Safety of endoscopy after recent bevacizumab use in metastatic colorectal cancer

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Background and Aims: Bevacizumab improves metastatic colorectal cancer (mCRC) survival but increases risks including GI perforation. This study compared 30-day postendoscopy (EGD/colonoscopy) perforation and bleeding risks between mCRC patients receiving recent (≤1 month) bevacizumab versus other active chemotherapy.

Methods: TriNetX, a multinational federated electronic health network database, was used to create and analyze 1:1 propensity score–matched cohorts of patients who underwent endoscopy for either diagnostic purposes (n = 396 total postmatch) or therapeutic purposes (n = 1306) as well as combined (n = 2100). Time-to-event analysis on 30-day perforation risk and 30-day postprocedural bleeding was conducted using Kaplan-Meier analysis on matched cohorts as well as adjusted Cox proportional hazards models on unmatched cohorts for sensitivity analysis.

Results: Baseline covariates were balanced post matching. No significant difference in 30-day perforation risk was found (Combined: hazard ratio [HR], 0.93; P = .791; Diagnostic: HR, 2.33; P = .143; Therapeutic: HR, 0.96; P = .925). Bevacizumab was associated with a significantly higher 30-day postprocedural bleeding risk in the Combined (matched HR, 1.28; P = .006) and Therapeutic (matched HR, 1.45; P = .001; adjusted HR, 1.46; P < .001) analyses but not in the Diagnostic subgroup (matched HR, 1.03; P = .894; adjusted HR, 0.98; P = .921).

Conclusions: Recent bevacizumab exposure was not associated with increased 30-day postendoscopy perforation risk compared with other active chemotherapy, but was associated with higher bleeding risk, primarily in therapeutic (specifically EGD) procedures. (Gastrointest Endosc 2026;104:77-85.)

INTRODUCTION

Bevacizumab, a monoclonal antibody that neutralizes vascular endothelial growth factor, remains a mainstay of modern regimens for metastatic colorectal cancer (mCRC), extending survival when added to fluoropyrimidine-based chemotherapy.[1,2] By suppressing physiologic angiogenesis, however, it also compromises tissue repair and is consistently linked to rare but serious adverse events, most notably gastrointestinal (GI) perforation.[3-5] Meta-analyses report an absolute incidence of 0.3% to 2.4% and a 1.5- to 3-fold risk increase versus chemotherapy alone, findings reflected in the U.S. Food and Drug Administration boxed warning.[4-6]

Patients with mCRC frequently undergo colonoscopy or esophagogastroduodenoscopy (EGD) for staging, surveillance, palliation, or tumor-directed therapy. Diagnostic endoscopy is generally safe (perforation <0.1%, major bleeding <0.5%), yet therapeutic maneuvers such as endoscopic mucosal resection (EMR) or submucosal dissection (ESD) carry higher procedural-site risks.[7,8] Whether bevacizumab amplifies those risks is uncertain. Surgical guidance advises holding the drug for ≥28 days to reduce wound-healing adverse events—an interval extrapolated from its 20-day terminal half-life—but parallel guidance for endoscopy is lacking.[3,6]

Evidence is limited to small, single-arm series that suggest low adverse-event rates but lack concurrent control groups and statistical power to detect uncommon adverse events.[9-11] Consequently, clinicians often balance urgent procedural needs against an ill-defined incremental risk, sometimes delaying anticancer therapy unnecessarily.

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We therefore used the multicenter TriNetX network to compare 30-day rates of GI perforation and postprocedural bleeding after colonoscopy or EGD in patients with mCRC recently exposed to bevacizumab versus propensity-matched patients receiving other systemic therapies without bevacizumab, with outcomes stratified by diagnostic and therapeutic intent.

PATIENTS AND METHOD

Data source and ethical considerations

This retrospective cohort study used deidentified patient data accessed on April 29, 2025, via the TriNetX Research Network, a private, commercial federated health research network that provides secure access to aggregated electronic health record (EHR) data. Unlike federally owned databases (eg, Veterans Affairs system), insurance claims databases, or disease-specific registries (eg, Surveillance, Epidemiology, and End Results [SEER] Program), TriNetX operates through partnerships with more than 250 health care organizations globally, including academic medical centers, community hospitals, and specialty practices.[12] The platform aggregates deidentified EHR data representing more than 300 million patients worldwide (117+ million U.S. patients), with data refreshed every 2 to 4 weeks. All data are harmonized to standardized clinical terminologies including International Classification of Diseases, 10th Revision, Clinical Modification (*ICD-10-CM*) for diagnoses, Current Procedural Terminology (*CPT*) and Systematized Nomenclature of Medicine–Clinical Terms (SNOMED) for procedures, RxNorm standardized drug nomenclature (National Library of Medicine) and Healthcare Common Procedure Coding System (HCPCS) for medications, and Logical Observation Identifiers Names and Codes for laboratory values, ensuring consistency across contributing organizations.[12] For this analysis, data were drawn from up to 103 participating U.S. health care organizations. TriNetX is fully Health Insurance Portability and Accountability Act (HIPAA) compliant, and all patient data are deidentified before researcher access. The platform has been used in hundreds of peer-reviewed publications across diverse therapeutic areas and has demonstrated capability to validate outcomes from randomized clinical trials with real-world evidence.[12,13]

Study design and population

We conducted a retrospective cohort study of adult patients with metastatic colorectal cancer (mCRC) who underwent an EGD or colonoscopy procedure. Patients were identified based on the presence of relevant *ICD-10-CM* codes for colorectal cancer (C18.x, C19.x, C20.x) and secondary malignant neoplasms (C77.x, C78.x, C79.x) recorded at any time before or on the index date.

Cohort definitions

Two primary cohorts were defined based on exposure to bevacizumab relative to the index endoscopy procedure. The Bevacizumab Group (Exposure Cohort) included patients meeting mCRC criteria who had at least 1 qualifying index EGD or colonoscopy procedure and received bevacizumab within 1 month (30 days) on or before the date of the index procedure. Bevacizumab exposure was identified using HCPCS codes J9035 (bevacizumab 10 mg injection), C9257 (bevacizumab 0.25 mg injection), Q5107 (bevacizumab-awwb biosimilar 10 mg), Q5118 (bevacizumab-bvzr biosimilar 10 mg), Q5126 (bevacizumab-maly biosimilar 1 mg), Q5129 (bevacizumab-adcd biosimilar 10 mg), or RxNorm code 253337 (bevacizumab including biosimilars).

The control group included patients with mCRC who had at least 1 qualifying index procedure but did not receive bevacizumab within 1 month (30 days) on or before the index procedure date. To ensure comparability regarding active treatment status, patients in this cohort were required to have evidence of receiving other standard mCRC chemotherapy agents (oxaliplatin [RxNorm 32592], capecitabine [194000], irinotecan [51499], fluorouracil [4492], or leucovorin [6313]) within 30 days before the procedure. Patients with any record of bevacizumab within 1 year before the index date were excluded from this cohort.

Procedure code groupings for analysis

Analyses were performed based on the type of index procedure, grouping EGD and colonoscopy codes together within each category. The Combined Procedures analysis included patients undergoing any qualifying EGD (*CPT* 43235, 43239, 43241, 43243, 43244, 43245, 43247, 43249, 43250, 43251, 43254, 43255, 43270) or colonoscopy (*CPT* 45378, 45380, 45381, 45382, 45384, 45385, 45390, 1022231; SNOMED 446745002). The Diagnostic subgroup included patients whose index procedure was coded as diagnostic only, using *CPT* codes 43235 (EGD, diagnostic), 45378 (Colonoscopy, diagnostic), or 1022231 (Colonoscopy, flexible), and excluding codes for therapeutic interventions performed during the same encounter (based on TriNetX query logic). The Therapeutic subgroup included patients whose index procedure involved any endoscopic therapeutic intervention, identified by *CPT* codes 43239 (EGD w/ biopsy), 43241 (EGD w/ tube), 43243 (EGD w/ sclerosis), 43244 (EGD w/ banding), 43245 (EGD w/ dilation), 43247 (EGD w/ foreign body removal), 43249 (EGD w/ balloon dilation), 43250 (EGD w/ hot biopsy forceps), 43251 (EGD w/ snare), 43254 (EGD w/ EMR), 43255 (EGD w/ bleeding control), 45380 (Colonoscopy w/ biopsy), 45381 (Colonoscopy w/ injection), 45382 (Colonoscopy w/ bleeding control), 45384 (Colonoscopy w/ hot biopsy forceps), 45385 (Colonoscopy w/ snare), 45390 (Colonoscopy w/ EMR), or SNOMED code 446745002 (Colonoscopy w/ biopsy).

Index event and follow-up

The index date for each patient was the date of the first qualifying EGD or colonoscopy procedure meeting the criteria for the respective analysis group (Combined, Diagnostic, or Therapeutic) and the cohort's bevacizumab

exposure/nonexposure criteria. The primary outcome window was defined as the period starting 1 day after the index date and ending 30 days after the index date.

Outcome definitions

Outcomes were assessed within the 30-day follow-up window. The primary outcome, GI perforation, was identified by the occurrence of relevant *ICD-10-CM* codes, including K63.1 (Perforation of intestine); K25.1, K25.2, K25.5, K25.6 (Gastric ulcer w/ perforation); K26.1, K26.2, K26.5, K26.6 (Duodenal ulcer w/ perforation); K27.1, K27.2, K27.5, K27.6 (Peptic ulcer w/ perforation); K28.1, K28.2, K28.5, K28.6 (Gastrojejunal ulcer w/ perforation); K91.71, K91.72 (Accidental puncture/laceration during procedure); K22.3 (Perforation of esophagus); or K91.89 (Other postprocedural adverse events). The secondary outcome, postprocedural bleeding, was identified by *ICD-10-CM* codes K92.1 (Melena), K92.2 (GI hemorrhage, unspecified), K91.840 (Postprocedural hemorrhage), or K62.5 (Hemorrhage of anus/rectum). Bleeding events were captured exclusively within the 30-day postprocedural window (days 1-30 after the index procedure), and analyses excluded patients with bleeding documented before this window to ensure events represented postprocedural adverse events rather than pre-existing conditions.

Covariates and propensity score matching

Baseline patient characteristics of age, sex, race, ethnicity, and comorbidities (hypertension, ischemic heart disease, heart failure, chronic obstructive pulmonary disease, asthma, chronic hepatitis, fibrosis/cirrhosis, alcoholic liver disease, other liver diseases, diabetes, Crohn's ulcerative colitis, toxic/radiation gastroenteritis, ileus/obstruction, diverticular disease, malnutrition, and abnormal weight loss) were assessed before the index date. Propensity score matching was performed separately for the Combined, Diagnostic, and Therapeutic analyses. Patients in the Bevacizumab Group were matched 1:1 to patients in the Control Group based on the estimated propensity score using a nearest-neighbor algorithm with a 0.1–standard deviation caliper.

Statistical analysis

Baseline characteristics were compared before and after matching using standardized differences (<0.1 indicating good balance). Outcome analyses were performed on the propensity score–matched cohorts for each of the 3 analysis groups (Combined, Diagnostic, Therapeutic). Kaplan-Meier survival analysis was used as the primary method to compare the time to event (perforation or bleeding) between cohorts using the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated from the Kaplan-Meier analysis. For perforation, analyses excluded patients with the outcome before the time window. For bleeding, Kaplan-Meier analyses included all matched patients, whereas secondary risk analyses (risk difference [RD], risk ratio [RR], odds ratio [OR]) excluded patients with bleeding before the time window (as reported by TriNetX). As a sensitivity analysis, multivariable Cox proportional hazards models were run on the full unmatched cohorts for each group, adjusting for the baseline covariates listed above, to estimate adjusted hazard ratios (aHRs). A 2-sided P value <.05 was considered statistically significant. Per TriNetX policy, any events with counts below 10 were noted as "<10" per policy for patient privacy.

Ethics

Per TriNetX recording and sharing policies, data are deidentified before researcher access of data. As this study involved a secondary analysis of existing, deidentified data, it was exempt from institutional review board review.

RESULTS

Cohort identification and baseline characteristics

From the TriNetX Research Network (accessed April 29, 2025; up to 103 health care organizations), we identified mCRC patients meeting inclusion criteria for the Combined Procedures (Control $n = 2903$; Bevacizumab $n = 1061$), Diagnostic subgroup (Control $n = 413$; Bevacizumab $n = 211$), and Therapeutic subgroup (Control $n = 1732$; Bevacizumab $n = 665$) analyses before matching. Propensity score matching yielded balanced cohorts for the 3 primary analyses: Combined (1050 pairs), Diagnostic (198 pairs), and Therapeutic (653 pairs). After matching, baseline characteristics including demographics and comorbidities were generally well balanced between the Bevacizumab and Control groups within each analysis set, with nearly all standardized differences between the exposure and control groups below 0.1 (see Table 1 for postmatch demographics, and see Supplementary Tables 1-3, for detailed characteristics before and after matching).

Table 2 shows the number of GI perforations and postprocedural bleeding events within the study period. Within the 30-day follow-up period in the matched cohorts, GI perforation occurred infrequently overall. In the combined group, 24 of 1050 patients (2.3%) in the Bevacizumab group sustained GI perforation, whereas 26 of 1050 (2.5%) in the Control group sustained GI perforation. In the Therapeutic subgroup, 14 of 653 (2.1%) sustained GI perforation, whereas in the Control group the rate was 14 of 653 (2.1%). In the Diagnostic subgroup, there were <10 events in both groups.

Postprocedural bleeding was more common. In the combined group, 268 of 1050 patients (25.5%) in the Bevacizumab group had postprocedural bleeding, whereas 215 of 1050 patients (20.5%) in the Control group had postprocedural bleeding. In the Therapeutic subgroup, this rate was 161 of 653 (24.7%), and 114 of 653 (17.5%)

TABLE 1. Demographics of propensity score–matched cohorts

	Diagnostic subgroup			Therapeutic subgroup			Combined procedures		
	Control (*n* = 198)	Bev (*n* = 198)	StDiff	Control (*n* = 653)	Bev (*n* = 653)	StDiff	Control (*n* = 1050)	Bev (*n* = 1050)	StDiff
Demographics									
Age at index, y, mean ± SD	58.0 ± 13.2	58.7 ± 12.8	0.06	59.8 ± 13.2	60.2 ± 12.6	0.04	60.0 ± 12.7	59.8 ± 12.5	0.02
Sex, *n* (%)									
Female	91 (46.0)	87 (43.9)	0.04	314 (48.1)	314 (48.1)	<0.001	509 (48.5)	491 (46.8)	0.03
Male	99 (50.0)	102 (51.5)	0.03	311 (47.6)	314 (48.1)	0.01	508 (48.4)	520 (49.5)	0.02
Race, *n* (%)									
White	145 (73.2)	143 (72.2)	0.02	466 (71.4)	467 (71.5)	0.00	741 (70.6)	744 (70.9)	0.01
Black or African American	<10 (<5.1)	11 (5.6)	0.02	50 (7.7)	52 (8.0)	0.01	97 (9.2)	89 (8.5)	0.03
Asian	13 (6.6)	15 (7.6)	0.04	31 (4.7)	40 (6.1)	0.06	62 (5.9)	61 (5.8)	0.00
Unknown	16 (8.1)	17 (8.6)	0.02	70 (10.7)	63 (9.6)	0.04	92 (8.8)	98 (9.3)	0.02
Ethnicity, *n* (%)									
Hispanic or Latino	19 (9.6)	20 (10.1)	0.02	56 (8.6)	54 (8.3)	0.01	100 (9.5)	95 (9.0)	0.02
Not Hispanic or Latino	145 (73.2)	143 (72.2)	0.02	497 (76.1)	508 (77.8)	0.04	795 (75.7)	803 (76.5)	0.02
Comorbidities, *n* (%)									
Malignant neoplasms of digestive organs	196 (99.0)	195 (98.5)	0.05	628 (96.2)	628 (96.2)	<0.001	1016 (96.8)	1016 (96.8)	<0.001
Malignant neoplasms of ill-defined sites	189 (95.5)	192 (97.0)	0.08	605 (92.6)	603 (92.3)	0.01	992 (94.5)	984 (93.7)	0.03
Hypertensive diseases	103 (52.0)	105 (53.0)	0.02	386 (59.1)	389 (59.6)	0.01	628 (59.8)	614 (58.5)	0.03
Ischemic heart diseases	33 (16.7)	39 (19.7)	0.08	153 (23.4)	148 (22.7)	0.02	247 (23.5)	238 (22.7)	0.02
Heart failure	11 (5.6)	15 (7.6)	0.08	61 (9.3)	61 (9.3)	<0.001	89 (8.5)	90 (8.6)	0.00
COPD	13 (6.6)	15 (7.6)	0.04	58 (8.9)	56 (8.6)	0.01	95 (9.0)	86 (8.2)	0.03
Asthma	18 (9.1)	15 (7.6)	0.06	73 (11.2)	62 (9.5)	0.06	107 (10.2)	100 (9.5)	0.02
Chronic hepatitis	0 (0)	0 (0)	–	<10 (<1.5)	<10 (<1.5)	<0.001	<10 (<1.0)	<10 (<1.0)	<0.001
Fibrosis and cirrhosis of liver	11 (5.6)	11 (5.6)	<0.001	59 (9.0)	47 (7.2)	0.07	80 (7.6)	73 (7.0)	0.03
Alcoholic liver disease	0 (0)	<10 (<5.1)	0.33	<10 (<1.5)	<10 (<1.5)	<0.001	<10 (<1.0)	<10 (<1.0)	<0.001
Other diseases of liver	103 (52.0)	102 (51.5)	0.01	367 (56.2)	369 (56.5)	0.01	584 (55.6)	586 (55.8)	0.00
Diabetes mellitus	38 (19.2)	45 (22.7)	0.09	172 (26.3)	172 (26.3)	<0.001	277 (26.4)	267 (25.4)	0.02
Crohn's disease	<10 (<5.1)	<10 (<5.1)	<0.001	20 (3.1)	14 (2.1)	0.06	21 (2.0)	20 (1.9)	0.01
Ulcerative colitis	<10 (<5.1)	<10 (<5.1)	<0.001	18 (2.8)	14 (2.1)	0.04	25 (2.4)	19 (1.8)	0.04
Toxic gastroenteritis and colitis	26 (13.1)	23 (11.6)	0.05	78 (11.9)	71 (10.9)	0.03	99 (9.4)	116 (11.0)	0.05
Gastroenteritis and colitis due to radiation	<10 (<5.1)	<10 (<5.1)	<0.001	<10 (<1.5)	<10 (<1.5)	<0.001	<10 (<1.0)	<10 (<1.0)	<0.001
Paralytic ileus and intestinal obstruction	80 (40.4)	80 (40.4)	<0.001	219 (33.5)	223 (34.2)	0.01	389 (37.0)	388 (37.0)	0.00
Diverticular disease of intestine	32 (16.2)	33 (16.7)	0.01	151 (23.1)	149 (22.8)	0.01	245 (23.3)	248 (23.6)	0.01
Malnutrition	41 (20.7)	49 (24.7)	0.10	166 (25.4)	158 (24.2)	0.03	244 (23.2)	246 (23.4)	0.01
Abnormal weight loss	41 (20.7)	40 (20.2)	0.01	101 (15.5)	108 (16.5)	0.03	182 (17.3)	179 (17.0)	0.01

Bev, Bevacizumab; *COPD*, chronic obstructive pulmonary disease; *StDiff*, standardized difference.

in the control group. For patients undergoing endoscopy for diagnostic purposes, the Bevacizumab group had 45 of 198 instances (22.7%) of postprocedural bleeding, whereas the control group had 44 of 198 instances (22.2%).

To further characterize bleeding risk by anatomic site, separate subanalyses were performed for EGD and colonoscopy procedures. In the EGD subgroup (379 matched pairs), postprocedural bleeding occurred in 74 of 379 Bevacizumab patients (19.5%) vs 53 of 379 control patients

TABLE 2. Thirty-day clinical outcomes after endoscopy in propensity score–matched cohorts (Kaplan-Meier analysis)

Outcome/analysis group	*N* matched pairs	Patients with outcome (Bevacizumab/Control)	Survival probability (Bevacizumab/Control), %	Hazard ratio (Bevacizumab vs Control) (95% CI)	*P* value
GI perforation					
Combined procedures	1050	24/26	97.4/97.2	0.93 (0.53-1.61)	.791
Diagnostic subgroup	198	<10/<10	94.7/97.8	2.33 (0.72-7.69)	.143
Therapeutic subgroup	653	14/14	97.6/97.5	0.96 (0.46-2.04)	.925
Postprocedural bleeding					
Combined procedures	1050	268/215	74.4/79.5	1.28 (1.06-1.54)	**.006**
Diagnostic subgroup	198	45/44	77.2/77.7	1.03 (0.69-1.56)	.894
Therapeutic subgroup	653	161/114	75.3/82.5	1.45 (1.15-1.85)	**.001**

P value from log-rank tests. *N* matched pairs indicates the number of pairs in each analysis. Perforation analysis excludes patients with outcome before time window. Bleeding analysis includes all matched patients. "<10" indicates event counts suppressed because of small numbers. Bold *P* values indicate statistical significance ($P < .05$).

(14.0%). In the colonoscopy subgroup (405 matched pairs), bleeding occurred in 42 of 405 Bevacizumab patients (10.4%) vs 35 of 405 Control patients (8.6%).

Thirty-day clinical outcomes in matched cohorts (Kaplan-Meier analysis)

The 30-day risks of GI perforation and postprocedural bleeding were compared between the matched Bevacizumab and Control groups using Kaplan-Meier analysis. Regarding GI perforation, across all 3 analysis sets (Combined, Diagnostic, and Therapeutic), there was no statistically significant difference in the 30-day hazard between the Bevacizumab and Control groups. HRs were close to 1.0, and *P* values were nonsignificant (Combined: HR, 0.93; $P = .791$; Diagnostic: HR, 2.33; $P = .143$; Therapeutic: HR, 0.96; $P = .925$). Event rates remained low across groups, with counts suppressed (<10) in the Diagnostic subgroup. Kaplan-Meier curves illustrating the time to perforation for the Combined analysis (Fig. 1) correspond to the nonsignificant log-rank test result.

For postprocedural bleeding, Kaplan-Meier analyses revealed a statistically significantly higher 30-day hazard ratio associated with bevacizumab exposure in the Combined analysis (HR, 1.28; 95% CI, 1.06-1.53; $P = .006$; Fig. 2) and the Therapeutic subgroup (HR, 1.45; 95% CI, 1.15-1.85; $P = .001$; Fig. 3). However, this association was not statistically significant in the Diagnostic subgroup (HR, 1.03, 95% CI, 0.69-1.56; $P = .894$).

Sensitivity analysis: adjusted Cox models (unmatched cohorts)

As a sensitivity analysis, multivariable Cox proportional hazards models were run on the full unmatched cohorts for the Diagnostic and Therapeutic subgroups, adjusting for baseline covariates listed in the Methods.

For GI perforation, the adjusted Cox models showed no significant difference in hazard between the Bevacizumab and Control groups in either the Diagnostic subgroup (aHR, 1.32; 95% CI, 0.61-2.87; $P = .478$) or the Therapeutic subgroup (aHR, 0.97; 95% CI, 0.59-1.60; $P = .898$).

For postprocedural bleeding, the adjusted Cox model confirmed a statistically significantly higher hazard associated with bevacizumab exposure compared with control chemotherapy in the Therapeutic subgroup (aHR, 1.46; 95% CI, 1.20-1.77; $P < .001$), but showed no significant difference in the Diagnostic subgroup (aHR, 0.98; 95% CI, 0.69-1.40; $P = .921$). These adjusted results align well with the findings from the primary matched Kaplan-Meier analyses.

Subanalysis by anatomic site

To provide additional granularity regarding bleeding risk, separate propensity-matched analyses were performed for EGD and colonoscopy procedures. In the EGD subgroup (379 matched pairs per arm), the Kaplan-Meier analysis showed a statistically significantly higher bleeding risk associated with bevacizumab exposure (matched HR, 1.42; 95% CI, 1.00-2.02; $P = .047$). In contrast, the colonoscopy subgroup (405 matched pairs per arm) showed no statistically significant difference in bleeding risk (matched HR, 1.20; 95% CI, 0.77-1.88; $P = .421$). These findings indicate that the elevated bleeding risk associated with bevacizumab is primarily driven by upper endoscopic procedures rather than lower endoscopic procedures (Supplementary Table 4).

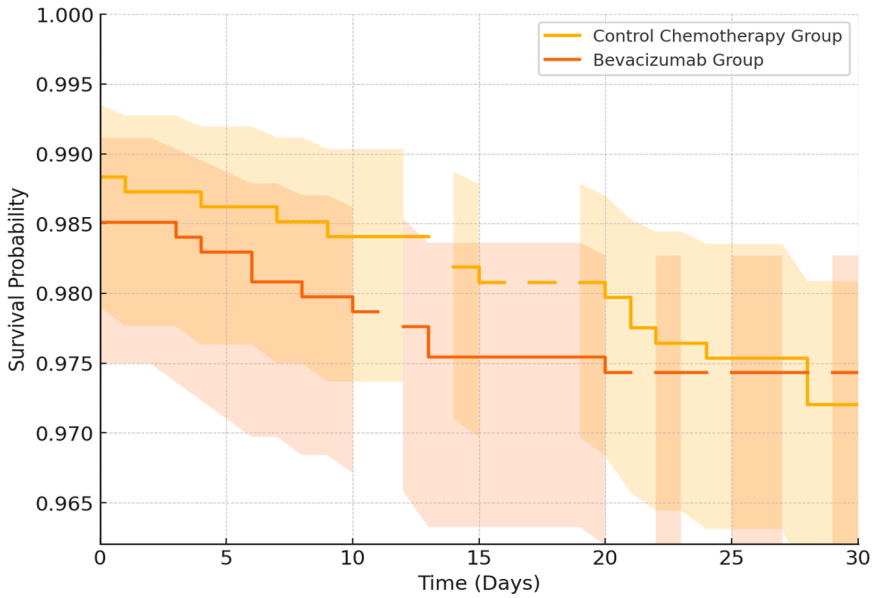

Figure 1. Diagnostic and therapeutic procedure–GI perforation risk analysis. Time-to-event analysis on propensity score–matched Bevacizumab and Control chemotherapy groups showed no significant difference in time to GI perforation.

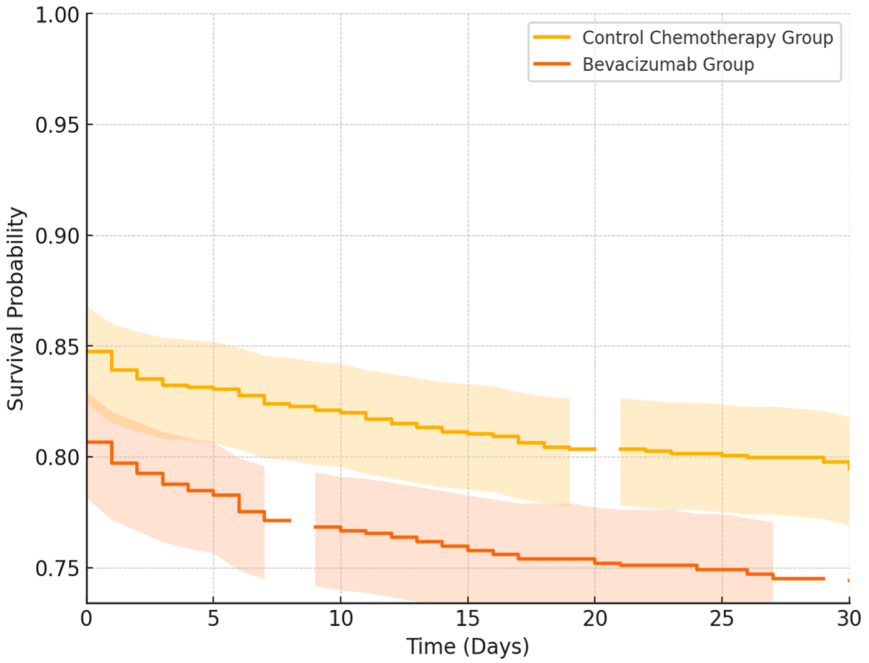

Figure 2. Combined group (diagnostic and therapeutic) procedure–postprocedural bleeding risk analysis. Patients in the Bevacizumab group had lower survival probability higher event rates of postprocedural bleeding than patients in the Control chemotherapy group when undergoing endoscopy for diagnostic and therapeutic purposes. Log-rank test showed $P = .006$.

DISCUSSION

Principal findings

In this large, retrospective cohort study of mCRC patients undergoing endoscopy, using propensity score matching against an active chemotherapy comparator group, we found that recent bevacizumab exposure (within 30 days) was not associated with a statistically significant increase in the 30-day risk of GI perforation. The Kaplan-Meier HRs comparing bevacizumab to control were nonsignificant and near unity across all groups (Combined: HR, 0.93; $P = .791$; Diagnostic: HR, 2.33; $P = .143$; Therapeutic: HR, 0.96; $P = .925$), as illustrated by the Kaplan-Meier survival curve in the Combined

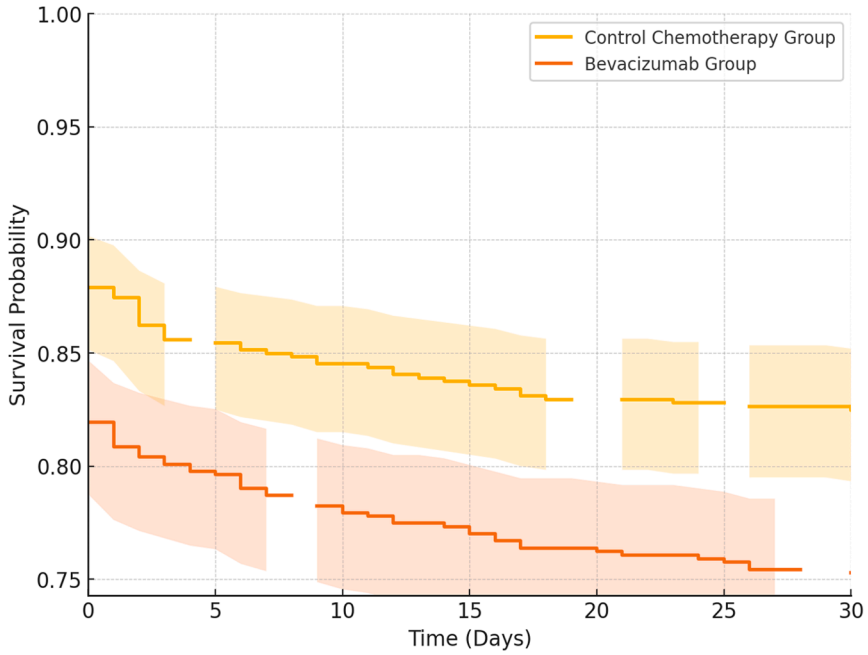

Figure 3. Therapeutic procedure–postprocedural bleeding risk analysis. Patients in the Bevacizumab group had lower survival probability higher event rates of postprocedural bleeding than patients in the Control chemotherapy group when undergoing endoscopy for therapeutic purposes. Log-rank test showed $P = .001$.

analysis (Fig. 1). This lack of association was further supported by adjusted Cox models on the unmatched cohorts (Diagnostic: aHR, 1.32; $P = .478$; Therapeutic: aHR, 0.97; $P = .898$).

However, the analysis did reveal a statistically significantly higher 30-day risk of postprocedural bleeding associated with bevacizumab exposure. This was seen in the control chemotherapy group relative to the bevacizumab group in both the combined (matched HR, 1.28; $P = .006$; Fig. 2) and therapeutic procedure cohorts (matched HR, 1.45; $P = .001$; aHR, 1.46; $P < .001$; Fig. 3) but not in the diagnostic subgroup (matched HR, 1.03; $P = .894$; aHR, 0.98; $P = .921$).

Interpretation regarding acute procedural safety

The lack of an observed increase in acute perforation risk, with nonsignificant HRs near 1.0 in both matched and adjusted analyses, and corresponding Kaplan-Meier curves showing minimal separation (Fig. 1), provides some reassurance regarding the safety of performing necessary endoscopic procedures within 30 days of bevacizumab administration, compared with the risks faced by similar patients receiving other active chemotherapy regimens. The consistency of the null perforation finding across the Combined, Diagnostic, and Therapeutic subgroups, with nonsignificant HRs near 1.0 in both matched and adjusted analyses, strengthens this conclusion, although power remains limited by low event counts, particularly in the Diagnostic subgroup where counts were <10. Although not negating the known systemic risks of bevacizumab or the inherent risks of endoscopy in this population, this suggests the incremental acute procedural risk of perforation may not be substantially elevated by recent bevacizumab exposure itself.

Our observation of heightened bleeding risk in the Combined and Therapeutic cohorts is biologically consistent with mechanistic studies showing that vascular endothelial growth factor neutralization impairs endothelial regeneration, reduces capillary stability, and delays re-epithelialization after mucosal injury. Preclinical models of bevacizumab exposure demonstrate disrupted platelet-endothelium cross-talk and diminished proangiogenic signaling, pathophysiologic changes that would be expected to amplify hemorrhage at sites of tissue manipulation.[3,7,14] The Kaplan-Meier curves visualize this difference by showing separation between the treatment groups for bleeding events in the Combined (Fig. 2) and Therapeutic (Fig. 3) analyses, consistent with the significant log-rank tests. It is also important to note that the active comparator group in this study compares bevacizumab not against no treatment but against other standard cytotoxic chemotherapies (like oxaliplatin, irinotecan, fluorouracil). These agents themselves carry risks of mucosal toxicity and thrombocytopenia, potentially elevating the baseline postprocedural bleeding risk in the control group. Therefore, the observed higher relative risk with bevacizumab in the therapeutic subgroup (where mucosal disruption is generally greater than in diagnostic procedures) may indicate it confers even higher acute bleeding risk in the 30-day postendoscopy period compared with that in patients on no chemotherapeutic

agents. The lack of a significant difference in the diagnostic group suggests this relative difference might be less pronounced or absent when only diagnostic procedures (with potentially less mucosal trauma) are considered. The consistency between known mechanism of action of bevacizumab, known increased bleeding risk systemic, propensity score–matched cohorts, and multivariable Cox adjusted analyses in relatively large cohorts all strengthen these findings.

The null finding for perforation aligns with some smaller observational studies suggesting low acute adverse event rates postendoscopy in patients on antiangiogenic agents,[15-18] but adds robustness through its large scale, active comparator design, subgroup analyses, and consistent results across matched and adjusted analyses. The established systemic perforation risk associated with bevacizumab (compared with chemotherapy alone)[4-6] likely reflects longer-term effects or different patient populations than those specifically undergoing endoscopy within 30 days of treatment in our study.

The updated finding of higher bleeding risk only in the Combined and Therapeutic groups (and not Diagnostic), as illustrated in Figures 2 and 3, aligns with the known systemic bleeding risks of bevacizumab.[3] The anatomic site–specific subanalysis further refines this understanding by demonstrating that bleeding risk is significantly elevated in EGD procedures (HR 1.42; $P = .047$) but not in colonoscopy procedures (HR 1.20; $P = .421$). This differential risk by anatomic site may reflect differences in vascular anatomy, mucosal healing characteristics, or procedural trauma between the upper and lower GI tract. The gastric and esophageal mucosa may be more vulnerable to bevacizumab-induced healing impairment than colonic mucosa, or upper endoscopic procedures may involve greater vascular disruption. Alternatively, the higher baseline vascularity of the upper GI tract, particularly in the setting of tumor-related angiogenesis, may amplify bleeding susceptibility when vascular endothelial growth factor signaling is inhibited. Most prior studies focused on overall bleeding during therapy, not specifically 30-day postprocedural risk compared to other active chemotherapy stratified by procedure type. Given the fact that these patients have higher risks of postprocedural bleeding, particularly with upper endoscopy, further research is warranted to determine risk factors for severe hemorrhage in this patient population. This can help ensure patients are not unduly exposed to preventable adverse events or, conversely, denied timely endoscopic therapy when the net clinical benefit remains favorable. Identifying predictors—such as thrombocytopenia, concurrent anticoagulation, type and extent of mucosal resection, or interval since the last bevacizumab dose—could guide individualized periprocedural strategies (eg, adjusted antithrombotic management, prophylactic clipping, or extended observation), ultimately optimizing both oncologic and procedural outcomes in this high-risk cohort.

Strengths and limitations

Strengths include the large real-world data set, propensity score matching balancing numerous covariates for the primary analysis, an active control group with mCRC and on active chemotherapeutic regimen, subgroup analyses by procedural intent, and confirmation via adjusted Cox models on the full cohorts. Limitations are inherent to retrospective database studies: reliance on coding accuracy, potential for unmeasured confounding (eg, performance status, precise indication for endoscopy, specific chemotherapy agents within the control group), and limited power for rare events like perforation. As with other EHR-based research networks, TriNetX data are dependent on documentation and coding practices at participating institutions, which may vary in completeness and accuracy.[13] Although the platform's data harmonization processes enhance consistency,[12] certain clinically relevant variables —such as ECOG performance status, precise endoscopic technique details, or clinical judgments regarding procedural complexity—are not systematically captured in structured EHR fields and thus were not available for this analysis. Additionally, participating health care organizations represent those that have joined the TriNetX network, which may introduce selection bias; findings may be most applicable to health care settings with comprehensive EHR systems and may not fully represent all U.S. cancer care delivery environments, particularly smaller or rural facilities.[13] Furthermore, we could not systematically assess important potential confounders of bleeding risk, including thrombocytopenia, concurrent anticoagulant or antiplatelet therapy, or nonsteroidal anti-inflammatory drug use. Although bevacizumab itself is not typically associated with thrombocytopenia, other chemotherapeutic agents in both study groups may cause bone marrow suppression, potentially contributing to bleeding risk. The inability to adjust for these factors represents an important limitation of this and similar large-database studies relying primarily on diagnostic codes. Moreover, the *CPT* code definitions used for diagnostic and therapeutic subgroups, although pragmatic, may allow for some misclassification.

Clinical and research implications

These results refine the risk-benefit conversation when scheduling endoscopy in mCRC patients who have received bevacizumab within the past month. These findings can help in mitigating excessive delays based solely on perforation concerns, provided the patient's overall status is suitable. Although our data reaffirm that bevacizumab does not heighten 30-day perforation rates relative to other active chemotherapy, they demonstrate a significantly higher 30-day bleeding risk, with important anatomic distinctions: the risk is significant for EGD procedures but not for colonoscopy. Accordingly, when bevacizumab has been administered within the preceding 30 days, clinicians should weigh

the elevated hemorrhagic risk primarily for upper endoscopy, whereas lower endoscopy appears to carry similar bleeding risk to other active chemotherapy regimens. The urgency and anatomic site of the planned procedure should be balanced against this procedure-specific hemorrhagic risk as the primary consideration for endoscopy in bevacizumab-exposed patients, rather than the customary concern for perforation. Future prospective work that stratifies by chemotherapeutic regimen, clearly delineates procedural intent, and examines site-specific outcomes will be essential to optimize periendoscopic management and refine guidelines for bevacizumab-exposed patients.

CONCLUSIONS

In mCRC patients, recent bevacizumab exposure was not associated with increased 30-day postendoscopy perforation risk compared with other active chemotherapy but was associated with higher bleeding risk in therapeutic (specifically EGD) procedures.

DISCLOSURE

All authors disclosed no financial relationships.

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Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CPT, Current Procedural Terminology*; EGD, esophagogastroduodenoscopy; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; FDA, U.S. Food and Drug Administration; GI, gastrointestinal; HCPCS, Healthcare Common Procedure Coding System; HR, hazard ratio;* ICD-10-CM, International Classification of Diseases, 10th Revision, Clinical Modification*; mCRC, metastatic colorectal cancer; OR, odds ratio; RD, risk difference; RR, risk ratio; RxNorm, RxNorm standardized drug nomenclature (National Library of Medicine); SD, standard deviation; SNOMED, Systematized Nomenclature of Medicine–Clinical Terms; StDiff, standardized difference.*

0016-5107/$36.00
https://doi.org/10.1016/j.gie.2025.11.024
Received August 25, 2025. Accepted November 6, 2025.

SUPPLEMENTARY TABLE 1. Baseline characteristics before and after propensity score matching (combined procedures analysis)

Characteristic	Before matching			After matching		
	Control (n = 2903)	Bevacizumab (n = 1061)	StDiff	Control (n = 1050)	Bevacizumab (n = 1050)	StDiff
Demographics						
Age at index, y, mean ± SD	59.9 ± 12.9	59.8 ± 12.5	0.015	60.0 ± 12.7	59.8 ± 12.5	0.019
Sex, *n* (%)						
Female	1138 (40.9)	492 (46.8)	0.120	509 (48.5)	491 (46.8)	0.034
Male	1529 (54.9)	520 (49.5)	0.109	508 (48.4)	520 (49.5)	0.023
Race, *n* (%)						
White	1869 (67.1)	745 (70.9)	0.081	741 (70.6)	744 (70.9)	0.006
Black or African American	347 (12.5)	89 (8.5)	0.131	97 (9.2)	89 (8.5)	0.027
Asian	139 (5.0)	61 (5.8)	0.036	62 (5.9)	61 (5.8)	0.004
Unknown	287 (10.3)	98 (9.3)	0.033	92 (8.8)	98 (9.3)	0.020
Ethnicity, *n* (%)						
Hispanic or Latino	286 (10.3)	95 (9.0)	0.042	100 (9.5)	95 (9.0)	0.016
Not Hispanic or Latino	2017 (72.4)	804 (76.5)	0.093	795 (75.7)	803 (76.5)	0.018
Comorbidities, *n* (%)						
Malignant neoplasms of digestive organs	2728 (98.0)	1017 (96.8)	0.077	1016 (96.8)	1016 (96.8)	<0.001
Malignant neoplasms of ill-defined sites	2417 (86.8)	985 (93.7)	0.234	992 (94.5)	984 (93.7)	0.032
Hypertensive diseases	1643 (59.0)	615 (58.5)	0.010	628 (59.8)	614 (58.5)	0.027
Ischemic heart diseases	653 (23.5)	239 (22.7)	0.017	247 (23.5)	238 (22.7)	0.020
Heart failure	276 (9.9)	91 (8.7)	0.043	89 (8.5)	90 (8.6)	0.003
COPD	276 (9.9)	86 (8.2)	0.060	95 (9.0)	86 (8.2)	0.031
Asthma	282 (10.1)	100 (9.5)	0.021	107 (10.2)	100 (9.5)	0.022
Chronic hepatitis	<10 (<0.4)	<10 (<1.0)	0.073	<10 (<1.0)	<10 (<1.0)	<0.001
Fibrosis and cirrhosis of liver	137 (4.9)	74 (7.0)	0.089	80 (7.6)	73 (7.0)	0.026
Alcoholic liver disease	39 (1.4)	<10 (<1.0)	0.042	<10 (<1.0)	<10 (<1.0)	<0.001
Other diseases of liver	1235 (44.4)	587 (55.9)	0.231	584 (55.6)	586 (55.8)	0.004
Diabetes mellitus	714 (25.6)	268 (25.5)	0.003	277 (26.4)	267 (25.4)	0.022
Crohn's disease	71 (2.6)	20 (1.9)	0.044	21 (2.0)	20 (1.9)	0.007
Ulcerative colitis	72 (2.6)	19 (1.8)	0.053	25 (2.4)	19 (1.8)	0.040
Toxic gastroenteritis and colitis	255 (9.2)	117 (11.1)	0.065	99 (9.4)	116 (11.0)	0.053
Gastroenteritis and colitis due to radiation	20 (0.7)	<10 (<1.0)	0.026	<10 (<1.0)	<10 (<1.0)	<0.001
Paralytic ileus and intestinal obstruction	1014 (36.4)	388 (36.9)	0.010	389 (37.0)	388 (37.0)	0.002
Diverticular disease of intestine	679 (24.4)	249 (23.7)	0.016	245 (23.3)	248 (23.6)	0.007
Malnutrition	751 (27.0)	246 (23.4)	0.082	244 (23.2)	246 (23.4)	0.005
Abnormal weight loss	551 (19.8)	180 (17.1)	0.069	182 (17.3)	179 (17.0)	0.008

Percentages are based on patients with available data. Some categories may not sum to total *N* due to missing data.
COPD, Chronic obstructive pulmonary disease; *StDiff*, standardized difference.

SUPPLEMENTARY TABLE 2. Baseline characteristics before and after propensity score matching (therapeutic subgroup analysis)

Characteristic	Before matching			After matching		
	Control (n = 1896)	Bevacizumab (n = 666)	StDiff	Control (n = 653)	Bevacizumab (n = 653)	StDiff
Demographics						
Age at index, y, mean ± SD	60.6 ± 12.9	60.2 ± 12.6	0.031	59.8 ± 13.2	60.2 ± 12.6	0.037
Sex, *n* (%)						
Female	736 (40.3)	319 (48.4)	0.164	314 (48.1)	314 (48.1)	<0.001
Male	1008 (55.2)	315 (47.8)	0.149	311 (47.6)	314 (48.1)	0.009
Race, *n* (%)						
White	1251 (68.5)	473 (71.8)	0.071	466 (71.4)	467 (71.5)	0.003
Black or African American	203 (11.1)	52 (7.9)	0.110	50 (7.7)	52 (8.0)	0.011
Asian	97 (5.3)	40 (6.1)	0.033	31 (4.7)	40 (6.1)	0.061
Unknown	184 (10.1)	63 (9.6)	0.017	70 (10.7)	63 (9.6)	0.035
Ethnicity, *n* (%)						
Hispanic or Latino	192 (10.5)	54 (8.2)	0.080	56 (8.6)	54 (8.3)	0.011
Not Hispanic or Latino	1300 (71.2)	514 (78.0)	0.157	497 (76.1)	508 (77.8)	0.040
Comorbidities, *n* (%)						
Malignant neoplasms of digestive organs	1779 (97.4)	632 (95.9)	0.085	628 (96.2)	628 (96.2)	<0.001
Malignant neoplasms of ill-defined sites	1574 (86.2)	609 (92.4)	0.202	605 (92.6)	603 (92.3)	0.012
Hypertensive diseases	1107 (60.6)	393 (59.6)	0.020	386 (59.1)	389 (59.6)	0.009
Ischemic heart diseases	459 (25.1)	149 (22.6)	0.059	153 (23.4)	148 (22.7)	0.018
Heart failure	178 (9.7)	62 (9.4)	0.012	61 (9.3)	61 (9.3)	<0.001
COPD	191 (10.5)	57 (8.6)	0.062	58 (8.9)	56 (8.6)	0.011
Asthma	196 (10.7)	63 (9.6)	0.039	73 (11.2)	62 (9.5)	0.055
Chronic hepatitis	<10 (<0.5)	<10 (<1.5)	0.096	<10 (<1.5)	<10 (<1.5)	<0.001
Fibrosis and cirrhosis of liver	89 (4.9)	50 (7.6)	0.112	59 (9.0)	47 (7.2)	0.067
Alcoholic liver disease	22 (1.2)	<10 (<1.5)	0.027	<10 (<1.5)	<10 (<1.5)	<0.001
Other diseases of liver	794 (43.5)	374 (56.8)	0.268	367 (56.2)	369 (56.5)	0.006
Diabetes mellitus	470 (25.7)	176 (26.7)	0.022	172 (26.3)	172 (26.3)	<0.001
Crohn's disease	47 (2.6)	14 (2.1)	0.030	20 (3.1)	14 (2.1)	0.058
Ulcerative colitis	51 (2.8)	14 (2.1)	0.043	18 (2.8)	14 (2.1)	0.040
Toxic gastroenteritis and colitis	176 (9.6)	72 (10.9)	0.042	78 (11.9)	71 (10.9)	0.034
Gastroenteritis and colitis due to radiation	11 (0.6)	<10 (<1.5)	0.089	<10 (<1.5)	<10 (<1.5)	<0.001
Paralytic ileus and intestinal obstruction	614 (33.6)	223 (33.8)	0.005	219 (33.5)	223 (34.2)	0.013
Diverticular disease of intestine	468 (25.6)	150 (22.8)	0.067	151 (23.1)	149 (22.8)	0.007
Malnutrition	473 (25.9)	158 (24.0)	0.045	166 (25.4)	158 (24.2)	0.028
Abnormal weight loss	356 (19.5)	109 (16.5)	0.077	101 (15.5)	108 (16.5)	0.029

Percentages are based on patients with available data. Some categories may not sum to total *N* due to missing data.
COPD, Chronic obstructive pulmonary disease; *StDiff*, standardized difference.

SUPPLEMENTARY TABLE 3. Baseline characteristics before and after propensity score matching (diagnostic subgroup analysis)

Characteristic	Before matching			After matching		
	Control (n = 462)	Bevacizumab (n = 208)	StDiff	Control (n = 198)	Bevacizumab (n = 198)	StDiff
Demographics						
Age at index, y, mean ± SD	57.2 ± 13.2	58.7 ± 12.7	0.118	58.0 ± 13.2	58.7 ± 12.8	0.058
Sex, *n* (%)						
Female	202 (45.0)	92 (44.7)	0.007	91 (46.0)	87 (43.9)	0.041
Male	230 (51.2)	105 (51.0)	0.005	99 (50.0)	102 (51.5)	0.030
Race, *n* (%)						
White	297 (66.1)	148 (71.8)	0.123	145 (73.2)	143 (72.2)	0.023
Black or African American	51 (11.4)	11 (5.3)	0.219	<10 (<5.1)	11 (5.6)	0.023
Asian	22 (4.9)	17 (8.3)	0.136	13 (6.6)	15 (7.6)	0.039
Unknown	53 (11.8)	17 (8.3)	0.118	16 (8.1)	17 (8.6)	0.018
Ethnicity, *n* (%)						
Hispanic or Latino	41 (9.1)	21 (10.2)	0.036	19 (9.6)	20 (10.1)	0.017
Not Hispanic or Latino	330 (73.5)	149 (72.3)	0.026	145 (73.2)	143 (72.2)	0.023
Comorbidities, *n* (%)						
Malignant neoplasms of digestive organs	444 (98.9)	203 (98.5)	0.030	196 (99.0)	195 (98.5)	0.045
Malignant neoplasms of ill-defined sites	402 (89.5)	200 (97.1)	0.306	189 (95.5)	192 (97.0)	0.079
Hypertensive diseases	225 (50.1)	109 (52.9)	0.056	103 (52.0)	105 (53.0)	0.020
Ischemic heart diseases	80 (17.8)	41 (19.9)	0.053	33 (16.7)	39 (19.7)	0.079
Heart failure	32 (7.1)	15 (7.3)	0.006	11 (5.6)	15 (7.6)	0.082
COPD	32 (7.1)	15 (7.3)	0.006	13 (6.6)	15 (7.6)	0.039
Asthma	41 (9.1)	16 (7.8)	0.049	18 (9.1)	15 (7.6)	0.055
Chronic hepatitis	0 (0)	0 (0)	–	0 (0)	0 (0)	–
Fibrosis and cirrhosis of liver	22 (4.9)	15 (7.3)	0.100	11 (5.6)	11 (5.6)	<0.001
Alcoholic liver disease	<10 (<2.2)	<10 (<4.9)	0.143	0 (0)	<10 (<5.1)	0.326
Other diseases of liver	207 (46.1)	109 (52.9)	0.137	103 (52.0)	102 (51.5)	0.010
Diabetes mellitus	85 (18.9)	47 (22.8)	0.096	38 (19.2)	45 (22.7)	0.087
Crohn's disease	12 (2.7)	<10 (<4.9)	0.115	<10 (<5.1)	<10 (<5.1)	<0.001
Ulcerative colitis	<10 (<2.2)	<10 (<4.9)	0.143	<10 (<5.1)	<10 (<5.1)	<0.001
Toxic gastroenteritis and colitis	34 (7.6)	28 (13.6)	0.197	26 (13.1)	23 (11.6)	0.046
Gastroenteritis and colitis due to radiation	<10 (<2.2)	<10 (<4.9)	0.143	<10 (<5.1)	<10 (<5.1)	<0.001
Paralytic ileus and intestinal obstruction	176 (39.2)	83 (40.3)	0.022	80 (40.4)	80 (40.4)	<0.001
Diverticular disease of intestine	58 (12.9)	38 (18.4)	0.152	32 (16.2)	33 (16.7)	0.014
Malnutrition	140 (31.2)	49 (23.8)	0.166	41 (20.7)	49 (24.7)	0.097
Abnormal weight loss	92 (20.5)	40 (19.4)	0.027	41 (20.7)	40 (20.2)	0.013

COPD, Chronic obstructive pulmonary disease; *StDiff*, standardized difference.

SUPPLEMENTARY TABLE 4. Subanalysis of postprocedural bleeding risk by anatomic site (propensity score–matched cohorts)

Anatomic site	*N* matched pairs	Patients with bleeding (Bevacizumab/Control)	Bleeding rate (Bevacizumab/Control), %	Hazard ratio (Bevacizumab vs Control) and 95% CI	*P* value
EGD procedures	379	74/53	19.5/14.0	1.42 (1.00-2.02)	**.047**
Colonoscopy procedures	405	42/35	10.4/8.6	1.20 (0.77-1.88)	.421

N matched pairs indicates the number of pairs in each analysis. *P* values are from log-rank tests. Hazard ratios represent the risk of bleeding in the Bevacizumab group relative to the Control group. Bold *P* values indicate statistical significance ($P < .05$).