 months, and the median OS was 8.0 months. According to the assessment of treatment responses based on the RECIST criteria, 14 (25.9%) patients presented with progressive disease (PD), 23 (42.6%) with stable disease (SD), and 5 (9.3%) with partial response (PR). In total, 12 (22.2%) patients did not undergo imaging evaluation. Among them, eight patients had progressive disease due to clinical progression, as indicated by rising tumor marker levels and deterioration of the overall condition, leading to transition to palliative care. The remaining four patients presented with stable disease, as there was no evidence of increased tumor marker levels or deterioration in overall health condition. Then, chemotherapy was continued in these patients. The disease control rate (DCR) was 66.7%.

Adverse events

Table 2 presents the adverse events (AEs). There were 57 AEs based on the blood test results. Neutropenia was the most common AE according to the blood test ($n = 20$ [35.1%]). In total, 24 (42.1%) patients developed grade 3 or higher AEs. Further, 57 AEs were identified based on the physical findings. Fatigue was the most common AE according to the physical findings ($n = 20$ [28.1%]). Five (8.8%) patients exhibited grade 3 or higher AEs. The immune-related adverse events (irAEs) were observed: grade 1 skin rash, $n = 1$; grade 2 skin rash, $n = 1$; and grade 2 intestinal pneumonias, $n = 1$

Details of dose reduction

The details and reasons for dose reduction are presented in Supplementary Table 1. Renal impairment was the most common reason for dose reduction. Seven patients did not receive gemcitabine and cisplatin on day 8. One patient received durvalumab monotherapy only from the first course due to a history of anaphylaxis to gemcitabine and cisplatin. The relative dose intensity of gemcitabine and cisplatin was calculated based on the administered doses relative to the planned doses across all patients. The average relative dose intensity of gemcitabine was 76.5%, and the average relative dose intensity of cisplatin was 67.1%. These details reflected dose reductions and treatment delays in some patients during the treatment course. These values were calculated as weighted averages, with consideration of the proportion of patients receiving each dose level.

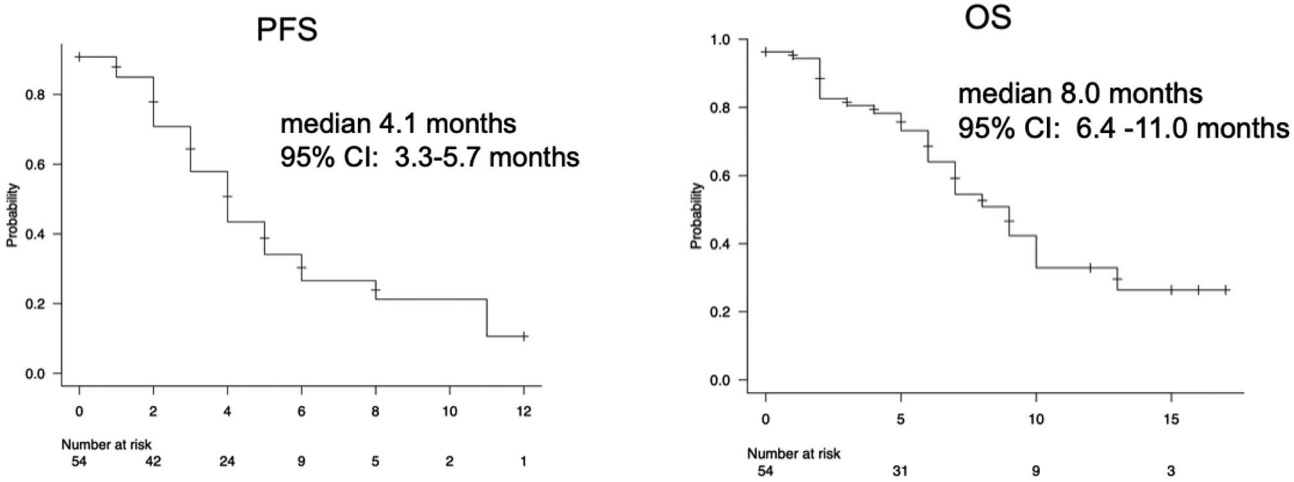


Fig. 1 Kaplan–Meier curves for PFS and OS

Table 2 Adverse events

Adverse events based on the blood test results						
	Grade 1	Grade 2	Grade 3	Grade 4	All grades (%)	Grade ≥ 3 (%)
Leukopenia	1	6	3	0	17.5	5.3
Neutropenia	1	11	8	0	35.1	14.0
Thrombocytopenia	0	3	2	2	12.3	7.0
Anemia	2	8	8	0	31.6	14.0
Hyperkalemia	0	1	0	0	1.8	0.0
Hyponatremia	0	0	1	0	1.8	1.8
All	4	29	22	2		42.1
Adverse events based on the physical findings						
	Grade 1	Grade 2	Grade 3	Grade 4	All grades (%)	Grade ≥ 3 (%)
Reduced appetite	1	10	1	0	21.1	1.8
Nausea and vomiting	6	0	0	0	10.5	0.0
Coughing	1	0	0	0	1.8	0.0
Interstitial pneumonia	0	1	0	0	1.8	0.0
Myalgia	0	1	0	0	1.8	0.0
Bloody bowel discharge	0	0	1	0	1.8	1.8
Vomiting blood	0	0	0	1	1.8	1.8
Duodenal ulcer	0	0	0	1	1.8	1.8
Hemorrhagic gastric ulcer	0	0	1	0	1.8	1.8
Skin rash	1	1	0	0	3.5	0.0
Extravascular leakage from the puncture site of the drip	0	1	0	0	1.8	0.0
Skin flushing	0	1	0	0	1.8	0.0
Ascites	0	1	0	0	1.8	0.0
Edema	1	0	0	0	1.8	0.0
Constipation	8	2	0	0	17.5	0.0
Fatigue	8	8	0	0	28.1	0.0
All	26	26	3	2		8.8
Immune-related adverse events						
Skin rash	Grade 1					
Skin rash	Grade 2					
Interstitial pneumonia	Grade 2					

Factors influencing PFS and OS

Table 3 shows the impact of various factors affecting PFS and OS. Based on the multivariate regression analysis using the Cox proportional hazards model, age, ECOG-PS score, and NLR significantly influenced PFS. In addition, ECOG-PS score and NLR significantly affected OS. Figure 2 presents the impact of NLR on OS. Patients with an NLR of ≥ 3 had a significantly poorer median OS than those with an NLR of < 3 (5.9 vs. 10.1 months, $P = 0.004$).

Discussion

The current study showed the initial experience in GCD combination chemotherapy in patients with unresectable advanced-stage BTC in a real-world clinical practice. The median age of our cohort was 72 years, and 27 (50%) patients exhibited recurrence after surgery. Further, 35 (64.8%) patients were treated with other chemotherapeutic agents before administering GCD combination chemotherapy. In total, 36 (66.7%) patients were administered with a reduced dose of GCD. The median PFS was 4.1 months, and the median OS was 8.0 months. Approximately 50.9% of patients presented with grade 3 or higher AEs. Therefore, GCD combination chemotherapy can be administered with safety. According to the Cox proportional hazards model, age, ECOG-PS score, and NLR significantly influenced PFS, while ECOG-PS score and NLR had a significant impact on OS. Patients with an NLR of ≥ 3 had a significantly poorer median OS than those with an NLR of < 3 (5.9 vs. 10.1 months, $P = 0.004$).

Table 4 shows the TOPAZ-1 trial data, Italian RWD [3], and German RWD [4]. Our cohort had a higher median age, a greater proportion of postoperative recurrence cases, and a lower number of patients who had received prior GCD combination chemotherapy as the first-line treatment. In our cohort, the median PFS was 4.1 months, and the median OS was 8.0 months. The differences in patient characteristics between our cohort and previous studies could have significantly influenced the observed PFS and OS outcomes. The higher median age in our cohort suggests that frailty and reduced tolerance to chemotherapy may have contributed to shorter

Table 3 Analysis of factors influencing PFS and OS

PFS						
	Univariate analysis			**Multivariate analysis**		
	HR	**95% CI**	**p value**	**HR**	**95% CI**	**p value**
Age	0.98	0.94–1.02	0.27	0.97	0.92–0.99	0.03
Sex	1.03	0.52–2.01	0.94			
BMI	0.77	0.51–1.16	0.21			
ECOG-PS score	2.62	1.24–5.51	0.01	3.54	1.56–8.00	< 0.01
Platelet count	1.13	0.34–3.72	0.84			
AST level	1.22	0.58–2.58	0.61			
ALT level	0.94	0.42–2.10	0.89			
NLR	1.19	1.02–1.38	0.03	1.31	1.10–1.57	< 0.01
CEA level	1.33	0.81–2.17	0.26			
CA19-9 level	1.01	0.58–1.78	0.96			
Primary tumor site	0.95	0.70–1.29	0.75			
Disease status	1.16	0.47–2.81	0.75			
Previous history of surgery	0.94	0.47–1.87	0.85			
Previous history of chemotherapy	1.27	0.60–2.70	0.53			
OS						
	Univariate analysis			Multivariate analysis		
	HR	95% CI	p value	HR	95% CI	p value
Age	1.00	0.96–1.05	0.95			
Sex	0.91	0.41–2.02	0.82			
BMI	0.87	0.55–1.37	0.54			
ECOG-PS score	2.57	1.15–5.73	0.02	2.59	1.08–6.22	0.03
Platelet count	1.08	0.32–3.63	0.91			
AST level	1.90	0.80–4.51	0.15			
ALT level	1.53	0.63–3.70	0.34			
NLR	1.41	1.18–1.68	< 0.01	1.50	1.23–1.82	< 0.01
CEA level	1.28	0.74–2.23	0.38			
CA19-9 level	1.10	0.58–2.09	0.78			
Primary tumor site	0.89	0.64–1.26	0.52			
Disease status	0.63	0.26–1.52	0.3			
Previous history of surgery	0.79	0.36–1.76	0.57			
Previous history of chemotherapy	1.02	0.42–2.48	0.97			

Abbreviations: PFS, progression-free survival; BMI, body mass index; ECOG-PS, Eastern Cooperative Oncology Group performance status; AST, aspartate aminotransferase; ALT, alanine transaminase; NLR, neutrophil-to-lymphocyte ratio; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19 – 9; OS, overall survival

survival outcomes. Additionally, the greater proportion of postoperative recurrent cases (50% vs. 19.6% in the TOPAZ-1 trial) likely impacted disease progression, as recurrent tumors tend to exhibit more aggressive behavior. Moreover, the high proportion of patients who had received prior chemotherapy (64.8%) suggests that many had already been exposed to multiple treatment regimens, potentially leading to lower responsiveness to GCD therapy.

Furthermore, the disease control rate (DCR) in our cohort was notably lower than in the TOPAZ-1 trial and the Italian RWD (66.7% vs. 85.3% and 87.6%, respectively), which may reflect the presence of a more treatment-resistant population. In terms of safety, the incidence of grade 3 or higher adverse events (AEs) in our study (45.7%) was lower than that reported in the TOPAZ-1 trial (75.7%) and German RWD (74.3%), suggesting possible differences in treatment intensity or dose modifications. Given these differences, caution should be exercised when generalizing our findings to broader BTC populations. Our study primarily represents patients with postoperative recurrence or prior chemotherapy exposure, and further investigations with larger, more diverse cohorts are necessary to validate the impact of GCD combination chemotherapy in different patient subsets.

In our study, regarding safety profile, 57 AEs occurred in 54 patients. The higher number of reported AEs can be attributed to the fact that both physical examination findings and blood test abnormalities were counted separately. However, the incidence of grade 3 or higher AEs in our study was lower compared with that in the TOPAZ-1

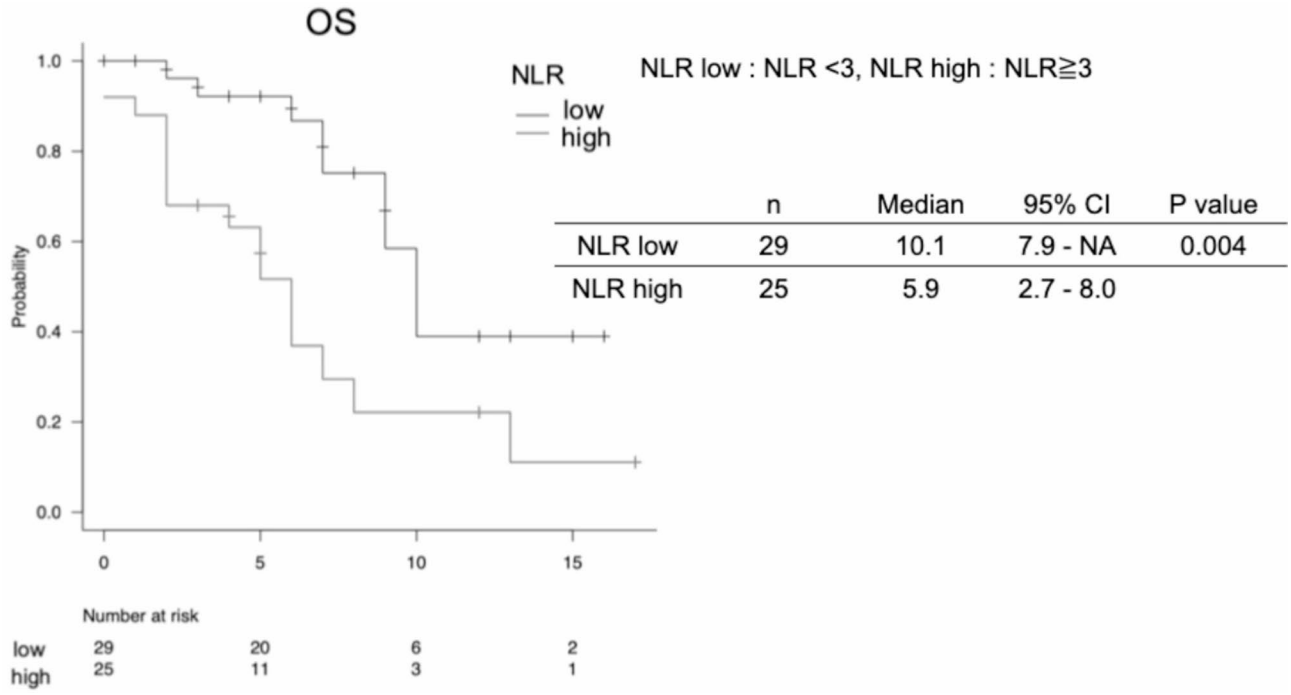


Fig. 2 Kaplan–Meier curves showing the impact of NLR on OS

Table 4 Comparison between our cohort and those in previous reports

	Our cohort	TOPAZ-1 trial*	Real-world data from Italy	Real-world data from Germany
Number of patients	54	341	145	35
Median age (range)	72 (51–86)	64 (20–85)	66 (35–84)	62 (27–80)
Median PFS (month)	4.1	7.2	8.9	5.1
Median OS (month)	8.0	12.8	12.9	10.3
DCR	66.7%	85.3%	87.6%	61.7%
≥ Grade 3 AEs	45.7%	75.7%	35.2%	74.3%
Recurrence after surgery	27 (50.0%)	67 (19.6%)	41 (28.3%)	9 (25.7%)
Previous chemotherapy	35 (64.8%)	67 (19.6%)	25 (18.1%)	8 (23%)

TOPAZ-1 trial [2],; Real-world data from Italy [3],; Real-world data from Germany [4],

Abbreviations: PFS, progression-free survival; OS, overall survival; DCR, disease control rate; AE, adverse events

trial (50.9% vs. 75.5%). In our study, three irAEs were observed: grade 1 skin rash, $n = 1$; grade 2 skin rash, $n = 1$; and grade 2 interstitial pneumonia, $n = 1$. However, there were no grade 3 or higher irAEs observed. Although our cohort had advanced median age (72 years), we safely introduced GCD combination chemotherapy by adjusting the intervals and doses of chemotherapy administration with consideration of the individual patient's situation. Supplementary Table 1 shows the details. Further, 38 (66.7%) of 54 patients received reduced doses of chemotherapy. Seven of these patients skipped the administration of GC on day 8 due to neutropenia, renal impairment, or fatigue.

Factors that influence prognosis, particularly their impact on PFS and OS, were investigated. As shown in Table 3, age, ECOG-PS score, and NLR were statistically significant factors affecting PFS. Meanwhile, ECOG-PS score and NLR had a statistically significant impact on OS. Patients with an NLR of ≥ 3 had a significantly poorer median OS than those with an NLR of < 3 (5.9 vs. 10.1 months, $P = 0.004$). As expected, a poor performance status is correlated with a shorter PFS [22, 23]. Performance status (PS) is a key prognostic factor in patients with various advanced-stage cancers. Despite being a somewhat subjective and imprecise measure of the physical condition of a patient with cancer, PS emerged as the most significant predictor of survival in patients with advanced-stage BTC undergoing chemotherapy. Consistent with our results, several studies have also shown that PS is a prognostic factor in patients with advanced-stage BTC [23–35]. An increased NLR is considered a marker of poor prognosis across various types of cancers [23, 36, 37]. Several studies emphasized the role of NLR in predicting OS. An increased NLR may indicate enhanced

immunocompetence or neutrophilia. Neutrophilia is widely recognized to play a role in stimulating the tumor microenvironment, specifically by promoting cell proliferation, angiogenesis, invasion, and metastasis in cancer [37–40]. Further, neutrophilia can contribute to immune suppression by inhibiting the cytolytic activity of immune cells such as lymphocytes, T cells, and natural killer cells [41]. Conversely, lymphocytes are essential mediators of the anti-tumor immune response. Previous studies have found that a reduced lymphocyte count within tumors is related to poorer chemotherapy responses and worse prognoses in patients with cancer. Consequently, a higher NLR might be associated with potential tumor growth. The NLR has also emerged as a significant prognostic biomarker for patients receiving immune checkpoint inhibitors (ICIs) for various types of cancers. Recent studies have investigated the prognostic value of NLR in patients with advanced-stage cancers treated with ICIs [42–44]. A higher NLR is associated with a poor OS and PFS and lower response rates across multiple types of cancer [43]. In upper gastrointestinal cancers, a lower NLR is correlated with a better OS and improved efficacy of ICIs [44]. Combined NLR and tumor mutational burden can further enhance the predictive capacity for the benefits of ICI [43]. Based on these findings, NLR can be a promising, easily accessible biomarker for predicting the efficacy of ICI in various types of cancer. Rimini et al. have reported that ICIs are associated with NLR in patients with BTC. In their study, patients with an NLR of ≥3 had a shorter PFS than those with an NLR of <3. However, they did not provide information regarding the association between NLR and OS [3]. As shown in Figs. 1 and 2, patients with an NLR of ≥3 had a significantly shorter OS. Thus, NLR is a factor influencing OS. To the best of our knowledge, this study first reported that NLR was a predictor of OS in patients with BTC who were treated with ICI anti-PD-L1 antibody.

The current study had several limitations. First, this study differs from the TOPAZ-1 trial in the following aspects: (1) a substantial number of patients in our cohort had received various chemotherapeutic regimens prior to the introduction of GCD combination chemotherapy, and (2) compared to the TOPAZ-1 trial, the proportion of patients with distal bile duct cancer was lower, and patients with ampulla of Vater cancer were included. These might have influenced the evaluation of PFS and OS. Second, the median follow-up period was relatively short at 6 months. Hence, studies with a longer follow-up period should be performed to more accurately assess OS. Third, due to the relatively small sample size, the generalizability of our findings may be limited. Further studies with larger cohorts are needed to confirm our results and improve external validity.

Conclusions

This study presented a real-world experience in the use of GCD combination chemotherapy in clinical practice. GCD therapy can be safely administered. To the best of our knowledge, this study first reported that NLR was a significant prognostic factor of OS in patients with unresectable advanced-stage BTC.

Abbreviations

BTC	Biliary tract cancer
GCD	Gemcitabine, cisplatin, and durvalumab
PFS	Progression-free survival
OS	Overall survival
AEs	Adverse events
RWD	Real-world data
ECOG-PS	Eastern Cooperative Oncology Group performance status
NLR	Neutrophil-to-lymphocyte ratio
irAEs	Immune-related adverse events

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12957-025-03834-x.

Supplementary Material 1

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Author contributions

All authors have fully satisfied the ICMJE authorship criteria as follows: study design: S.M, H.K, T.T, Z.M, A.H, and K.S; data collection: S.M, H.K, Z.M, M.K, Y.K; statistical analysis and interpretation of results: S.M, H.K, T.T, Z.M, A.H, and K.S; drafting of the manuscript: S.M, H.K, T.T, Z.M, A.H, and K.S; and critical revision of the manuscript for important intellectual content: H.K, T.T, Z.M, A.H, and K.S. All authors have read and approved the final manuscript and are accountable for all aspects of the work, particularly in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Consent for publication

Not applicable. Individual identifying data were not included in this manuscript.

Competing interests

The authors declare no competing interests.

Ethical approval and consent to participate statement

This study was approved by the institutional review board of Fujita Health University (HM24-011). This study was also performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Informed consent for this study was obtained through an opt-out method.

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