

Safety and efficacy of the FOLFOX regimen in patients with metastatic gastrointestinal cancers and severe hyperbilirubinemia: A real-world experience

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Abstract. Patients with gastrointestinal (GI) malignancies and hyperbilirubinemia secondary to liver metastases are routinely excluded from clinical trials, leaving their management without evidence-based guidance. Oxaliplatin, cleared through non-enzymatic biotransformation and renal excretion, is a rational candidate in this setting. The present study examined the feasibility, safety and outcomes of folinic acid, fluorouracil and oxaliplatin (FOLFOX)-based chemotherapy in this population. The present retrospective, single-center analysis included 27 patients with histologically confirmed metastatic GI cancers (gastric, biliary tract, pancreatic and colorectal) with serum total bilirubin of ≥ 4.5 mg/dl at treatment initiation who received individualized FOLFOX-based chemotherapy at Etlik City Hospital (Ankara, Türkiye) between July 2023 and March 2025. Bilirubin response was defined as a $\geq 50\%$ reduction within 4–8 weeks or normalization to ≤ 1.2 mg/dl within 12 weeks. Survival was estimated by Kaplan-Meier analysis; Cox regression identified predictors of progression-free survival (PFS) and overall survival (OS). Median baseline bilirubin was 6.9 mg/dl. Bilirubin declined significantly at weeks 4, 8 and 12 (medians 3.0, 2.5 and 0.8 mg/dl; $P < 0.001$, $P = 0.009$ and $P = 0.001$ vs. baseline). Among Response Evaluation Criteria in Solid Tumors-evaluable patients (11/27), the objective response rate was 72.7% and disease control rate 81.8%. Median PFS was 2.56 months [95% confidence interval (CI) 1.81–3.65] and median OS 3.65 months (95% CI 2.56–5.72). A $\geq 50\%$ bilirubin reduction at week 4 was associated with longer PFS [univariable hazard ratio (HR) 0.37; 95% CI 0.14–0.93; log-rank $P = 0.028$] and longer OS (univariable HR 0.37; 95%

CI 0.14–0.94; log-rank $P = 0.030$) in a week 4 landmark analysis performed to address immortal time bias. In the present cohort of patients with Eastern Cooperative Oncology Group Performance Status 0–1 and severe hyperbilirubinemia due to liver metastases, FOLFOX achieved rapid bilirubin reductions without grade ≥ 3 hepatotoxicity. Early bilirubin response was associated with longer survival in the present small, exploratory analysis; these hypothesis-generating findings warrant prospective validation.

Introduction

Gastrointestinal (GI) malignancies, particularly gastric, colorectal, pancreatic and biliary tract cancers, collectively account for a substantial proportion of cancer-related mortality worldwide; in 2022, colorectal, gastric and pancreatic cancer accounted for $\sim 17\%$ of new cancer cases and 21% of cancer deaths globally (1). A shared anatomical feature of these tumors is their predilection for hepatic spread: The liver, by virtue of its portal venous drainage, is the most common site of distant metastasis from GI primaries, and diffuse parenchymal infiltration frequently impairs hepatic synthetic and excretory function (2). The resulting hyperbilirubinemia, when caused by parenchymal tumor burden rather than biliary obstruction, cannot reliably be managed by drainage procedures and instead demands systemic therapy, yet this is precisely the patient group excluded from nearly all registration trials.

Most pivotal Phase III trials restrict enrollment to patients with serum bilirubin < 1.5 times the upper limit of normal (ULN). Patients with more severe dysfunction are therefore underrepresented in the evidence base, and standard dosing recommendations do not apply (3). Clinicians are left to extrapolate from pharmacokinetic principles and small retrospective series when making treatment decisions for this population.

FOLFOX, which combines oxaliplatin with leucovorin (folinic acid) and bolus and infusional 5-fluorouracil every 2 weeks, is an important chemotherapy backbone across GI malignancy. The pharmacokinetic rationale for using oxaliplatin in hepatic dysfunction rests on its predominantly

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non-hepatic elimination. Oxaliplatin is rapidly cleared from plasma by non-enzymatic biotransformation, with urinary excretion accounting for ~54% of drug removal (4). By contrast irinotecan requires hepatic bioactivation and detoxification of its active metabolite SN-38, and to the taxanes, which depend on hepatobiliary extraction and are contraindicated in moderate-to-severe liver dysfunction. Fluoropyrimidines undergo primary hepatic metabolism but have been used cautiously in dose-adjusted regimens even in patients with impaired liver function (5).

Several case reports and small series have documented the feasibility of oxaliplatin- and fluoropyrimidine-based regimens in patients with hyperbilirubinemia from liver metastases. The largest published case series, by Quidde *et al* (6), described 12 patients with GI cancer and a median bilirubin of 6.1 mg/dl who received oxaliplatin combined with 5-fluorouracil and leucovorin; bilirubin normalized or fell >50% within 8 weeks in half of the patients, and median OS was notably longer in those who responded. Comparable observations have been reported in individual case reports of colorectal and gastric cancer (7,8).

Despite these encouraging reports, the available evidence remains limited by small sample sizes, heterogeneous treatment regimens and single-tumor-type focus. Real-world data from a broader population of patients with GI cancer including gastric, biliary, pancreatic and colorectal primaries managed with individualized FOLFOX-based regimens are lacking. The present study aimed to evaluate bilirubin response, toxicity and survival outcomes in 27 patients with metastatic GI cancer and marked hyperbilirubinemia who received individualized FOLFOX-based chemotherapy and to investigate whether early bilirubin response was associated with survival.

Materials and methods

Study design and patients. The present study was retrospective, including a single-center cohort conducted at the Department of Medical Oncology, Etlik City Hospital (Ankara, Türkiye). Patients treated between July 2023 and March 2025 were identified through a review of institutional electronic records and oncology databases. The present study was approved by the institutional ethics committee (approval no. AEŞH-BADEK2-2025-432) and conducted in accordance with the Declaration of Helsinki. Informed consent was waived given the retrospective design and anonymized data. Medical records were accessed and data were extracted for research purposes between October 1 and October 30, 2025, after ethics committee approval was obtained on September 16, 2025.

Eligibility criteria. Patients were eligible if they were aged ≥18 years, had histologically confirmed metastatic GI malignancy (gastric, biliary tract, pancreatic or colorectal), had radiologically evident liver metastases and had a serum total bilirubin ≥4.5 mg/dl at the time of treatment initiation. This threshold was set above the National Cancer Institute Organ Dysfunction Working Group definition of severe hepatic impairment (bilirubin >3x ULN, corresponding to 3.6 mg/dl using Etlik City Hospital ULN of 1.2 mg/dl) (9). Patients were included whether or not a drainage procedure had been

performed: Those ineligible for biliary drainage and those with persistently elevated bilirubin despite technically feasible drainage were both eligible.

Patients were excluded if hyperbilirubinemia was attributable to non-malignant hepatic conditions (viral hepatitis, cirrhosis or drug-induced injury), or if chemotherapy had been administered within 14 days before bilirubin elevation was documented.

Treatment protocol. All patients received an individualized FOLFOX backbone rather than a single standardized mFOLFOX6 protocol, given variation in oxaliplatin dosing, 5-fluorouracil administration route and dose modifications described below. Oxaliplatin was administered intravenously at 60-85 mg/m²; 5-fluorouracil was given as a 46-h continuous infusion (2,400 mg/m²) or in bolus form according to individual tolerability; and leucovorin was administered at 400-500 mg/m². Cycles were repeated every two weeks. Monoclonal antibodies (bevacizumab, cetuximab or panitumumab) were added at the discretion of the treating physician based on molecular tumor characteristics. Dose escalation was permitted in patients showing biochemical improvement and acceptable toxicity.

Definitions and endpoints. Bilirubin response was defined as: i) A reduction of ≥50% in total bilirubin within 4-8 weeks of treatment initiation; or ii) normalization of total bilirubin to ≤1.2 mg/dl within 12 weeks. Bilirubin at each nominal timepoint was measured within ±10 days of that timepoint. Patients were categorized as responders or non-responders based on these criteria. Radiologic response was assessed by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Toxicity was graded using Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (10,11) The primary endpoint was bilirubin response rate; secondary endpoints were progression-free survival (PFS), overall survival (OS) and treatment safety.

Statistical analysis. Continuous variables are presented as median with ranges or interquartile ranges (IQR); categorical variables are presented as frequencies and proportions. Changes in bilirubin over time were assessed with the Wilcoxon signed-rank test, restricted to patients with paired bilirubin measurements at baseline and the corresponding follow-up assessment. PFS and OS were measured from the date of initiation of FOLFOX-based chemotherapy to progression or death, respectively; patients without the corresponding event were censored at the date of last follow-up. PFS and OS were estimated by the Kaplan-Meier method; differences between groups were compared using the log-rank test. Cox proportional hazards regression was used to examine potential predictors of PFS and OS; variables with P<0.20 in univariate analysis were entered into the multivariate model. To address potential immortal time bias arising from classification according to week 4 bilirubin response, post hoc week 4 landmark analysis was performed for both PFS and OS. The week 4 landmark was defined as day 28 after treatment initiation, and landmark response classification was based exclusively on bilirubin measurements obtained on or before day 28. For the PFS landmark analysis, only

patients who were alive, progression-free and under observation at week 4 were included; for the OS landmark analysis, patients who were alive and under observation at week 4 were included. Survival time was reset to zero at the day 28 landmark. Kaplan-Meier curves were generated according to week 4 bilirubin response (≥ 50 vs. $< 50\%$ reduction in total bilirubin), groups were compared using the log-rank test and univariable Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). Toxicities were compared between patients with Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0 and 1 using two-sided Fisher's exact tests because of the small sample size and sparse cell counts. Radiologic response categories and the prespecified bilirubin-response endpoint, including each of its components, were summarized descriptively as counts and percentages. All analyses were performed in SPSS version 26.0 (IBM Corp.); a two-sided $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics. A total of 27 patients were included in the present analysis. The median age was 62 years (range 25-80), and 21 (77.8%) were men. The most common primary site was gastric cancer ($n=10$, 37.0%), followed by biliary tract cancer ($n=8$, 29.6%), pancreatic cancer ($n=5$, 18.5%) and colorectal cancer ($n=4$, 14.8%). At treatment initiation, 16 patients (59.3%) had an ECOG PS of 0 and 11 (40.7%) had a status of 1. The median modified Charlson comorbidity index was 8 (range 6-11). Liver metastasis was present in all 27 patients (100%), and 8 patients (29.6%) had undergone percutaneous transhepatic biliary drainage (PTBD) before or at the time of diagnosis. All 20 tested patients had microsatellite-stable disease, as assessed by immunohistochemistry. Targeted therapy was administered only to patients with colorectal primaries, in whom it was clinically indicated (bevacizumab, $n=3$; cetuximab, $n=1$); it was not used in patients with gastric, biliary or pancreatic primaries. Baseline laboratory and clinical characteristics are summarized in Table I.

Bilirubin response. The median total bilirubin at baseline was 6.9 mg/dl (IQR 5.5-9.5). Following initiation of FOLFOX, bilirubin levels decreased significantly at each subsequent evaluation. At week 4, the median total bilirubin was 3.0 mg/dl (IQR 2.3-5.4; $P < 0.001$ vs. baseline). The decline continued at week 8, with a median of 2.5 mg/dl (IQR 1.0-3.7; $P = 0.009$). By week 12, the median bilirubin had fallen to 0.8 mg/dl (IQR 0.7-1.4; $P = 0.001$), within the normal range (Fig. 1). Bilirubin measurements were available in 27 patients at baseline, 27 at week 4, 20 at week 8 and 11 at week 12; longitudinal comparisons were restricted to patients with paired baseline and corresponding follow-up measurements, giving paired sample sizes of 27, 20 and 11 at weeks 4, 8 and 12, respectively. Patients without a measurement of a given timepoint had not remained on treatment or under follow-up long enough to reach it, primarily due to death or clinical progression. In total 2 patients died before the day 28 landmark, on days 18 and 26. Their last available bilirubin measurements were retained in the descriptive week 4 analysis. Both

Table I. Baseline patient and disease characteristics.

Characteristics	Patients (n=27)
Age, years	62 (25-80)
Sex	
Male	21 (77.8)
Female	6 (22.2)
Primary tumor site	
Gastric cancer	10 (37.0)
Biliary tract cancer	8 (29.6)
Pancreatic cancer	5 (18.5)
Colorectal cancer	4 (14.8)
Eastern Cooperative Oncology Group Performance Status	
0	16 (59.3)
1	11 (40.7)
Modified Charlson comorbidity index score	8 (6-11)
Metastatic site ^a	
Liver metastasis	27 (100.0)
Peritoneal carcinomatosis	7 (25.9)
Pulmonary	4 (14.8)
Bone/bone marrow	3 (11.1)
Vascular invasion	1 (3.7)
Microsatellite instability status	
Microsatellite stable	20 (74.1)
Unknown	7 (25.9)
Percutaneous transhepatic biliary drainage at diagnosis or relapse	
Yes	8 (29.6)
No	19 (70.4)
Baseline laboratory values	
Total bilirubin, mg/dl	6.9 (5.0-18.2)
Direct bilirubin, mg/dl	5.4 (3.0-13.4)
Hemoglobin, g/dl	10.3 (7.0-13.1)
White blood cell count, $\times 10^3/\mu\text{l}$	9.2 (3.5-17.4)
Platelet count, $\times 10^3/\mu\text{l}$	246.0 (39.0-577.0)

^aCertain patients had a > 1 metastatic sites. Data are presented as median (min-max) or n (%).

patients were classified as non-responders in the exploratory overall-cohort Cox analyses as neither achieved a $\geq 50\%$ reduction in bilirubin. Both were excluded from the day 28 landmark analysis, leaving 25 eligible patients (16 responders and 9 non-responders). All landmark response classifications were based on bilirubin measurements obtained on or before day 28.

Longitudinal bilirubin kinetics are illustrated in Fig. 1. The prespecified composite bilirubin-response endpoint was achieved by 21 of 27 patients (77.8%); 20 patients (74.1%) achieved a $\geq 50\%$ reduction in total bilirubin within weeks 4-8 and 11 (40.7%) achieved normalization to ≤ 1.2 mg/dl within 12 weeks (Table SI).

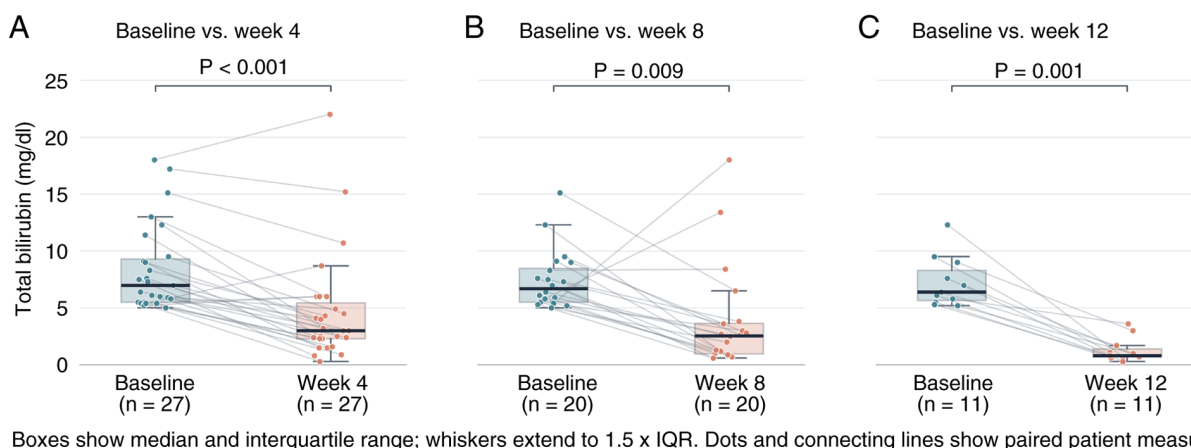


Figure 1. Paired changes in total bilirubin levels during folinic acid, fluorouracil and oxaliplatin-based chemotherapy. (A) Baseline vs. week 4 (n=27 pairs; $P<0.001$). (B) Baseline vs. week 8 (n=20 pairs; $P=0.009$). (C) Baseline vs. week 12 (n=11 pairs; $P=0.001$). Each panel includes only patients with bilirubin measurements at both baseline and the corresponding follow-up timepoint. Boxes indicate the median and interquartile range (IQR), with whiskers extending to 1.5 times the IQR; individual dots and connecting lines represent paired measurements. P-values were calculated using two-sided exact Wilcoxon signed-rank tests. Bilirubin concentrations are expressed in mg/dl. Nominal timepoints were assessed within ± 10 days. For the two patients who died before day 28 (on days 18 and 26), week 4 values represent their last measurements before death. Both were classified as non-responders in the exploratory overall-cohort Cox analyses and excluded from the day 28 landmark analyses. The nominal week 4 sampling window (days 18-38) was used for descriptive longitudinal analyses only; landmark response classification was based exclusively on measurements obtained on or before day 28.

Treatment response and survival. Radiologic response was evaluable according to RECIST v1.1 in 11 of 27 patients (40.7%); the remaining 16 patients (59.3%) were non-evaluable because radiologic assessment was not feasible before the first scheduled imaging evaluation, most often due to clinical deterioration or death. Among the 11 RECIST-evaluable patients, no complete responses were observed, 8 (72.7%) achieved a partial response, 1 (9.1%) had stable disease and 2 (18.2%) had progressive disease. Accordingly, among patients who were RECIST-evaluable, the objective response rate (ORR) was 72.7% (8/11) and the disease control rate (DCR) was 81.8% (9/11) (Table SI). Median PFS was 2.56 months (95% CI 1.81-3.65); PFS rates at weeks 4, 8 and 12 were 92.6, 59.3 and 48.1%, respectively. Median OS was 3.65 months (95% CI 2.56-5.72); OS rates at weeks 4, 8 and 12 were 92.6, 66.7 and 51.9%, respectively. More than half of the cohort (51.9%) was alive at 12 weeks (Table II). To address potential immortal time bias arising from week 4 response classification, post hoc week 4 landmark analysis was performed. In the PFS landmark analysis (n=25 patients alive and progression-free at week 4; 16 responders, 9 non-responders), median landmark PFS was 2.89 months (95% CI 1.08-10.09) in responders vs. 0.53 months (95% CI 0.13-3.58) in non-responders (univariable HR 0.37; 95% CI 0.14-0.93; log-rank $P=0.028$). In the OS landmark analysis (n=25 patients alive at week 4; 16 responders and 9 non-responders), median landmark OS was 5.52 months (95% CI 1.28-14.24) in responders vs. 0.53 months (95% CI 0.13-6.51) in non-responders (univariable HR 0.37; 95% CI 0.14-0.94; log-rank $P=0.030$) (Fig. 2).

Toxicity and dose modifications. Toxicity was generally manageable, except for two grade 5 acute kidney injury events (Table III). No patient developed grade 3 or 4 hepatotoxicity. Grade 1 hepatotoxicity was observed in seven patients (25.9%) and grade 2 in 1 (3.7%). Grade 5 acute kidney injury occurred in 2 patients (7.4%) and grade 2 nephrotoxicity in 1 (3.7%).

Hematological toxicity of grade 2 was the most frequent finding (7 patients, 25.9%); grade 3 hematological toxicity occurred in 1 patient (3.7%). Overall, 8 patients (29.6%) received treatment at full dose throughout; the remainder required dose reductions ranging from 10-50%. The most common reduction level was 20% (n=8, 29.6%). Toxicity did not differ significantly between patients with ECOG PS 0 and 1, although nephrotoxicity was observed only among patients with ECOG PS 1 (27.3 vs. 0%; Fisher's exact $P=0.056$; Table SII).

Predictors of survival. On univariate Cox regression, a $\geq 50\%$ reduction in total bilirubin at week 4 was associated with significantly longer PFS (HR 0.38, 95% CI 0.16-0.91; $P=0.030$) and OS (HR 0.37, 95% CI 0.15-0.91; $P=0.030$). On multivariate analysis, this association persisted for both PFS (HR 0.30, 95% CI 0.12-0.76; $P=0.011$) and OS (HR 0.29, 95% CI 0.11-0.76; $P=0.012$), although these estimates derive from the overall cohort without landmark restriction and should be interpreted alongside the aforementioned week 4 landmark analysis, which was performed to address immortal time bias. ECOG PS (1 vs. 0) was not significantly associated with PFS (univariate HR 1.66, 95% CI 0.71-3.90; $P=0.245$) or OS (univariate HR 1.83, 95% CI 0.77-4.37; $P=0.175$; multivariate HR 1.10, 95% CI 0.36-3.35; $P=0.862$). No other variable reached statistical significance on univariate or multivariate analysis (Tables IV and V).

Discussion

The present retrospective series adds to the limited body of evidence supporting oxaliplatin- and fluoropyrimidine-based chemotherapy in patients with GI cancer and notable hepatic dysfunction. Among 27 patients with a median baseline bilirubin of 6.9 mg/dl, a level at which most guidelines would preclude cytotoxic therapy, FOLFOX produced a rapid and statistically notable bilirubin reduction at each evaluated

Table II. Summary of survival outcomes (PFS and OS).

Outcome measure	PFS	OS
Median survival, months (95% confidence interval)	2.56 (1.81-3.65)	3.65 (2.56-5.72)
Survival rate, n (%)		
At week 4	25 (92.6)	25 (92.6)
At week 8	16 (59.3)	18 (66.7)
At week 12	13 (48.1)	14 (51.6)

Survival was calculated from the initiation of folinic acid, fluorouracil and oxaliplatin-based chemotherapy. The numbers in parentheses represent the number of patients remaining at risk at the corresponding timepoint. PFS, progression-free survival; OS, overall survival.

Table III. Adverse events and dose modifications during FOLFOX-based treatment.

Event	Patients (n=27)
Hepatotoxicity	
Grade 0	19 (70.4)
Grade 1	7 (25.9)
Grade 2	1 (3.7)
Grade 3/4	0 (0.0)
Nephrotoxicity	
Grade 0	24 (88.9)
Grade 2	1 (3.7)
Grade 1/3/4	0 (0.0)
Grade 5	2 (7.4) ^a
Hematological toxicity	
Grade 0	15 (55.6)
Grade 1	4 (14.8)
Grade 2	7 (25.9)
Grade 3	1 (3.7)
Grade 4	0 (0.0)
Dose reductions	
No reduction	8 (29.6)
10% reduction	5 (18.5)
20% reduction	8 (29.6)
25% reduction	2 (7.4)
30% reduction	1 (3.7)
50% reduction	3 (11.1)

Data are presented as n (%). Adverse events were graded according to the Common Terminology Criteria for Adverse Events version 5.0. ^aBoth grade 5 events were acute kidney injury occurring in the setting of sepsis and multiorgan failure; the contribution of FOLFOX to the renal injury is uncertain (see discussion). FOLFOX, folinic acid, fluorouracil and oxaliplatin.

timepoint, with median levels falling to within the normal range by week 12 (3,6). Grade ≥ 3 hepatotoxicity was not observed despite the severity of hepatic impairment at baseline.

The principal challenge in this population is the near-total absence of prospective data. Most pivotal chemotherapy trials restrict inclusion to patients with bilirubin <1.5 times the ULN, so patients such as those enrolled in the present study fall outside the evidence base almost by definition. The pharmacokinetic argument for oxaliplatin rests on solid ground: Unlike irinotecan, which depends on hepatic UDP-glucuronosyltransferase family1 member A1-mediated detoxification of its active metabolite SN-38, oxaliplatin undergoes rapid nonenzymatic hydrolysis and is eliminated primarily by the kidney (4,12,13). These pharmacokinetic properties make FOLFOX a rational candidate where irinotecan- or taxane-based regimens would carry substantially greater risk.

The present findings are consistent with those of Quidde *et al* (6) who described 12 patients with a median bilirubin of 6.1 mg/dl treated with oxaliplatin/fluoropyrimidine combinations, half of whom achieved bilirubin normalization or a $>50\%$ reduction within 8-12 weeks, with a median OS of 9.7 months in bilirubin responders vs. 3.0 months in non-responders. The absolute survival figures in the present cohort (median OS 3.65 months) reflect a population with more advanced disease burden and a higher proportion of non-colorectal primaries; gastric, biliary and pancreatic cancers tend to carry worse prognoses than metastatic colorectal cancer in this setting. However, the pattern of bilirubin response was strikingly similar, supporting the generalizability of these observations across tumor types (7,8,14,15).

The ORR of 72.7% among RECIST-evaluable patients warrants cautious interpretation, as only 11 of 27 patients (40.7%) underwent formal radiologic assessment before death or clinical deterioration. It should be interpreted alongside the bilirubin response data: Improvements in bilirubin may in some cases reflect antitumor activity reducing hepatic tumor burden, even in patients who do not meet formal radiologic response criteria. Conversely, bilirubin normalization without radiologic shrinkage may reflect relief of biliary compression rather than treatment efficacy. The 8 patients who underwent PTBD are an important confounder in the present study, as drainage lowers bilirubin independent of tumor response. Bilirubin did not fully normalize in this subgroup despite drainage, indicating that mechanical decompression alone does not account for the full decline. PTBD status was not notably associated with PFS or OS, but bilirubin response rates were not compared by PTBD status and its contribution to the decline seen in this subgroup cannot be excluded. Separating these mechanisms was not possible in a retrospective design, and this distinction warrants prospective investigation. Future prospective studies should stratify bilirubin kinetics by PTBD status to disentangle the relative contributions of mechanical decompression and antitumor activity.

Dose reductions were required in more than two-thirds of patients, reflecting the difficulty of delivering standard doses in the context of hepatic impairment. The absence of grade ≥ 3 hepatotoxicity despite these modifications supports a cautious dose-escalation approach as tolerated, consistent with the treatment algorithm proposed by Quidde *et al* (6) which recommends starting at 60-75% of standard doses and escalating if early tolerance is acceptable.

Table IV. Cox proportional hazards regression analysis for progression-free survival.

Variable	Univariate HR (95% CI)	P-value	Multivariate HR (95% CI) ^a	P-value
Eastern Cooperative Oncology Group Performance Status (1 vs. 0)	1.66 (0.71-3.90)	0.245	-	-
Baseline total bilirubin (>6.9 vs. ≤6.9 mg/dl)	0.92 (0.40-2.12)	0.850	-	-
≥50% Bilirubin reduction at week 4 (yes vs. no)	0.38 (0.16-0.91)	0.030	0.30 (0.12-0.76)	0.011
Percutaneous transhepatic biliary drainage procedure (yes vs. no)	0.65 (0.26-1.66)	0.369	-	-
Dose reduction (yes vs. no)	1.21 (0.50-2.95)	0.677	-	-

^aVariables with P<0.2 in univariate analysis were included in the multivariate model. Only week 4 bilirubin dynamics were included in survival analyses. HR, hazard ratio; CI, confidence interval.

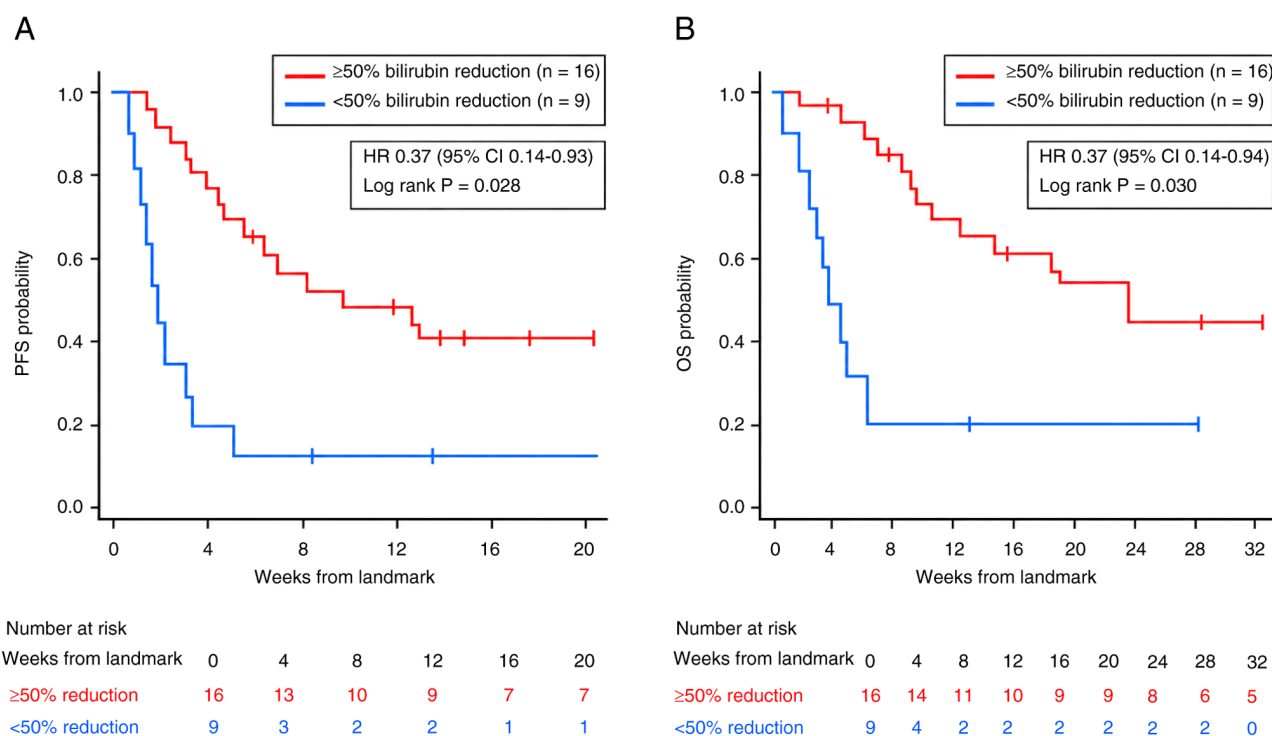


Figure 2. Week 4 landmark Kaplan-Meier curves for progression-free and OS according to bilirubin response. (A) PFS among patients alive, progression-free and under observation at week 4 (n=25; 22 progression events). Median landmark PFS was 2.89 months (95% CI 1.08-10.09) in patients with a ≥50% reduction in total bilirubin by week 4 vs. 0.53 months (95% CI 0.13-3.58) in those with a <50% reduction (univariable HR 0.37; 95% CI 0.14-0.93; log-rank P=0.028). (B) OS among patients alive and under observation at week 4 (n=25; 21 deaths). Median landmark OS was 5.52 months (95% CI 1.28-14.24) in patients with a ≥50% bilirubin reduction vs. 0.53 months (95% CI 0.13-6.51) in those with a <50% reduction (univariable HR 0.37; 95% CI 0.14-0.94; log-rank P=0.030). Bilirubin-response status was determined exclusively using measurements obtained on or before day 28. The 2 patients who died before day 28 (on days 18 and 26) were excluded from both landmark analyses, leaving 25 eligible patients (16 responders and 9 non-responders); both were classified as non-responders in the exploratory overall-cohort analyses. Survival time was reset to zero at the day 28 landmark. Median survival times and their 95% CIs were estimated from the landmark Kaplan-Meier curves using log-log transformed confidence limits. The univariable HRs shown here differ from the multivariable HRs reported in Tables IV and V, which were derived from the overall cohort without landmark restriction and adjusted for additional covariates. Tick marks indicate censored observations; numbers at risk are shown below each panel. PFS, progression-free survival; OS, overall survival; CI, confidence interval; HR, hazard ratio.

Grade 5 acute kidney injury occurred in 2 patients, both with normal baseline renal function. A patient developed acute kidney injury during bacteremic sepsis while receiving a nephrotoxic antibiotic. The other patient had advanced disease with ascites and probable infection, with renal decline evident

around the time of treatment initiation. Both patients required renal replacement therapy, and neither recovered renal function; consequently, both patients died.

CTCAE v5.0 assigns grade 5 when death is associated with the adverse event, irrespective of whether the event was

Table V. Cox proportional hazards regression analysis for overall survival.

Variable	Univariate HR (95% CI)	P-value	Multivariate HR (95% CI) ^a	P-value
Eastern Cooperative Oncology Group Performance Status (1 vs. 0)	1.83 (0.77-4.37)	0.175	1.10 (0.36-3.35)	0.862
Baseline total bilirubin (>6.9 vs. ≤6.9 mg/dl)	1.04 (0.45-2.41)	0.933	-	-
≥50% Bilirubin reduction at week 4 (yes vs. no)	0.37 (0.15-0.91)	0.030	0.29 (0.11-0.76)	0.012
Percutaneous transhepatic biliary drainage procedure (yes vs. no)	0.72 (0.28-1.85)	0.495	-	-
Dose reduction (yes vs. no)	1.34 (0.52-3.43)	0.546	-	-

^aVariables with P<0.2 in univariate analysis were included in the multivariate model. Only week 4 bilirubin dynamics were included in survival analysis. HR, hazard ratio; CI, confidence interval.

the primary cause of mortality (11). In both patients, acute kidney injury was part of the multiorgan failure preceding death, both remained dialysis-dependent until death and a contribution of renal failure to death therefore cannot be excluded. Both events accordingly have been classified as grade 5. This grading reflects the severity of the event and its association to mortality, not its attribution to treatment. Whether FOLFOX caused the renal injury is a separate question. Oxaliplatin is cleared renally, so a contribution from treatment cannot be excluded, but sepsis, hemodynamic compromise and, in one patient, a concurrent nephrotoxic antibiotic are more likely explanations (4). Hydration or volume status was not systematically documented at the time of these events, the role of FOLFOX in these two cases are regarded as uncertain rather than established. Renal function should be monitored closely in this population, particularly during concurrent infection (4).

An important exploratory finding in the present study was an association between early bilirubin dynamics and survival. A ≥50% reduction in total bilirubin at week 4 was associated with longer PFS and OS in the overall cohort; however, because response status is necessarily determined after a minimum survival time, this raw association is susceptible to immortal time bias. A post hoc week 4 landmark analysis, restricted to patients alive and progression-free at week 4, confirmed a statistically significant association for both PFS, indicating the association is unlikely to be solely an artifact of immortal time bias, although residual confounding cannot be excluded given the small sample size. This pattern is consistent with the survival advantage observed in bilirubin responders in the Quidde *et al* (6) study and raises the hypothesis-generating possibility that early hepatic response may reflect tumor sensitivity to FOLFOX in this population; however, this remains exploratory and has not been validated as an independent predictor or surrogate endpoint. However, the mechanisms underlying bilirubin reduction in this setting are not uniform. In some patients, declining bilirubin may reflect genuine antitumor activity with reduction of hepatic tumor burden, whereas in others it may result from relief of biliary compression independent of tumor response, a distinction that radiologic assessment alone cannot always resolve.

The observation that a proportion of bilirubin responders did not meet formal RECIST response criteria suggests that hepatic functional improvement may, in some cases, occur independently of measurable tumor shrinkage, although this cannot be confirmed retrospectively. Prospective studies incorporating paired imaging, hepatic function testing and bilirubin kinetics would be needed to dissect these mechanisms and validate early bilirubin response as a formal surrogate endpoint. While this finding requires validation in larger cohorts, it has potential clinical utility: Patients achieving rapid bilirubin reduction within the first month may be candidates for treatment continuation or dose escalation, whereas those without early response may warrant earlier reassessment of goals of care.

Several limitations of the present study deserve acknowledgment. The retrospective design introduces the possibility of selection bias, as patients who received FOLFOX in this setting may have been those judged by their treating clinicians to have sufficient performance reserve. The association between week 4 bilirubin response and survival is susceptible to immortal time bias, as patients had to survive to week 4 to be classified as responders. Although a post hoc week 4 landmark analysis yielded a similar direction of association, this analysis was restricted to univariable comparisons given the limited number of events in the landmark subgroup (25 patients for both PFS and OS), and residual immortal time bias or unmeasured confounding cannot be excluded; early bilirubin response should therefore not yet be regarded as a validated independent predictor or surrogate marker of survival. The sample size of 27 patients limits power for subgroup analyses and multivariate modeling. This is especially relevant for the multivariate Cox models, given the limited number of events relative to the covariates included; the resulting estimates should be interpreted with caution.

Bilirubin data were not available for all patients at all time-points, 11 of 27 had week 12 assessments and 20 of 27 had week 8 assessments, because patients who died or progressed earlier were, by definition, excluded from later evaluation. This survival-conditioned sampling likely favors more favorable trajectories and may overstate the durability of bilirubin normalization at weeks 8 and 12; the week 4 findings, for which

bilirubin measurements were available in all 27 patients, are less susceptible to this bias. Similarly, radiologic response data were available only for a subset able to undergo imaging before death or clinical deterioration; the reported ORR and DCR are therefore based on the RECIST-evaluable subgroup only, and incomplete radiologic assessment limits their interpretation and generalizability. Finally, the present study used a single-center cohort, and the distribution of tumor types and baseline characteristics may differ from those of Western or East Asian populations.

Despite these limitations, the present study adds real-world data to a clinical scenario where physicians frequently face treatment decisions without adequate evidence. The consistency of findings with prior case series across different tumor types and institutional contexts strengthens the overall argument for FOLFOX feasibility in this population (7,8,14,15). Prospective registries or multi-center retrospective analyses with standardized bilirubin response definitions and structured toxicity monitoring are the next logical step.

Overall, FOLFOX-based chemotherapy yielded rapid and sustained reductions in bilirubin levels across a heterogeneous population of patients with GI cancer with liver metastasis-related hyperbilirubinemia, without grade ≥ 3 hepatotoxicity. A $\geq 50\%$ reduction in total bilirubin by week 4 was associated with longer PFS and OS in exploratory analyses, including a week 4 landmark analysis performed to address immortal time bias; these present findings are hypothesis-generating and require prospective validation before early bilirubin response can be considered a validated prognostic marker. In patients with ECOG PS 0-1 and no irreversible non-malignant hepatic disease, this regimen appears feasible and may confer clinical benefit. These findings provide preliminary evidence supporting consideration of FOLFOX in patients who would otherwise be referred for symptom-directed care without anticancer therapy, pending validation in larger prospective studies in this underserved population.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

KB, KBY, OS and DMK conceived and designed the study. KB, GCU and DMK analyzed and interpreted the data. EY, KBY, OS and EH interpreted data. KB wrote the manuscript. KBY, OS and DMK supervised the study. KB and GCU confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Institutional Ethics Committee of Etlik City Hospital (Ankara, Türkiye) (approval no. AEŞH-BADEK2-2025-432) and was conducted in accordance with the Declaration of Helsinki.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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