Systematic Review/Meta-analysis

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Comparison of second-line chemotherapy regimens in advanced biliary tract cancer: a systematic review, meta-analysis, and population-based cohort study

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Background: Biliary tract cancers (BTCs) are aggressive malignancies with limited treatment options, especially after first-line chemotherapy failure. FOLFIRINOX, though established for pancreatic cancer, has shown promise in advanced BTC, yet its role as a second-line treatment remains unclear. To address this gap, we conducted a retrospective cohort study to evaluate the efficacy and safety of FOLFIRINOX and performed a systematic review with meta-analysis to compare its outcomes with currently recommended regimens, including FOLFIRI, FOLFOX, and nal-IRI/FL.

Methods: We retrospectively analyzed 54 patients with BTC treated with FOLFIRINOX as second-line therapy after progression on first-line chemotherapy at a single tertiary hospital between 2011 and 2022. A systematic review and meta-analysis, registered with PROSPERO, incorporated 21 studies comparing second-line regimens for BTC, assessing progression-free survival (PFS), overall survival (OS), objective response rate (ORR), disease control rate (DCR), and safety.

Results: In our cohort, median PFS and OS were 2 · 7 and 8 · 9 months, respectively. ORR was 12 · 5%, and DCR was 52 · 1%, with 4 · 2% achieving complete response. Meta-analysis revealed pooled PFS and OS for FOLFIRINOX at 4 · 15 and 8 · 91 months, respectively, suggesting a potential benefit over FOLFIRI and FOLFOX. Grade 3–5 neutropenia occurred in 40 · 7% of patients, leading to dose reductions in 29.6% but low discontinuation rates (3 · 7%).

Conclusion: FOLFIRINOX demonstrates numerically favorable outcomes compared to current second-line regimens for advanced BTC, with manageable toxicities. These findings suggest FOLFIRINOX as a potential second-line option, warranting further prospective validation and patient selection refinement.

Keywords: biliary tract cancer, FOLFIRINOX, meta-analysis, retrospective cohort study

Introduction

Biliary tract cancers (BTCs), including intrahepatic, perihilar, or extrahepatic cholangiocarcinoma, and gallbladder carcinoma, are aggressive malignancies that pose significant challenges in diagnosis and treatment. Surgical resection is the only curative treatment option for BTC; however, fewer than a quarter of patients are diagnosed at the localized stage and are eligible for surgery[1-3]. For patients with unresectable or metastatic BTC, systemic chemotherapy is crucial[4]. Currently, durvalumab or pembrolizumab plus gemcitabine and cisplatin are preferred as first-line chemotherapies[5]. However, both regimens offer limited overall survival (OS; <1 year) and progression-free survival (PFS; <8 months)[6,7]. Most patients require subsequent chemotherapy after disease progression, yet no regimen has been strongly recommended for subsequent therapy[5].

The FOLFOX regimen has been investigated as second-line chemotherapy in advanced BTC. However, this regimen only extended OS by approximately 1 month compared to supportive

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care[8]. Second-line FOLFIRI has also been evaluated. Retrospective studies reported a median OS of 5 · 0–6 · 6 months, not inferior to FOLFOX (6 · 2 months), but PFS with FOLFIRI was (1 · 7–2 · 4 months) shorter than FOLFOX (4 · 0 months)[9,10]. The NIFTY study revealed that liposomal irinotecan plus fluorouracil (nal-IRI/FL) could improve PFS in patients with advanced BTC previously treated with gemcitabine plus cisplatin, compared to fluorouracil and leucovorin, although the benefit was modest (≤4 months)[11].

The FOLFIRINOX regimen, initially proven to improve survival in pancreatic cancer compared to gemcitabine, is now being explored for efficacy in BTC. A recent phase II study proposed FOLFIRINOX as an effective alternative to FOLFOX or FOLFIRI as second-line chemotherapy, with median PFS and OS of 6 · 2 and 10 · 7 months, respectively[12]. Another phase II study with modified FOLFIRINOX in Korea showed median PFS and OS of 2 · 8 and 6 · 2 months, respectively, suggesting modest effectiveness[13].

The optimal regimen for second-line treatment of advanced BTC remains uncertain. To help address this gap, we first evaluated the efficacy and safety of FOLFIRINOX in patients with advanced BTC who had progressed following first-line chemotherapy, using data from a 12-year retrospective analysis at a single tertiary center. These real-world findings were subsequently compared with outcomes from a systematic review and meta-analysis of published studies on currently recommended second-line treatment regimens.

This study complies with the TITAN 2025 (Transparency In The reporting of Artificial INtelligence) guidelines to ensure responsible and transparent use of AI tools during the data extraction and analysis process[14].

HIGHLIGHTS

- Real-world data from a 12-year institutional cohort showed FOLFIRINOX achieved a median OS of 8.9 months and PFS of 2.7 months in patients with advanced BTC.
- Meta-analysis showed FOLFIRINOX was associated with numerically favorable or comparable survival outcomes to recommended regimens such as FOLFOX, FOLFIRI, and nal-IRI/FL.
- Findings support the potential of FOLFIRINOX as an effective second-line therapy for BTC, warranting further prospective trials and biomarker-based patient selection.

Materials and methods

Cohort of patients with advanced BTC

Patients

From January 2011 to December 2022, a total of 1308 patients diagnosed with BTC underwent chemotherapy at a single tertiary center in Korea. Among them, 54 patients with histologically or cytologically confirmed advanced, unresectable, or metastatic BTC who received FOLFIRINOX or modified FOLFIRINOX as second-line chemotherapy after progression on first-line treatment were identified and included in this retrospective cohort study. Inclusion criteria were applied consistently to minimize selection bias and are summarized in Supplementary Digital Content Table S1, available at: http://links.lww.com/JS9/F13. No additional exclusion criteria were applied beyond this definition. The median follow-up period was 20.3 months.

Statistical analysis

To determine the efficacy of FOLFIRINOX, Kaplan–Meier estimation was performed to analyze median PFS and OS. PFS was defined as the time from the first day of FOLFIRINOX or modified FOLFIRINOX (mFOLFIRINOX) administration to the date of disease progression. OS was defined as the time from the first day of treatment to the date of death or last follow-up. For patients who were lost to follow-up without a confirmed outcome event, the date of their last follow-up was used as the censoring time point in the Kaplan–Meier survival analysis. No exclusion criteria were applied for outliers, and all eligible patients were included in the analysis. Continuous variables were summarized as means with standard deviations or medians with interquartile ranges, depending on their distribution. Categorical variables were reported as counts and percentages. In addition to Kaplan–Meier estimates for PFS and OS, descriptive statistics were used to summarize objective response rate (ORR), disease control rate (DCR), and safety outcomes. All analyses were conducted using SPSS version 26.0 (PASW Statistics Inc., Chicago, IL, USA), and a *P*-value of less than 0.05 was considered statistically significant.

Systematic review and meta-analysis

Protocol and registration

The study protocol was registered with PROSPERO and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Assessing the Methodological Quality of Systematic Reviews (AMSTAR) guidelines[15–17].

Eligibility criteria

Inclusion criteria were based on the predefined Population, Intervention, Comparator, Outcome, Study Design, and Time (PICOST) framework (Table 1). The primary objective was to assess the outcomes of nal-IRI/FL, FOLFIRINOX, FOLFIRI, and FOLFOX as second-line therapies in adults with advanced, unresectable, or metastatic BTC who had previously received first-line treatment. Eligible studies included randomized controlled trials (RCTs), single-arm trials, and non-randomized studies reporting efficacy and safety outcomes for the specified regimens. Efficacy outcomes included median PFS, median OS, ORR, and DCR. ORR was defined as the sum of complete and partial responses, while DCR included complete response (CR), partial response (PR), and stable disease (SD). Safety outcomes included any-cause and treatment-related adverse events (AEs), serious (grade 3–5) AEs, treatment discontinuation due to AEs, and deaths attributed to AEs.

Exclusion criteria included: (1) studies involving patients with other cancers (e.g., hepatocellular carcinoma or pancreatic cancer) or molecularly selected populations (e.g., HER2-positive only); (2) studies that did not evaluate the regimens of interest; (3) animal or *in vitro* studies, case reports, case series, editorials, commentaries, letters, reviews, and meta-analyses; and (4) studies focusing solely on genetic biomarkers or cost-effectiveness. No restrictions were placed on language or publication year.

Information source and search strategy

A comprehensive search was conducted for studies published through 4 December 2024. Databases included Medline,

Table 1

PICOST eligibility criteria for the systematic review and meta-analysis

Criteria	Inclusion criteria	Exclusion criteria
Population	Adults (≥18 years) with advanced (unresectable and/or metastatic) biliary tract cancer, including intrahepatic or extrahepatic cholangiocarcinoma and gallbladder cancer • Previously treated for first-line therapy	• Patients with other types of cancer (e.g., hepatocellular carcinoma, pancreatic cancer) • Individuals with specific conditions (e.g., HER2-positive only populations)
Interventions/ comparators	• Nal-IRI/FL (nanoliposomal irinotecan + 5-FU + leucovorin) • FOLFIRINOX (irinotecan + 5-FU + leucovorin + oxaliplatin) • FOLFIRI (irinotecan + 5-FU + leucovorin) • FOLFOX (5-FU + leucovorin + oxaliplatin) • Including modified versions	• Monotherapy (e.g., irinotecan monotherapy, 5-FU monotherapy) • Other regimens (e.g., immune checkpoint inhibitors) • Mixed regimens (e.g., FOLFIRI + nivolumab, gFOLFOXIRITAX)
Outcomes	Efficacy outcomes • Median progression-free survival • Median overall survival • Objective response rate (complete response and partial response) • Disease control rate • Safety outcomes: • Any-cause and treatment-related overall adverse events • Any-cause and treatment-related serious (grade 3–5) adverse events • Discontinuation due to adverse events • Deaths due to adverse events	NA
Study design	• Randomized controlled trials • Single-arm trials • Nonrandomized trials	• Animal or *in vitro* studies • Case reports or case series • Editorials, commentaries, letters, reviews, or meta-analyses • Genetic studies (molecular, biomarkers, phenotypes) • Cost-effectiveness studies
Time	No restriction	NA
Language	No restriction	NA

NA, not applicable.

Embase, Scopus, Web of Science, ClinicalTrials.gov, Cochrane CENTRAL, and the International Clinical Trials Registry Platform (ICTRP). Additional sources included grey literature via Google and Google Scholar, and manual reference checks. MeSH and entry terms related to BTC and relevant regimens were prioritized, with supplemental terms added to ensure a comprehensive search. Final search strategies were developed collaboratively by all authors (Supplementary Digital Content Table S2, available at: http://links.lww.com/JS9/F13).

Study selection

Initial data extraction and review were conducted by the corresponding authors. Title, abstract, and full-text screening were independently performed by the first authors using the predefined PICOST criteria. Reference lists and grey literature were also reviewed. Discrepancies were resolved through discussion among the authors.

Effect measures and data synthesis

Overall survival and progression-free survival. OS was defined as the time from the first dose to death from any cause, and PFS as the time from the first dose to either disease progression or death. Individual patient-level data were reconstructed from Kaplan–Meier curves using the Guyot algorithm and WebPlotDigitizer (https://automeris.io/), and the curves were pooled[18]. Reconstructed pseudo-individual patient-level data for each trial arm were used to generate pooled survival curves, facilitating time-dependent survival modeling despite the lack of raw patient data. Survival probabilities at each time point were arcsine transformed and analyzed using a random-effects meta-analysis, following the method of Combescure *et al*[19]. Confidence intervals (CIs) were calculated using Monte Carlo's method[20]. Pooled median survival times and CIs were estimated from the summary survival curve using linear interpolation. Survival curve pooling was conducted using the metasurv package in R (version 4.2.2).

In parallel, we also performed a separate meta-analysis using the generic inverse variance method for studies that reported only summary statistics, such as median survival times with corresponding CIs, in the absence of Kaplan–Meier curves[21]. These two approaches were not mathematically combined but analyzed and interpreted separately, providing complementary perspectives depending on the level of data availability. Pooled hazard ratios were not calculated, as most included studies did not report hazard ratios or their standard errors, precluding reconstruction.

Heterogeneity was assessed using the I^2 statistic[22,23]. A random-effects model was applied when heterogeneity exceeded 50% ($I^2 > 50\%$), and a fixed-effects model was used otherwise[24,25]. Forest plots were generated using R (version 4.2.2), incorporating data from the present cohort study.

Additional details on materials and methods are available in the Supplementary Digital Content Materials and Methods, available at: http://links.lww.com/JS9/F14.

Results

Cohort study

Patient demographics

We reviewed the clinical records of all patients who received chemotherapy for BTC at our institution between 2011 and 2022. A total of 1760 patients with BTC received chemotherapy. Among them, 54 patients received at least one cycle of FOLFIRINOX as a second-line regimen. Of these patients, six patients were lost to follow-up after receiving at least one cycle of FOLFIRINOX but before the first response evaluation, and thus their treatment response could not be assessed. As a result, the initial analysis of the FOLFIRINOX response was conducted in 48 patients. Of the 48 patients who initiated second-line FOLFIRINOX, 12 were excluded from the full analysis set, which included only those who received treatment until the first scheduled tumor response evaluation. The excluded patients consisted of four who died prior to scheduled imaging (due to pneumonia, gallbladder perforation, or septic shock), one who was referred to hospice care, two who refused treatment, and five who showed incidental findings of disease progression based on clinical symptoms (e.g., gastrointestinal bleeding, jaundice, or fever) before formal evaluation (Fig. 1). These events precluded objective assessment of radiologic response, but such patients were included in the intention-to-treat survival analysis, including both PFS and OS. Treatment response to chemotherapy was assessed every 2 to 3 months following treatment initiation using imaging modalities such as computed tomography (CT) or magnetic resonance imaging (MRI). Assessments were conducted in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, a standardized method for evaluating treatment response in solid tumors[26].

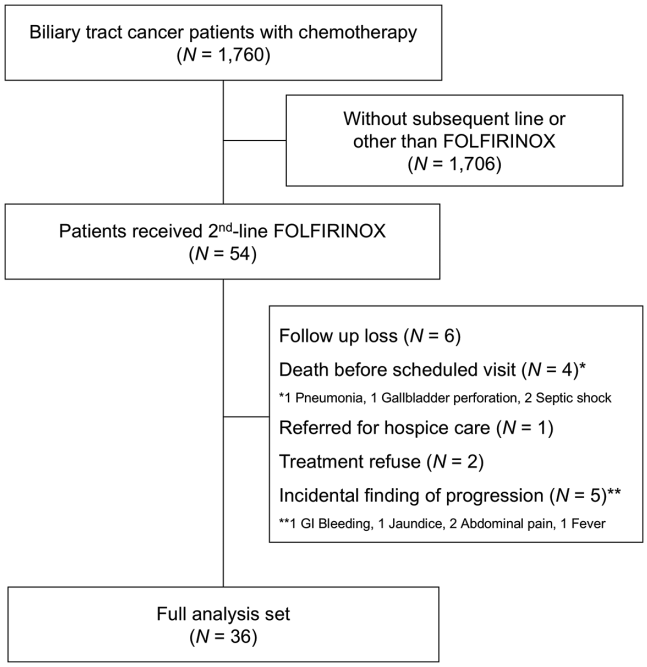

Figure 1. Flow diagram of cohort study.

Supplementary Digital Content Table S3, available at: http://links.lww.com/JS9/F13, summarizes the baseline characteristics of enrolled patients. The mean patient age was 61 · 6 years, and 59 · 3% were male. Among the 54 patients, 14 (26 · 0%) had extrahepatic cholangiocarcinoma, 11 (20 · 0%) had intrahepatic cholangiocarcinoma, 7 (13 · 0%) had perihilar cholangiocarcinoma, and 22 (41 · 0%) had gallbladder cancer. Twenty-four (44 · 4%) patients underwent curative surgery and experienced tumor recurrence. As primary chemotherapy, most patients received gemcitabine-based chemotherapy (gemcitabine monotherapy in 6 [11 · 1%], gemcitabine + cisplatin in 15 [27 · 8%], and gemcitabine + cisplatin + Abraxane in 32 [59 · 3%]), except for one patient who received fluorouracil (5-FU) + cisplatin. As second-line salvage therapy, 52 patients (96 · 3%) received the FOLFIRINOX regimen (intravenous administration of irinotecan [180 mg/m^2], oxaliplatin [85 mg/m^2], leucovorin [400 mg/m^2], and 5FU [2800 mg/m^2, including the bolus injection and the 46-h constant infusion]). Two patients (3 · 7%) received the mFOLFIRINOX regimen (intravenous administration of irinotecan [120 mg/m^2], oxaliplatin [60 mg/m^2], leucovorin [400 mg/m^2], and 5-FU [2800 mg/m^2, including the bolus injection and 46-h constant infusion]). Three patients (5.6%) underwent concurrent radiotherapy.

Efficacy

With a median follow-up of 20 · 3 months, the mPFS and OS were 2 · 7 months (95% confidence interval [CI], 0 · 9–4 · 5) and 8 · 9 months (95% CI, 6 · 2–11 · 6), respectively (Fig. 2 and Supplementary Digital Content Table S4, available at: http://links.lww.com/JS9/F13). There was no significant difference in the median PFS and median OS among cancer types (Supplementary Digital Content Figure S1, available at: http://links.lww.com/JS9/F12). Tumor response was assessed in 48 patients, excluding the six who were lost to follow-up before the first response evaluation. The objective response rate (ORR, CR + PR) was 12 · 5%, and the disease control rate (DCR, CR + PR + SD) was 52 · 1%. Supplementary Digital Content Figure S2, available at: http://links.lww.com/JS9/F12, illustrates the maximal changes in target lesion size from baseline. Notably, two patients achieved CR after 17 and 12 cycles of FOLFIRINOX and remained disease-free for 14 · 0 and 1 · 9 months without any treatment, respectively (Table 2 and Supplementary Digital Content Figure S3A, available at: http://links.lww.com/JS9/F12). Additionally, more than 25% of patients were long-term responders who were able to continue chemotherapy without progression for over 6 months (Supplementary Digital Content Table S4, available at: http://links.lww.com/JS9/F13 and Supplementary Digital Content Figure S3B, available at: http://links.lww.com/JS9/F12). To ensure an accurate assessment of tumor response, we defined the full analysis set as patients who underwent at least one scheduled response evaluation. Patients who could not complete initial imaging assessments due to rapid clinical deterioration or severe toxicities were excluded from this subset. In this group, the median PFS was 4 · 2 months and the median OS was 11 · 4 months (Table 2). The ORR and DCR were 16 · 7 and 63 · 9%, respectively, with over 38% classified as long-term responders.

Safety

A total of 26 patients (48 · 1%) experienced serious adverse events of Common Terminology Criteria for Adverse Events(CTCAE)

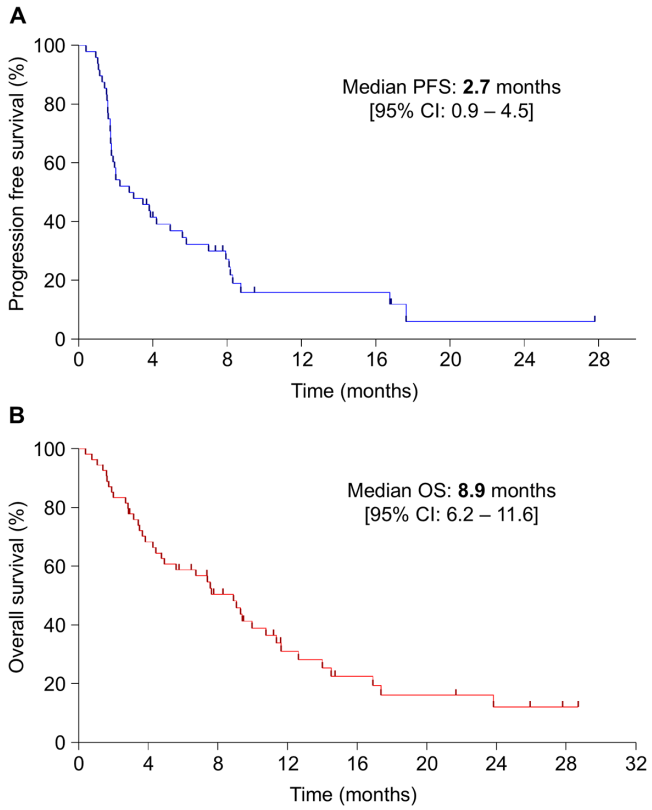

Figure 2. Kaplan–Meier curves for progression-free survival (A) and overall survival (B) in the cohort study. PFS, progression-free survival; OS, overall survival; CI, confidence interval.

Table 2

Clinical outcomes of cohort patients (full analysis set)

Best responses (*N* = 36)	
Complete response (CR)	2 (5 · 6)
Partial response (PR)	4 (11 · 1)
Stable disease (SD)	17 (47 · 2)
Progressive disease (PD)	13 (36 · 1)
Objective response rate (ORR, CR + PR)	6 (16 · 7)
Disease control rate (DCR, CR + PR + SD)	23 (63 · 9)
Treatment cycles	6 ± 9
Progression-free survival (months)	4 · 2 (1 · 49–6 · 91)
Ratio of long-term responder (≥6 months)	14 (38 · 9)
Overall survival (months)	11 · 4 (8 · 33–14 · 40)

Full analysis set is defined as patients who have undergone at least one scheduled response evaluation.
Data are presented as *n* (%) or median (95% confidence interval).

Grade 3-5 (Supplementary Digital Content Table S5, available at: http://links.lww.com/JS9/F13)[27]. In total, 22 patients (40 · 7%) experienced neutropenia, and 1 (1 · 9%) experienced febrile neutropenia. The next most common were eight anemia events (14 · 8%) and four thrombocytopenia events (7 · 4%). Two patients (3 · 7%) discontinued chemotherapy owing to chemotherapy-related side effects, drug-induced negative myoclonus, and gallbladder perforation. A total of 16 patients (29 · 6%) required dose reduction owing to treatment-related adverse events, with 13 (81 · 3%) specifically due to grade 3–5 neutropenia.

Systematic review and meta-analysis

Study selection and general characteristics of included studies

The initial search yielded records from Embase, Medline, Scopus, Web of Science, ClinicalTrials.gov, ICTRP, and CENTRAL. After removing 1032 duplicates, 2241 records remained for screening. Following title and abstract review, 2042 records were excluded, leaving 198 for full-text review. Of these, 20 studies met the inclusion criteria. Reasons for exclusion included review articles, case reports or series, duplicate data, studies on first-line therapies or mixed regimens, non-eligible diseases or treatments, irrelevant outcomes, and insufficient data. An additional three records were identified through reference list searches and gray literature screening, resulting in one more eligible study. In total, 21 studies were included in the final analysis[8,9,11–13,28–43]. The PRISMA flow diagram illustrating this process is shown in Supplementary Digital Content Figure S4, available at: http://links.lww.com/JS9/F12.

The included studies comprised four RCTs, seven single-arm trials, and ten cohort studies conducted across 11 countries. Most RCTs and single-arm trials were open-label. Sample sizes ranged from 7 to 88 patients, and most studies used gemcitabine plus platinum as first-line therapy. The median age of participants ranged from 54 to 66 years. Study characteristics are summarized in Table 3.

Summary of reported outcomes

Progression-free survival. The pooled PFS curve integrating the Kaplan–Meier curves for the individual studies is shown in Figure 3. The mPFS for the FOLFIRINOX treatment group was estimated at 3 · 34 months (95% CI: 1 · 75–4 · 58) based on three studies[12,13,38]. The FOLFIRI group showed an mPFS of 2 · 13 months (95% CI: 1 · 28–3 · 08) derived from four studies[9,31,39,40]. The mPFS for the FOLFOX group was 2 · 97 months (95% CI: 2 · 23–3 · 72), as reported in five studies[8,31,32,35,41]. For the nal-IRI/FL group, the mPFS was 2 · 82 months (95% CI: 2 · 01–3 · 90), based on three studies[11,28,42].

The pooled PFS, calculated using the generic inverse variance method without the survival curve, is presented in Supplementary Digital Content Figure S5, available at: http://links.lww.com/JS9/F12. The mPFS for the FOLFIRINOX group was calculated at 4 · 60 months (95% CI: 2.60–8.32, I^2 = 57 · 7%) from three studies[12,13,38]. The FOLFIRI group, evaluated from five studies, reported an mPFS of 2 · 88 months (95% CI: 2 · 09–3 · 97, I^2 = 54 · 6%)[9,31,34,39,40]. The mPFS for the FOLFOX group was 3 · 05 months (95% CI: 2 · 17–4 · 28, I^2 = 93 · 0%), based on six studies[8,30,31,33,35,41]. For the nal-IRI/FL group, the mPFS was 3 · 46 months (95% CI: 2 · 79–4 · 30, I^2 = 19 · 7%), as reported in five studies[11,28,36,42,43].

Overall survival. The pooled OS curve integrating the Kaplan–Meier curves for the individual studies is shown in Figure 4. The mOS for the FOLFIRINOX group was 6 · 17 months (95% CI: 4 · 34–6 · 95), based on three studies[12,13,38]. The mOS for the

Table 3

Baseline patient characteristics for included studies in the systematic review

Author	Year	Study design	Region	*N*	First-line	Second-line	Age, median (range)	ORR, n (%)	DCR, n (%)	ECOG status 0, 1, 2 (%)	Median PFS (95% CI)	Median OS (95% CI)
Vogel A ·	2024	RCT	Germany	49	gemcitabine-based	nal-IRI/FL	66 (59-70)	7 (14 · 6%)	25 (52 · 1%)	33 (67%), 16 (33%), 0 (0%)	2 · 5 (1 · 7-3 · 6)	6 · 9 (5 · 3-10 · 6)
Ying J ·	2024	Single-arm	China	7	gemcitabine-based	nal-IRI/FL	NR	1 (14 · 3%)	5 (71 · 4%)	NR	4 · 2 (1 · 4-24)	11 · 5 (3 · 9-24)
Weinberg B ·	2023	Single-arm	NS	25	gemcitabine + platinum	nal-IRI/FL	NR	NR	NR	NR	3 · 9 (2 · 7-5 · 2)	8 · 6 (5 · 4-10 · 5)
Hyung J ·	2023	RCT	Korea	88	gemcitabine + cisplatin	nal-IRI/FL	63 (38-84)	17 (19 · 3%)	64 (72 · 7%)	23 (26%), 65 (74%), 0 (0%)	3 · 9 (2 · 7-5 · 2)	8 · 6 (5 · 4-10 · 5)
Müller C	2023	Cohort	Germany	19	gemcitabine + cisplatin	FOLFIRI	NR	NR	NR	NR	2 · 8 (1 · 5-4 · 1)	3 · 4 (1 · 7-5 · 0)
Balarine M ·	2022	Cohort	Brazil	26	gemcitabine + cisplatin	FOLFOX	NR	NR	NR	NR	NR	NR
Balarine M ·	2022	Cohort	Brazil	25	gemcitabine + cisplatin	FOLFIRI	NR	NR	NR	NR	NR	NR
Lee Y ··P ·	2022	Single-arm	Korea	34	gemcitabine + cisplatin	mFOLFIRINOX	65 (40-78)	5 (14 · 7%)	21 (61 · 7%)	8 (23 · 5%), 26(76 · 4%), 0 (0%)	2 · 8 (1 · 6-4 · 0)	6 · 2 (5 · 0-7 · 4)
Allo G ·	2022	Cohort	Germany	7	Platinum-based	nal-IRI/FL	NR	0 (0%)	6 (54 · 5%)	NR	6 · 1(1 · 1-11 · 5)	12 · 1 (5 · 1-22 · 2)
Huang P ·	2022	Cohort	China	9	gemcitabine + platinum + PD-1 inhibitors and/or lenvatinib	FOLFIRI	53 (39-68)	2 (22 · 2%)	5 (55 · 5%)	5 (55 · 6%), 2 (22 · 2%), 2 (22 · 2%)	5 · 0 (2 · 7-7 · 3)	8 · 0 (6 · 0-10 · 0)
Choi I · S ·	2021	RCT	Korea	59	gemcitabine + cisplatin	mFOLFIRI	63 (26-82)	2 (4%)	32 (64%)	ECOG 0-1: 52 (88 · 1%), ECOG 2: 7 (11 · 9%)	2 · 8 (2 · 3-3 · 3)	6 · 3 (4 · 4-8 · 2)
Choi I · S ·	2021	RCT	Korea	59	gemcitabine + cisplatin	mFOLFOX	63 (26-82)	3 (5 · 9%)	34 (66 · 7%)	ECOG 0-1: 52 (88 · 1%), ECOG 2: 7 (11 · 9%)	2 · 1 (1 · 1-3 · 1)	5 · 7 (4 · 7-6 · 7)
Ye L ··F ·	2021	Cohort	China	15	gemcitabine, S-1, gemcitabine + (cisplatin or S-1 or capecitabine or albumin-bound paclitaxel)	mFOLFIRINOX	59 (37-68)	4 (26 · 7%)	12 (80%)	1 (7 · 7%), 12 (92 · 3%), 0 (0%)	6 · 7 (2 · 3-11 · 1)	13 · 2 (7 · 3-19 · 1)
Lamarca A ·	2021	RCT	U · K ·	81	gemcitabine + cisplatin	FOLFOX	65 (59-72)	4 (4 · 9%)	27 (33%)	25 (31%), 55 (68%), 0 (0%)	4 · 0 (3 · 2-5 · 0)	6 · 2 (5 · 4-7 · 6)
Belkouz A ·	2020	Single-arm	Netherlands	30	gemcitabine + cisplatin	FOLFIRINOX	60 (38-74)	3 (10%)	22 (73 · 3%)	21 (70%), 9(30%)	6 · 2 (3 · 0-9 · 1)	10 · 7 (5 · 5-15 · 4)
Talwar V ·	2020	Cohort	India	21	gemcitabine + platinum	FOLFOX	57 (29-66)	NR	NR	NR	5 · 4 (2 · 6-8 · 4)	NR
Caparica R ·	2019	Cohort	Belgium	12	gemcitabine + platinum	FOLFIRI	60 (37-82)	0 (0%)	2 (16 · 7%)	4 (33%), 5 (42%), 1 (8%)	1 · 7 (0 · 7-2 · 7)	5 · 0 (2 · 8-7 · 2)
Dang K ·	2019	Single-arm	India	29	gemcitabine + cisplatin or carboplatin	FOLFOX	54 (34-72)	9 (31%)	10 (34 · 5%)	ECOG 0-1: 25 (87 · 1%),	NR	NR
Sebbagh S ·	2016	Cohort	France	52	gemcitabine + oxaliplatin	FOLFIRI	64 (38-79)	NR	NR	13 (25 · 0%), 20 (38 · 5%), 13 (25 · 0%)	3 · 2 (2 · 2-4 · 0)	8 · 4 (6 · 0-17 · 7)
Hwang I · G ·	2015	Single-arm	Korea	30	gemcitabine/gemcitabine + cisplatin	mFOLFOX	63 (42-76)	1 (3 · 6%)	13 (46 · 4%)	2 (7%), 28 (93%), 0 (0%)	1 · 6 (1 · 5-1 · 7)	4 · 4 (2 · 6-6 · 2)
Leal J · L ·	2014	Cohort	Chile	18	gemcitabine-based	FOLFOX4	NR	0 (0%)	4 (26 · 7%)	NR	NR	NR
He S ·	2014	Single-arm	China	37	gemcitabine + cisplatin	FOLFOX	57 (32-70)	8 (21 · 6%)	23 (62 · 2%)	ECOG 0-1: 29 (78 · 4%), ECOG 2: 8 (21 · 6%)	3 · 1 (2 · 3-3 · 6)	6 · 9 (4 · 8-7 · 9)
Carbó C · H ·	2012	Cohort	Spain	11	gemcitabine + cisplatin	FOLFOX	65 (35-79)	2 (18 · 1%)	5 (45 · 5%)	NR	3 · 6 (1 · 5-5 · 7)	6 · 7 (4 · 5-9 · 0)

CR, complete response; DCR, disease control rate; ECOG, Eastern Cooperative Oncology Group; ORR, objective response rate; OS, overall survival; NR, not reported; NS, not specified; PFS, progression-free survival; PR, partial response; RCT, randomized-controlled trial.

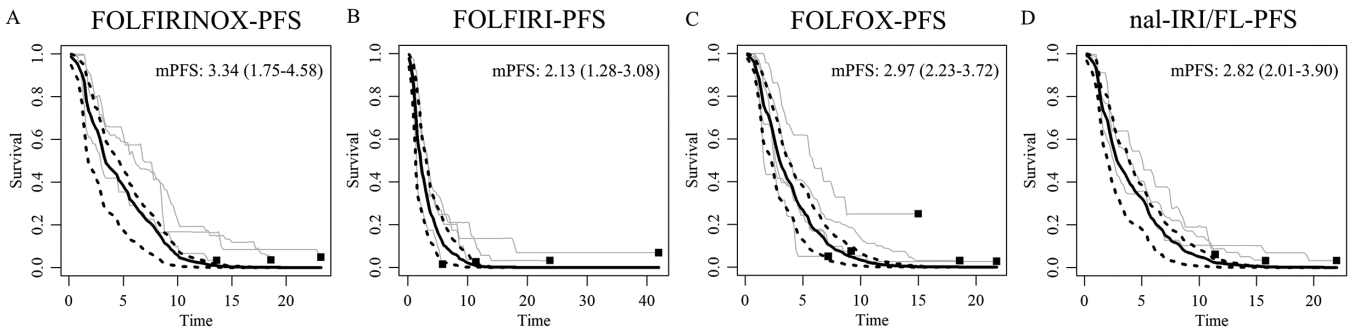

Figure 3. Kaplan–Meier estimates of progression-free survival for different second-line regimens (A) FOLFIRINOX, (B) FOLFIRI, (C) FOLFOX, and (D) nal-IRI/FL. The gray lines represent the Kaplan–Meier estimates of the overall survival for each trial arm. Black squares represent the end of the follow-up for each trial.

FOLFIRI group was 3 · 88 months (95% CI: 2 · 57–5 · 61), as reported in five studies[9,31,34,39,40]. The mOS for the FOLFOX group was 5 · 11 months (95% CI: 3 · 18–5 · 90), based on three studies[8,31,35]. For the nal-IRI/FL group, the mOS was 5 · 95 months (95% CI: 3 · 92–7 · 02), based on three studies[11,28,42].

The pooled OS using the generic inverse variance method without the survival curve is presented in Supplementary Digital Content Figure S6, available at: http://links.lww.com/JS9/F12. The mOS for the FOLFIRINOX group was 9 · 13 months (95% CI: 5 · 66–14 · 75, I^2 = 72 · 8%), based on three studies[12,13,38]. The FOLFIRI group showed an mOS of 5 · 93 months (95% CI: 4 · 45–7 · 91, I^2 = 71 · 1%), based on five studies[9,31,34,39,40]. The mOS for the FOLFOX group was 6 · 26 months (95% CI: 5 · 57–7 · 02, I^2 = 0%), evaluated from six studies[8,29–31,33,35]. For the nal-IRI/FL group, the mOS was 8 · 41 months (95% CI: 6 · 85–10 · 33, I^2 = 0%), based on five studies[11,28,36,42,43].

Objective response rate. The forest plot of the pooled ORR for each regimen is shown in Supplementary Digital Content Figure S7, available at: http://links.lww.com/JS9/F12. The ORR for FOLFIRINOX was 0 · 15 (95% CI: 0 · 07–0 · 24, I^2 = 0%), based on three studies[12,13,38]. The ORR for FOLFIRI was 0 · 03 (95% CI: 0 · 00–0 · 10, I^2 = 44%), derived from three studies[9,31,34]. The ORR for the FOLFOX group was 0 · 10 (95% CI: 0 · 03–0 · 19, I^2 = 71%), based on seven studies[8,30–33,35,37]. For the nal-IRI/FL group, the ORR was 0 · 14 (95% CI: 0 · 08–0 · 20, I^2 = 31%), based on four studies[11,28,36,42].

Disease control rate. The forest plot of the pooled DCR for each regimen is shown in Supplementary Digital Content Figure S8, available at: http://links.lww.com/JS9/F12. The DCR for FOLFIRINOX was 0 · 70 (95% CI: 0 · 59–0 · 80, I^2 = 0%), based on three studies[12,13,38]. The DCR for FOLFIRI was 0 · 47 (95% CI: 0 · 20–0 · 75, I^2 = 71%), derived from three studies[9,31,34]. The DCR for the FOLFOX group was 0 · 46 (95% CI: 0 · 34–0 · 58, I^2 = 71%), based on seven studies[8,30–33,35,37]. For the nal-IRI/FL group, the DCR was 0 · 63 (95% CI: 0 · 49–0 · 75, I^2 = 53%), based on four studies[11,28,36,42].

Safety outcomes. The detailed safety outcomes of the treatments are presented in Supplementary Digital Content Table S6, available at: http://links.lww.com/JS9/F13. While many studies reported the number of cases for specific adverse events (e.g., neutropenia, fatigue, diarrhea), only a few provided the total number of patients who experienced adverse events. The incidence of any-cause adverse events was reported to be as high as 98 · 2%, with serious adverse events (Grade 3–5) reaching up to 69%. Similarly, treatment-related adverse events were reported in up to 98 · 9% of cases, with treatment-related serious adverse events accounting for 57% of cases. Discontinuation due to adverse events occurred in up to 12% of cases, whereas mortality due to adverse events was reported in up to 22%.

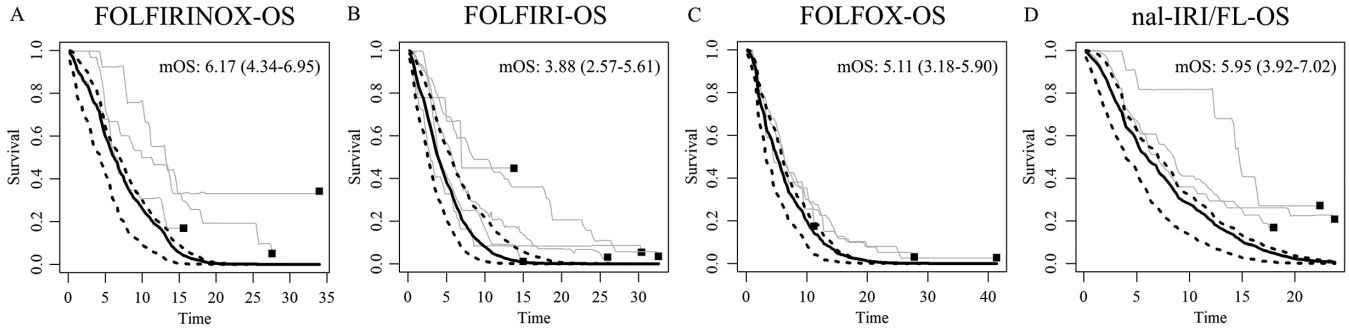

Figure 4. Kaplan–Meier estimates of overall survival for different second-line regimens. (A) FOLFIRINOX, (B) FOLFIRI, (C) FOLFOX, and (D) nal-IRI/FL. Grey lines represent Kaplan–Meier estimates of overall survival for each trial arm. Black squares represent the end of follow-up for each trial.

Risk of bias within studies. The risk of bias assessments for the included studies are summarized in Supplementary Digital Content Tables S7, S8, available at: http://links.lww.com/JS9/F13. All RCTs were open-label studies, resulting in a high risk of bias in the performance and detection bias domains. For single-arm trials and cohort studies, the outcome domains were generally rated as having a low risk of bias. Additionally, outcomes such as adverse events and survival rates were reported without adjustments, leaving these domains unrated.

Discussion

In this study, we conducted a meta-analysis integrating 12 years of real-world data on the use of FOLFIRINOX or mFOLFIRINOX as salvage treatment in patients with advanced BTC at a single tertiary center, along with all available published studies on second-line chemotherapy regimens for advanced BTC. We evaluated the efficacy and safety of currently recommended second-line regimens, including FOLFIRI, FOLFOX, and nal-IRI/FL, in comparison with FOLFIRINOX, which is not yet an established or widely endorsed option. Our analysis included PFS, OS, ORR, DCR, and toxicity profiles of these regimens. To our knowledge, this is the first systematic review and meta-analysis to include FOLFIRINOX in a comparative evaluation of currently used second-line chemotherapy regimens including FOLFOX, FOLFIRI, and nal-IRI/FL for patients with BTC previously treated with first-line chemotherapy. While previous studies have reported outcomes of individual regimens, no study to date has synthesized both real-world data and published evidence across multiple regimens in a single comprehensive analysis. Our findings provide valuable comparative insights that may inform clinical decision-making and guide future trial designs in this challenging patient population.

This systematic review and meta-analysis identified numerically favorable survival outcomes for FOLFIRINOX compared to currently recommended second-line regimens in patients with advanced BTC previously treated with first-line chemotherapy. The ORR and DCR of the currently recommended regimens were also lower than those of FOLFIRINOX. Notably, two patients (4 · 2%) in our cohort achieved CR after 17 and 12 cycles of chemotherapy, despite prior disease progression following first-line treatment. This finding is particularly significant when compared to previous prospective studies, which reported CR rates of only 1% with FOLFOX and 0% with nal-IRI/FL, respectively[8,11]. Further studies are warranted to identify predictive markers, such as genetic differences, that may help clarify which patients are more likely to benefit from FOLFIRINOX.

In comparing our cohort results to previous studies on FOLFIRINOX in BTC, our observed mPFS of 2 · 7 months, mOS of 8 · 9 months, and ORR of 12 · 5% were generally lower than those reported by Belkouz *et al* (mPFS 6 · 2 months, mOS 10 · 7 months, ORR 10%)[12], Ye *et al* (mPFS 6 · 7 months, mOS 13 · 2 months, ORR 26 · 7%)[38], and Lee *et al* (mPFS 2 · 8 months, mOS 6 · 2 months, ORR 14 · 7%)[13]. These discrepancies may be partially explained by the inclusion of patients in our cohort who were unable to continue treatment until the first scheduled response evaluation due to clinical deterioration or treatment-limiting complications. These patients were included in the intention-to-treat population, which may have led to an underestimation of treatment efficacy, particularly for PFS and OS. When we analyzed the full analysis set, defined as patients who completed treatment until the first scheduled evaluation, the mPFS increased to 4 · 2 months, mOS to 11 · 4 months, and ORR to 16 · 7%, aligning more closely with previously reported outcomes. This finding underscores the importance of baseline patient condition, treatment adherence, and study design when interpreting and comparing survival and response outcomes across studies. In addition, differences in study design (prospective clinical trials vs. retrospective real-world analysis), baseline performance status, and disease burden may have influenced outcomes. For instance, the Belkouz *et al* study enrolled patients with ECOG performance status 0–1 in a controlled trial setting[12], whereas our cohort included a broader spectrum of patients, including those with poorer general condition. Variations in treatment protocol may also contribute; our cohort included both standard and modified FOLFIRINOX regimens, with frequent dose reductions (in nearly 30% of patients), while the previous study employed a full-dose regimen in a more selectively enrolled population. Geographic differences in patient demographics, comorbidity profiles, and supportive care practices between Western and Asian populations may further contribute to outcome variability.

Notably, two patients (4 · 2%) in our cohort achieved a CR, a rare outcome that has seldom been reported in prior studies of second-line treatment for BTC. The DCR in this subset was 63.9%, which was comparable to that of nal-IRI/FL (63 · 0%) and higher than the rates reported for FOLFOX (45 · 9%) and FOLFIRI (46 · 7%). Regarding safety, grade 3–5 neutropenia occurred in 40.7% of patients in our cohort, which was higher than the 23 · 1% reported in pancreatic cancer populations and the 32 · 3% observed by Lee *et al* in BTC. Nonetheless, the treatment discontinuation rate was low at 3 · 7%, suggesting that toxicity was generally manageable with dose modifications and supportive care. These comparative findings suggest that, although FOLFIRINOX is associated with hematologic risks, it may offer favorable clinical outcomes compared to established second-line options, particularly in carefully selected patients.

While safety data for FOLFIRINOX were largely unreported across most included studies, the limited available evidence, along with our institutional cohort findings, suggests a substantial toxicity burden. In our cohort, 47.2% of patients experienced grade 3–4 neutropenia, and 11.1% discontinued treatment due to adverse events. Similarly, Belkouz *et al* reported grade 3–5 toxicities in 30% of patients and a 10% treatment discontinuation rate with standard FOLFIRINOX[12]. In contrast, nal-IRI/FL appeared to exhibit a more favorable toxicity profile in certain studies, although sample sizes were limited and safety reporting was inconsistent. Any-cause adverse events ranged from 42% to 56.2%, with discontinuation due to toxicity observed in 7% to 12% of patients. FOLFOX and FOLFIRI regimens demonstrated considerable variability, with grade 3–5 adverse event rates ranging from 55.4% to 69% among FOLFOX-treated patients, and from 22.2% to 56% in those receiving FOLFIRI. Taken together, these observations underscore the importance of individualized treatment selection based not only on efficacy but also on the anticipated toxicity burden, particularly given the heterogeneity in safety outcomes reported across different second-line regimens.

Most studies included in this meta-analysis reported the number of specific adverse events (e.g., neutropenia, fatigue,

diarrhea), but did not provide data on the total number of patients who experienced any adverse event. In contrast, our study presented detailed safety outcomes for each treatment regimen. However, this limitation in the included studies restricted our ability to perform a comprehensive comparative analysis of safety profiles. In our cohort, 26 patients (48 · 1%) experienced serious adverse events, with neutropenia being the most common (40 · 7%). Sixteen patients (29 · 6%) required dose reductions due to treatment-related adverse events, but only two patients (3 · 7%) discontinued chemotherapy because of drug-induced side effects. Grade 3–4 neutropenia is a well-known adverse event associated with FOLFIRINOX, with a higher incidence than that observed with other regimens[44]. A recent meta-analysis reported a 23 · 1% incidence of grade 3–4 neutropenia in patients with pancreatic cancer treated with FOLFIRINOX[45]. In a phase II study on FOLFIRINOX in BTC, the incidence of grade 3–4 neutropenia was 32 · 3%[13], which is slightly lower than our findings. These results underscore the importance of careful monitoring and timely dose adjustments when administering FOLFIRINOX. Furthermore, given that patients who were able to continue treatment until the first scheduled response evaluation showed durable responses and prolonged survival, it is essential to carefully consider each patient's general condition, including ECOG performance status, when selecting FOLFIRINOX as a treatment option.

FOLFIRINOX is associated with a high incidence of severe adverse events, particularly grade 3–5 neutropenia, which can negatively impact patient safety and quality of life. In a prospective study, Takahara *et al* reported that the incidence of grade 3–4 neutropenia was as high as 54 · 3%, and febrile neutropenia reached 17 · 1% in patients with advanced BTC receiving FOLFIRINOX as first-line therapy[46]. In our cohort study, neutropenia occurred in 40.7% of BTC patients treated with second-line FOLFIRINOX, with grade 3–5 neutropenia observed in 59.1% of these cases. According to the latest NCCN Clinical Practice Guidelines for Hematopoietic Growth Factors (Version 1.2025), FOLFIRINOX falls into the intermediate-risk category for febrile neutropenia, and prophylactic long-term administration of granulocyte colony-stimulating factor (G-CSF) is recommended to prevent neutropenia in patients receiving such intensive chemotherapy regimens[47]. Although no clinical trials have specifically evaluated the use of primary prophylactic G-CSF in BTC patients receiving second-line FOLFIRINOX, multiple studies have demonstrated that G-CSF administration significantly reduces the risk of severe neutropenia and febrile neutropenia in patients with pancreatic cancer[48–51]. These findings suggest that, with appropriate supportive care such as primary prophylactic G-CSF, FOLFIRINOX may be administered more safely as a second-line treatment for patients with BTC.

New treatment strategies, including immunotherapy and targeted therapies, are emerging to address the poor prognosis associated with BTC[52]. In a multicenter phase III study, ivosidenib, a targeted inhibitor of mutant IDH1, achieved a PFS and OS of 6 and 10 · 7 months, respectively, in patients with previously treated advanced cholangiocarcinoma harboring IDH1 mutation[53]. Similarly, a multicenter phase II study of pemigatinib, a selective fibroblast growth factor receptor 1 (FGFR1) to FGFR3 inhibitor, reported a median PFS of 6.9 months in patients with FGFR-mutated cholangiocarcinoma who had received at least one prior line of systemic therapy[54]. In addition, a single-arm, multi-cohort phase II "basket" trial, neratinib, an irreversible pan-HER oral tyrosine kinase inhibitor, showed a PFS and OS of 2 · 8 and 5 · 4 months, respectively, in patients with advanced disease previously treated with first-line chemotherapy[55]. While these studies highlight the potential of targeted therapies, their applicability remains limited due to the low prevalence of actionable mutations, which range from approximately 9% to 13% in BTC populations[53–55]. Furthermore, the high costs associated with these therapies pose affordability challenges for the average patient.

There are several limitations in this study. First, considerable heterogeneity was observed across studies in pooled outcomes such as PFS and OS, particularly in the FOLFIRINOX and FOLFIRI groups. Potential contributors to this heterogeneity include variations in BTC subtype (intrahepatic, perihilar, extrahepatic cholangiocarcinoma, gallbladder cancer), first-line therapy, and chemotherapy dose modifications. For example, the meta-analysis of PFS in the FOLFOX group yielded an I^2 of 93.0%, indicating substantial heterogeneity. This may be attributable to differences in study design (e.g., RCTs vs retrospective cohort studies), geographic variation in patient populations, or variations in chemotherapy administration protocols. While we applied a random-effects model to account for such variability, further exploration was limited by the availability of stratified data. To address this, we reviewed our institutional cohort data and found no significant differences in FOLFIRINOX efficacy across BTC subtypes (Supplementary Digital Content Figure S1, available at: http://links.lww.com/JS9/F12). Based on this observation, we cautiously hypothesize that other regimens may similarly exhibit limited variation in efficacy across subtypes. Additionally, the limited number of studies per regimen prevented us from conducting robust sensitivity analyses to test the stability of our pooled estimates. Second, the retrospective nature of our cohort study may have introduced inherent biases, including unmeasured confounding and incomplete clinical documentation. Moreover, patients who experienced early treatment discontinuation due to rapid clinical deterioration or severe toxicity were excluded from the response-evaluable population. This may have introduced selection bias, potentially overestimating treatment efficacy. Third, although our inclusion and exclusion criteria were designed to ensure methodological consistency, they may limit the generalizability of our findings to broader BTC populations, particularly those receiving alternative or mixed treatment regimens. The single-center nature of our cohort study may further reduce the external validity of its results. Fourth, some pooled estimates exhibited wide CIs, particularly in regimens with fewer included studies or smaller sample sizes. This limited statistical precision emphasizes the exploratory nature of our findings. Further large-scale, prospective investigations are needed to validate these observations and improve the evidence base for second-line treatments in advanced BTC. Finally, the favorable outcomes observed in the full analysis set (PFS 4.2 months, OS 11.4 months) relative to the total cohort (PFS 2.7 months, OS 8.9 months) are likely influenced by the exclusion of patients with poor prognosis or rapid deterioration. Specifically, patients who were lost to follow-up or died from complications such as septic shock or gallbladder perforation before scheduled imaging may have had more aggressive disease biology or lower functional reserve. These exclusions may introduce selection bias favoring the full analysis set. As such, the full analysis set represents a clinically fitter subset of patients, and

results should be interpreted with caution regarding generalizability to the broader BTC population receiving second-line therapy.

Although biomarker discovery was beyond the scope of this study, prior literature highlights several candidate biomarkers that may inform future strategies for optimizing chemotherapy selection in BTC. For example, BRCA1 and BRCA2 mutations have been associated with improved PFS in patients receiving first-line platinum-based chemotherapy, suggesting a potential predictive role in this setting[56]. In addition, mutations in TP53 and ATM have shown prognostic significance, correlating with poorer OS in patients with advanced disease undergoing systemic therapy[56]. Furthermore, the expression of human equilibrative nucleoside transporter 1 (hENT1), a key mediator of nucleoside analog uptake, has been linked to prolonged PFS and OS in patients treated with gemcitabine-based chemotherapy in both adjuvant and palliative settings[57]. These findings support the integration of biomarker-based strategies to better personalize treatment selection in advanced BTC.

In conclusion, this systematic review and meta-analysis, incorporating 12 years of real-world data from our institutional cohort, suggests that FOLFIRINOX may offer a potential benefit as a second-line treatment option for BTC following progression on first-line chemotherapy. While FOLFIRINOX showed numerically favorable survival outcomes in our analysis, it is not currently an established second-line standard, and the observed benefits should be interpreted with caution due to the study's observational design and variability in available data. Given the higher incidence of grade 3–4 neutropenia, appropriate patient selection and close toxicity monitoring are essential. Further large-scale, prospective studies are warranted to confirm its clinical utility and to identify patients most likely to benefit from this regimen.

Ethical approval

Not applicable.

Consent

Not applicable.

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Author contributions

Conception and design: G.L., K.K., J.K., Y.H.K., S.B. Administrative support: G.L., H.S.L., M.J.C., J.Y.P., S.W.P., S.B. Patients data collection and assessment: G.L., H.S.L., M.J.C., J.Y.P., S.W.P., S.B. Analysis of population-based cohort study: G.L., J.K., S.B. Analysis of meta-analysis and systematic review: G.L., K.K., Y.H.K. Data analysis and interpretation: G.L., K.K., J.K., Y.H.K., S.B. Manuscript writing: All authors Final approval of manuscript: All authors.

Conflicts of interest disclosure

The authors declare no potential conflicts of interest.

Research registration unique identifying number (UIN)

Our protocols were registered in PROSPERO under the identifier CRD42024621717.

Guarantor

Yun Hak Kim and Seungmin Bang had full responsibility for the work and the conduct of the study. Yun Hak Kim and Seungmin Bang had access to the data and controlled the decision to publish.

Data sharing

The collected data and methods of analysis are available from the corresponding author upon reasonable request.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Declaration of AI Use

No artificial intelligence (AI) tools were used in the conduct of the research or the development of the manuscript.

References

[1] Valle J, Wasan H, Palmer DH, *et al*. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med 2010;362:1273–81.
[2] Jarnagin WR, Fong Y, DeMatteo RP, *et al*. Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. Ann Surg 2001;234:507–517;discussion517–509.
[3] Wu L, Tsilimigras DI, Paredes AZ, *et al*. Trends in the incidence, treatment and outcomes of patients with intrahepatic cholangiocarcinoma in the USA: facility type is associated with margin status, use of lymphadenectomy and overall survival. World J Surg 2019;43:1777–87.
[4] Endo I. Recent progress in the treatment for unresectable biliary tract cancer. Annals of Gastroenterol Surg 2023;7:540–42.
[5] National Comprehensive Cancer Network. Biliary tract cancers (Version 2.2025). Accessed July 15, 2025. Available at: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1517 .
[6] Kelley RK, Ueno M, Yoo C, *et al*. Pembrolizumab in combination with gemcitabine and cisplatin compared with gemcitabine and cisplatin alone for patients with advanced biliary tract cancer (KEYNOTE-966): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2023;401:1853–65.
[7] Oh DY, Ruth He A, Qin S, *et al*. Durvalumab plus gemcitabine and cisplatin in advanced biliary tract cancer. NEJM Evid 2022;1:EVIDoa2200015.
[8] Lamarca A, Palmer DH, Wasan HS, *et al*. Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. Lancet Oncol 2021;22:690–701.
[9] Caparica R, Lengele A, Bekolo W, Hendlisz A. FOLFIRI as second-line treatment of metastatic biliary tract cancer patients. Autops Case Rep 2019;9:e2019087.
[10] Mizrahi JD, Gunchick V, Mody K, *et al*. Multi-institutional retrospective analysis of FOLFIRI in patients with advanced biliary tract cancers. World J Gastrointest Oncol 2020;12:83–91.

[11] Hyung J, Kim I, Kim K-P, *et al*. Treatment with liposomal irinotecan plus fluorouracil and leucovorin for patients with previously treated metastatic biliary tract cancer: the phase 2b NIFTY randomized clinical trial. JAMA Oncol 2023;9:692–99.
[12] Belkouz A, de Vos-geelen J, Mathôt RA, *et al*. Efficacy and safety of FOLFIRINOX as salvage treatment in advanced biliary tract cancer: an open-label, single arm, phase 2 trial. Br J Cancer 2020;122:634–39.
[13] Lee Y-P, Oh SY, Kim KM, *et al*. Modified FOLFIRINOX as a second-line treatment for patients with gemcitabine-failed advanced biliary tract cancer: a prospective multicenter phase II study. Cancers (Basel) 2022;14:1950.
[14] Agha RA, Mathew G, Rashid R, *et al*. Transparency in the reporting of artificial intelligence–the TITAN guideline. Prem J Sci 2025;10: 100082.
[15] Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
[16] Page MJ, Moher D, Bossuyt PM, *et al*. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ 2021;372:n160.
[17] Shea BJ, Reeves BC, Wells G, *et al*. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ 2017;358;j4008.
[18] Patricia Guyot AA, Ouwens MJNM, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Method 2012;12:9.
[19] Combescure C, Foucher Y, Jackson D. Meta-analysis of single-arm survival studies: a distribution-free approach for estimating summary survival curves with random effects. Stat Med 2014;33:2521–37.
[20] Buckland ST. Monte Carlo Confidence Intervals. Biometrics 1984;40:811–17.
[21] Borenstein M, Hedges LV, Higgins JP, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. Res Synth Methods 2010;1:97–111.
[22] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
[23] Kim S, Han D, Ryu J, Kim K, Kim YH. Effects of mobile phone usage on sperm quality–no time-dependent relationship on usage: a systematic review and updated meta-analysis. Environ Res 2021;202:111784.
[24] Yoon S, Kim K, Shin K, *et al*. The safety of systemic Janus kinase inhibitors in atopic dermatitis: a systematic review and meta-analysis of randomized controlled trials. J Eur Acad Dermatol Venereol 2024;38:52–61.
[25] Ahn D, Kim J, Kang J, Kim YH, Kim K. Congenital anomalies and maternal age: a systematic review and meta-analysis of observational studies. Acta Obstet Gynecol Scand 2022;101:484–98.
[26] Eisenhauer EA, Therasse P, Bogaerts J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.
[27] Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 [https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf]
[28] Allo G, Can AD, Wahba R, *et al*. Nanoliposomal irinotecan in combination with leucovorin and 5-fluorouracil in advanced biliary tract cancers. Mol Clin Oncol 2022;16:1–6.
[29] Balarine M, Felismino T, Camandaroba M. P-52 FOLFIRI or FOLFOX in second line of advanced biliary tract cancer: a retrospective analysis. Ann Oncol 2022:33:S265.
[30] Carbó CH, Pérez MFJ, Zen Y, Maisey N, Ross P, Sarker D. P-0143 the role of chemotherapy in advanced biliary tract cancers: clinical experience from a specialist UK cancer centre. Ann Oncol 2012;23:iv72.
[31] Choi IS, Kim KH, Lee JH, *et al*. A randomised phase II study of oxaliplatin/5-FU (mFOLFOX) versus irinotecan/5-FU (mFOLFIRI) chemotherapy in locally advanced or metastatic biliary tract cancer refractory to first-line gemcitabine/cisplatin chemotherapy. Eur J Cancer 2021;154:288–95.
[32] Dang K, Gupta D, Sehrawat A, Gupta S, Parthasarathy K. Efficacy and safety of folfox as a second-line chemotherapy for patients with locally advanced and/or metastatic carcinoma gall bladder–experience from a tertiary care center in India. Indian J Med Paediatr Oncol 2019;40:240–43.
[33] He S, Shen J, Sun X, Liu L, Dong J. A phase II FOLFOX-4 regimen as second-line treatment in advanced biliary tract cancer refractory to gemcitabine/cisplatin. J Chemother 2014;26:243–47.
[34] Huang P, Huang X, Zhou Y, *et al*. The efficacy and safety of hepatic arterial infusion chemotherapy based on FOLFIRI for advanced intrahepatic cholangiocarcinoma as second-line and successive treatment: a real-world study. Can J Gastroenterol Hepatol 2022;2022:9680933.
[35] Hwang IG, Jang J-S, Oh SY, *et al*. Phase II study of mFOLFOX3 (5-fluorouracil, leucovorin, oxaliplatin) as second-line treatment after gemcitabine failure in patients with unresectable/metastatic biliary tract cancer. Cancer Chemother Pharmacol 2015;75:757–62.
[36] Ying J, Cheng X, Xu Q, *et al*. A phase II study of liposomal irinotecan-based chemotherapy with or without PD-1 inhibitor in patients with unresectable locally advanced or metastatic biliary tract cancer. J Clin Oncol 2024;42:e15077.
[37] Leal JL, Roa JC, Jarufe N, *et al*. Second-line FOLFOX chemotherapy in patients with metastatic gallbladder cancer and cholangiocarcinoma. J Clin Oncol 2014;32:322–322.
[38] Ye L-F, Ren C, Bai L, *et al*. Efficacy and safety of modified FOLFIRINOX as salvage therapy for patients with refractory advanced biliary tract cancer: a retrospective study. Invest New Drugs 2021;39:836–45.
[39] Müller C, Omari J, Mohnike K, *et al*. Multidisciplinary treatment of patients with progressive biliary tract cancer after first-line gemcitabine and cisplatin: a single-center experience. Cancers (Basel) 2023;15:2598.
[40] Sebbagh S, Roux J, Dreyer C, *et al*. Efficacy of a sequential treatment strategy with GEMOX-based followed by FOLFIRI-based chemotherapy in advanced biliary tract cancers. Acta Oncol 2016;55:1168–74.
[41] Talwar V, Raina S, Goel V, Dash P, Doval DC. Nab-paclitaxel: an effective third-line chemotherapy in patients with advanced, unresectable gallbladder cancer. Indian J Med Res 2020;152:475–81.
[42] Vogel A, Saborowski A, Wenzel P, *et al*. Nanoliposomal irinotecan and fluorouracil plus leucovorin versus fluorouracil plus leucovorin in patients with cholangiocarcinoma and gallbladder carcinoma previously treated with gemcitabine-based therapies (AIO NALIRICC): a multicentre, open-label, randomised, phase 2 trial. Lancet Gastroenterol Hepatol 2024;9:734–44.
[43] Weinberg B, He A, Tan B, *et al*. P-231 interim results of a phase II study of fluorouracil (FU), leucovorin (LV), and nanoliposomal irinotecan (nal-IRI) in previously treated advanced biliary tract cancer (NAPOLI-2). Ann Oncol 2023;34:S97–S98.
[44] Gresham GK, Wells GA, Gill S, Cameron C, Jonker DJ. Chemotherapy regimens for advanced pancreatic cancer: a systematic review and network meta-analysis. BMC Cancer 2014;14:471.
[45] Tong H, Fan Z, Liu B, Lu T. The benefits of modified FOLFIRINOX for advanced pancreatic cancer and its induced adverse events: a systematic review and meta-analysis. Sci Rep 2018;8:8666.
[46] Takahara N, Nakai Y, Isayama H, *et al*. A prospective multicenter phase II study of FOLFIRINOX as a first-line treatment for patients with advanced and recurrent biliary tract cancer. Invest New Drugs 2023;41:76–85.
[47] National Comprehensive Cancer Network. Hematopoietic growth factors (Version 1.2025). NCCN clinical practice guidelines in oncology. Accessed July 15, 2025. Available at: https://www.nccn.org/guidelines/guidelines-detail?category=3&id=1493 .
[48] Jung JH, Shin DW, Kim J, Lee J-C, Hwang J-H. Primary granulocyte colony-stimulating factor prophylaxis in metastatic pancreatic cancer patients treated with FOLFIRINOX as the first-line treatment. Cancers 2020;12:3137.
[49] Macaire P, Paris J, Vincent J, Ghiringhelli F, Bengrine-Lefevre L, Schmitt A. Impact of granulocyte colony-stimulating factor on FOLFIRINOX-induced neutropenia prevention: a population pharmacokinetic/pharmacodynamic approach. Br J Clin Pharmacol 2020;86:2473–85.
[50] Terazawa T, Goto M, Miyamoto T, *et al*. Efficacy of prophylactic G-CSF in patients receiving FOLFIRINOX: a preliminary retrospective study. Internal Medicine 2015;54:2969–73.
[51] Lee CK, Kim I-H, Kim CG, and Choi HJ. Primary prophylaxis with pegylated-granulocyte colony-stimulating factor for patients with unresectable pancreatic cancer treated with modified-FOLFIRINOX: a randomized phase II trial. Am Soc Clin Oncol 2024;42:4145.
[52] Mizrahi JD, Shroff RT. New treatment options for advanced biliary tract cancer. Curr Treat Options Oncol 2020;21:63.
[53] Abou-Alfa GK, Macarulla T, Javle MM, *et al*. Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol 2020;21:796–807.

[54] Abou-Alfa GK, Sahai V, Hollebecque A, *et al*. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. Lancet Oncol 2020;21:671–84.
[55] Harding JJ, Piha-Paul SA, Shah RH, *et al*. Antitumour activity of neratinib in patients with HER2-mutant advanced biliary tract cancers. Nat Commun 2023;14:630.
[56] Kim H, Kim JY, Park KU. Clinical implications of BRCA mutations in advanced biliary tract cancer. Oncology 2023;101:41–48.
[57] Belkouz A, Labeur TA, Dierks J, *et al*. Prognostic immunohistochemical biomarkers of chemotherapy efficacy in biliary tract cancer: a systematic review and meta-analysis. Crit Rev Oncol/hematol 2019;141:82–94.