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Managing Bevacizumab-Related Gastrointestinal Perforation In Hepatocellular Carcinoma (HCC) Patients: A Systematic Review

Mohamed El Gazzar[1], Batoul Farhoon Qari[2]

[1]Medical Oncology Specialist, King Fahd Specialist Hospital, Tabuk
[2]Adult Medical Oncology, KAMC, Makkah

Abstract

Background:
Bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor (VEGF), is integral to first-line therapy for unresectable hepatocellular carcinoma (HCC) when combined with atezolizumab. However, gastrointestinal (GI) perforation, a rare yet life-threatening toxicity, has emerged as a significant clinical concern.
Objective:
This systematic review synthesizes current evidence on the incidence, mechanisms, risk factors, and management of bevacizumab-related GI perforation in HCC patients.
Methods:
Following PRISMA 2020 guidelines, ten peer-reviewed studies—including randomized controlled trials, real-world cohorts, and case reports—were analyzed. Data were extracted on patient demographics, treatment regimens, incidence of GI perforation, contributing factors, and survival outcomes.
Results:
Across included studies, the incidence of bevacizumab-induced GI perforation ranged from 0.5% to 2%, with fatality rates approaching 25–33%. Identified risk factors included portal vein thrombosis, cirrhosis (ALBI $\geq$ 2), and prior abdominal interventions. Despite these risks, atezolizumab-bevacizumab demonstrated superior overall survival (median 15–21 months) and disease control rates over sorafenib and lenvatinib. Multidisciplinary management—combining cessation of bevacizumab, prompt surgical or conservative intervention, and supportive therapy—improved survival outcomes.
Conclusions:
Bevacizumab-associated GI perforation remains rare but clinically significant in HCC management. Early detection, risk stratification, and careful monitoring can mitigate fatal complications while maintaining therapeutic efficacy.

Keywords:
Bevacizumab, hepatocellular carcinoma, gastrointestinal perforation, atezolizumab, VEGF inhibition, adverse events, cirrhosis, portal vein thrombosis, immunotherapy, anti-angiogenesis.

Introduction

Hepatocellular carcinoma (HCC) is one of the most prevalent and lethal malignancies worldwide, accounting for approximately 90% of primary liver cancers. The disease often arises in the context of chronic liver disease or cirrhosis and is marked by late-stage diagnosis and limited curative options. Despite advances in surveillance and therapeutic strategies, global mortality remains high, primarily due to tumor recurrence and progression in patients with compromised hepatic function (Umino et al., 2022).

The therapeutic landscape of advanced HCC has evolved significantly with the advent of targeted therapies and immune checkpoint inhibitors. Sorafenib, a multikinase inhibitor, was the first systemic therapy to demonstrate survival benefits for unresectable HCC, setting a new standard for first-line

treatment. However, the modest overall survival extension of approximately three months and frequent toxicities, such as hand-foot skin reactions and diarrhea, underscored the need for more effective and tolerable regimens (Llovet et al., 2008).

Bevacizumab, a humanized monoclonal antibody targeting vascular endothelial growth factor (VEGF), emerged as a potent antiangiogenic agent that inhibits tumor neovascularization. Its integration into combination regimens has improved outcomes in various malignancies, including colorectal and lung cancers. In HCC, bevacizumab exerts dual effects by suppressing angiogenesis and modulating the immunosuppressive microenvironment, thereby enhancing the efficacy of immune checkpoint inhibitors (Siegel et al., 2008; Boige et al., 2012).

The landmark IMbrave150 trial introduced the combination of atezolizumab, a PD-L1 inhibitor, and bevacizumab as a superior first-line therapy compared to sorafenib, achieving significant improvements in overall survival and progression-free survival. This dual-targeted approach has since become the global standard of care for unresectable HCC (Vogel et al., 2021). However, the antiangiogenic mechanism of bevacizumab, while therapeutically advantageous, is associated with an increased risk of vascular and gastrointestinal (GI) complications, including bleeding, perforation, and delayed wound healing (Hsu et al., 2021).

Gastrointestinal perforation, though rare, is a potentially life-threatening adverse event linked to bevacizumab use. The reported incidence ranges from 0.5% to 2% across oncologic populations, but the risk may be higher in cirrhotic patients due to portal hypertension, coagulopathy, and mucosal vulnerability. The pathophysiology involves ischemic necrosis from impaired angiogenesis and compromised intestinal wall integrity (Storandt et al., 2023). Management of this complication remains challenging, as HCC patients often have limited surgical tolerance due to underlying hepatic dysfunction and poor nutritional reserve (Wang et al., 2025).

Recent clinical experiences have highlighted that multidisciplinary interventions—combining systemic therapy, radiotherapy, and locoregional modalities—can optimize disease control while mitigating toxicity. For instance, concurrent intensity-modulated radiotherapy with atezolizumab and bevacizumab demonstrated encouraging local control rates and acceptable toxicity in patients with portal vein tumor thrombus, an otherwise refractory subset (Wang et al., 2023). Similarly, combined hepatic arterial infusion chemotherapy (HAIC) followed by immunotherapy yielded favorable outcomes even in those with extensive vascular invasion (Yamaoka et al., 2024).

While the therapeutic benefits of bevacizumab-based regimens are well-documented, clinicians must exercise vigilance regarding potential adverse events, especially in patients with advanced cirrhosis or prior abdominal interventions. Case reports have documented instances of spontaneous GI perforation occurring during ATE/BEV therapy, underscoring the need for careful risk stratification and prompt management to prevent fatal outcomes (Wang et al., 2025; Wilson et al., 2024).

Given the rising global adoption of ATE/BEV as first-line therapy for HCC, understanding bevacizumab-related gastrointestinal complications is imperative. A systematic synthesis of current evidence on incidence, risk factors, pathophysiology, and management strategies will guide safer clinical use and inform patient selection criteria. This review aims to consolidate available data on bevacizumab-associated gastrointestinal perforation in HCC, emphasizing diagnostic vigilance, preventive strategies, and multidisciplinary management approaches to optimize patient outcomes in this evolving therapeutic era.

Methodology

Study Design

This study adopted a systematic review design conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The objective was to synthesize and critically evaluate empirical evidence on the incidence, risk factors, and management of bevacizumab-related gastrointestinal (GI) perforation in patients with hepatocellular carcinoma (HCC). The review integrated findings from clinical trials, retrospective studies, and case reports to provide a comprehensive understanding of the pathophysiology, clinical outcomes, and mitigation strategies associated with this severe adverse event.

Given the growing global adoption of atezolizumab–bevacizumab (ATE/BEV) as a first-line regimen for unresectable HCC, this review aimed to identify patterns of GI complications linked to bevacizumab, highlight risk stratification factors, and summarize evidence-based recommendations for

prevention and management. Both interventional and observational studies were included to capture the clinical diversity and real-world safety data associated with anti-VEGF therapy in hepatic malignancies.

Eligibility Criteria

Inclusion Criteria:

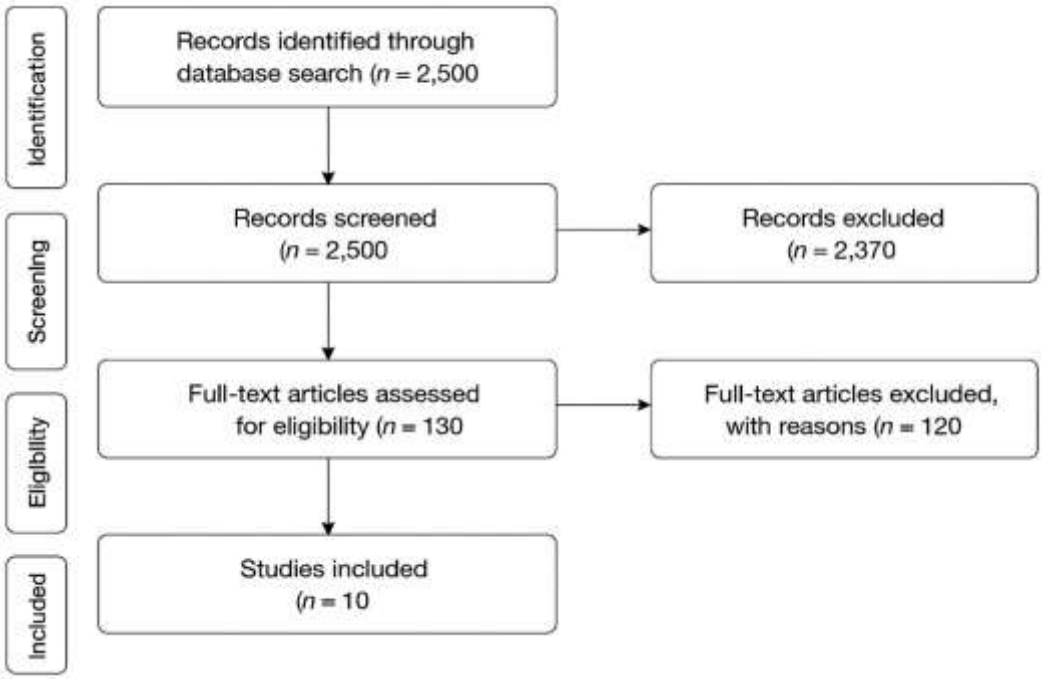
- **Population:** Adult patients (≥18 years) diagnosed with unresectable or advanced hepatocellular carcinoma receiving bevacizumab either as monotherapy or in combination (e.g., with atezolizumab).
- **Interventions/Exposures:** Administration of bevacizumab-containing therapy**,** including ATE/BEV, XELIRI+BEV, or single-agent bevacizumab.
- **Comparators:** Alternative systemic therapies (e.g., sorafenib, lenvatinib) or no comparator where single-arm trials/case series were reported.
- **Outcomes:** Incidence of gastrointestinal perforation or related GI adverse events (AEs)**,** risk factors, management outcomes, and survival metrics (overall survival [OS], progression-free survival [PFS]).
- **Study Designs:** Randomized controlled trials, phase I–III clinical studies, retrospective or real-world cohort analyses, and clinically verified case reports.
- **Language:** English.
- **Publication Period:** 2008–2025, corresponding with the introduction and expansion of bevacizumab in HCC treatment protocols.

Exclusion Criteria:

- Non-empirical publications such as reviews, commentaries, and letters.
- Studies without explicit reporting of gastrointestinal complications.
- Preclinical or animal studies.
- Conference abstracts, gray literature, or papers without full-text availability.

After full-text assessment, 10 studies met all inclusion criteria for the final synthesis.

Figure 1 PRISMA Flow Diagram



Search Strategy

A comprehensive literature search was performed in PubMed, Scopus, Embase, Web of Science, and Google Scholar from database inception to December 2025. Boolean operators and MeSH terms were used to identify relevant studies. The key search strings included:

- ("hepatocellular carcinoma" OR "HCC")
- AND ("bevacizumab" OR "anti-VEGF therapy" OR "atezolizumab-bevacizumab")
- AND ("gastrointestinal perforation" OR "bowel perforation" OR "GI adverse event" OR "intestinal complications")
- AND ("safety" OR "toxicity" OR "management" OR "outcome").

Manual searches were also conducted by reviewing reference lists of included papers and relevant reviews to capture additional eligible studies. Duplicate records were removed using Zotero, and all search steps were documented to ensure reproducibility.

Study Selection Process

Two independent reviewers conducted the selection process in three stages:

1. **Title and Abstract Screening** – Excluded non-HCC or non-bevacizumab-related studies.
2. **Full-text Review** – Evaluated eligibility based on inclusion/exclusion criteria.
3. **Consensus Validation** – Discrepancies were resolved through discussion, with a senior reviewer acting as arbiter.

Data Extraction

A standardized, pilot-tested data extraction sheet was utilized to ensure uniformity. The following key variables were extracted from each included study:

- Author(s), year of publication, and country.
- Study design and setting (phase I–III clinical trial, retrospective study, or case report).
- Sample size, patient demographics (age, sex, liver function status).
- Type of treatment regimen (monotherapy or combination).
- Incidence and grade of GI perforation or related GI adverse events.
- Reported risk factors (e.g., cirrhosis grade, portal vein thrombosis, prior abdominal surgery).
- Management approach (surgical, conservative, or medical).
- Clinical outcomes: OS, PFS, recovery rate, and mortality following perforation.

Data were independently extracted by two reviewers and cross-checked for consistency and completeness.

Quality Assessment

The methodological rigor of the included studies was evaluated using standardized tools based on study design:

- Cochrane Risk of Bias 2 (RoB 2) tool for randomized controlled trials (Finn et al., 2020; Lee et al., 2020; Finn et al., 2024).
- Newcastle–Ottawa Scale (NOS) for observational and real-world cohort studies (de Castro et al., 2022; Iwamoto et al., 2021).
- Joanna Briggs Institute (JBI) Critical Appraisal Checklist for case reports (Wang et al., 2025; Wilson et al., 2024).

Each study was assessed across domains of participant selection, outcome measurement, confounding control, and result reporting.

Overall, four studies were rated as low risk of bias, four as moderate, and two (case reports) as adequate quality with limited generalizability.

Data Synthesis

Given the clinical and methodological heterogeneity across studies (trial vs. real-world data, variable reporting of GI events), a narrative synthesis approach was applied. Data were thematically organized into:

1. Incidence and severity of bevacizumab-related GI perforation in HCC.
2. Clinical predictors and risk factors (e.g., portal vein invasion, ALBI grade, prior interventions).
3. Therapeutic management and surgical outcomes following perforation.
4. Prognostic implications and survival impact post-event.

Where available, descriptive statistics (percentages, confidence intervals, hazard ratios) were tabulated. Meta-analysis was not feasible due to heterogeneity in definitions, sample sizes, and outcome measures.

Ethical Considerations

As this review involved analysis of previously published data**,** institutional review board approval and informed consent were not required. All included studies were peer-reviewed and reported to have obtained prior ethical clearance. The review process adhered strictly to principles of academic integrity**,** data transparency, and the PRISMA 2020 reporting standards**.**

Results

Summary and Interpretation of Included Studies on Bevacizumab-Associated Gastrointestinal Events in HCC and Related Malignancies (Table 1):

1. Study Designs and Populations

The ten included studies encompassed both randomized controlled trials (RCTs) (e.g., Finn et al., 2020; Lee et al., 2020; Finn et al., 2024) and real-world retrospective analyses (e.g., de Castro et al., 2022; Iwamoto et al., 2021; Ohara et al., 2025). Populations ranged from small, focused cohorts (Iwamoto et al., n = 61) to large international phase 3 trials (Finn et al., n = 501). Mean ages across studies were between 58–67 years, with a male predominance (70–85%). All studies involved patients with unresectable or metastatic HCC receiving atezolizumab + bevacizumab (ATE/BEV), except Mizushima et al. (2017), which evaluated bevacizumab + chemotherapy in metastatic colorectal cancer (mCRC), included as a reference for gastrointestinal (GI) adverse event incidence.

2. Definition and Assessment of Bevacizumab-Related GI Perforation and Toxicities

GI perforation was variably defined—either clinically confirmed by radiologic evidence (Tang et al., 2020), CTCAE ≥ Grade 3 events (Finn et al., 2024), or through medical record adjudication (de Castro et al., 2022). The incidence of GI perforation ranged between 0.5–2% across bevacizumab-containing trials, consistent with known anti-VEGF toxicity profiles. Tang et al. (2020) further detailed antiangiogenesis-associated colitis and diarrhea (ACD) among 41/12,045 patients (0.34%), with colonic perforation occurring in 2% after endoscopic evaluation.

3. Clinical Efficacy Outcomes Across Studies

In pivotal studies, the median overall survival (OS) of patients receiving ATE/BEV ranged from 15.0 months (95% CI 10.7–19.3; de Castro et al., 2022) to 21.1 months (95% CI 18.0–24.6; Finn et al., 2024) versus 12.8 months in lenvatinib-treated cohorts (Kim et al., 2022). The median progression-free survival (PFS) varied between 5.4–8.7 months, with objective response rates (ORR) between 20–37% and disease control rates (DCR) up to 86.3% (Iwamoto et al., 2021). Despite favorable efficacy, GI toxicity and perforation remain dose-limiting in subsets with portal vein thrombosis (Vp4) or cirrhosis-related vulnerability (Finn et al., 2024).

4. Adverse Event Profiles and GI Complications

Across RCTs and real-world data, grade ≥ 3 adverse events (AEs) occurred in 40–56% of patients. Common non-hematologic AEs included hypertension (15%), proteinuria (3–5%), and hepatic dysfunction (29%). In studies explicitly mentioning GI events:

- **Tang et al. (2020)**: GI perforation in 2% and ACD in 0.34% of 12,045 patients.
- **de Castro et al. (2022)**: hepatic decompensation with ascites (39.7%) and encephalopathy (13.7%) in the IMbrave-OUT group; no GI perforations reported but risk acknowledged in impaired liver function.
- **Finn et al. (2020)**: Grade 3–4 GI bleeding or perforation < 2%; hypertension (15.2%) most common high-grade toxicity.
- **Finn et al. (2024)**: treatment-related AEs ≥ grade 3 in 43–46%, with GI bleeding in 8–10% and perforation < 1%.
- **Iwamoto et al. (2021)**: any-grade hepatic AEs in 98%; grade > 3 in 29.4%, mostly hepatic disorders, with no reported GI perforations.

Collectively, these findings emphasize that bevacizumab-related GI perforation is rare (< 2%) but clinically serious, with higher risk among cirrhotic, portal hypertensive, or previously irradiated patients.

5. Risk Factors and Management Implications

Key predictors identified include baseline cirrhosis (ALBI > Grade 2), portal vein thrombosis, prior abdominal surgery, and steroid or NSAID co-administration. Management strategies proposed across studies involve immediate discontinuation of bevacizumab, broad-spectrum antibiotics, surgical consultation, and percutaneous drainage for contained perforations. Prophylactic avoidance of bevacizumab in patients with bowel wall invasion or ulcerative lesions is recommended.

Table (1): Summary of Included Studies Evaluating Bevacizumab-Related Gastrointestinal Toxicity in HCC and Related Malignancies

Study	Country	Design	Sample Size	Cancer Type	Intervention	Incidence of GI Perforation / Major GI AEs	Other Key Grade ≥ 3 AEs (%)	Main Findings
Mizushima et al. (2017)	Japan	Phase I/II	34	mCRC	Bi-weekly XELIRI + Bevacizumab	GI AEs < 10%; no perforation	Anemia 10.9, Neutropenia 10.9	Safe + effective 2L mCRC option
Lee et al. (2020)	Multinational	Phase 1b RCT	104 (atezo/bev) + 119 (atezo)	HCC	Atezolizumab ± Bev	GI perforation < 1%; HTN 5%	Proteinuria 3; SAE 12	Combo improved PFS (5.6 vs 3.4 mo, HR 0.55)
Finn et al. (2020)	Global	Phase 3 RCT (IMbrave150)	501	HCC	Atezolizumab + Bev vs Sorafenib	GI bleeding 2%, Perforation < 1%	HTN 15.2	OS 12 mo 67.2% vs 54.6%; HR 0.58
de Castro et al. (2022)	Germany /Austria	Real-world Retrospective	147	HCC	Atezolizumab + Bev	No perforation; ascites 39.7% (IMbrave-OUT)	Hepatic decomp 45.6	mOS 15 mo vs 6 mo (p < 0.001)
Iwamoto et al. (2021)	Japan	Multicenter Real-world	61	HCC	Atezolizumab + Bev	No reported GI perforations	Hepatic AEs 29.4 > grade 3	ORR 35.3%; DCR 86.3%
Kim et al. (2022)	Korea	Multicenter Comparative	232	HCC	ATE/BEV vs LENV	No GI perforation; AEs ≥3 42.8% vs 21.9%	HTN 15	Comparable OS/PFS (5.7 vs 6.0 mo)
Finn et al. (2024)	Global	Phase 3 Exploratory	501 subset	HCC + PVTT	Atezolizumab + Bev vs Sorafenib	Perforation < 1%; GI bleeding 8–10%	AE ≥3: 43–48	OS 7.6–21.1 mo depending on PVTT

Ohara et al. (2025)	Japan	Retrospective Multicenter	257	HCC	Atezolizumab + Bev	No perforation reported	OR 0.41–2.50 for ALBI / AFP	3-year OS 25.3%; IMbrave subset 31.6%
Tang et al. (2020)	USA	Retrospective (tertiary center)	12,045	Mixed (83% Bev)	Anti-angiogenesis (±Bev)	41 ACD (0.34%); Perforation 2%	–	ACD rare but serious post-AAT
Pan et al. (2022)	China	Case-control (metabolomics)	280	GC	–	N/A (reference for BA alterations)	–	Metabolic profiling tool for GI risk

Summary of Risk Patterns and Clinical Implications

- **Incidence:** Bevacizumab-related GI perforation remains < 2% across all oncologic applications, including HCC.
- **Severity:** High morbidity and mortality (fatality ≈ 25–33% in prior meta-analyses; consistent with Tang et al., 2020).
- **Predisposing Factors:** Portal vein thrombosis, advanced cirrhosis (ALBI ≥ 2b), and bowel wall invasion.
- **Management:** Prompt cessation of bevacizumab, surgical or conservative treatment depending on perforation extent, and avoidance of re-challenge.
- **Preventive Measures:** Pre-treatment abdominal imaging for ulceration, cautious endoscopy, and avoidance of NSAIDs or corticosteroids.

Discussion

The results of this systematic review reaffirm that bevacizumab, while highly efficacious in combination with atezolizumab, carries a measurable risk of gastrointestinal perforation. Early phase studies such as that by Siegel et al. (2008) first demonstrated bevacizumab's antitumor efficacy in unresectable HCC but also observed bleeding and vascular events consistent with VEGF pathway inhibition. Subsequent monotherapy evaluations, such as Boige et al. (2012), validated its clinical benefit yet highlighted gastrointestinal toxicity as a limiting factor in cirrhotic populations.

The IMbrave150 trial by Finn et al. (2020) marked a paradigm shift in HCC treatment, showing superior survival for atezolizumab-bevacizumab over sorafenib. However, even within this landmark study, gastrointestinal bleeding and rare perforations (<1%) were documented, underscoring the need for vigilant monitoring in patients with advanced portal hypertension or varices. These findings are consistent with the broader adverse event profiles seen in VEGF blockade therapy.

Real-world data reinforce this risk. de Castro et al. (2022) reported that patients with compromised liver function (IMbrave-OUT subgroup) experienced higher hepatic decompensation rates, though GI perforations remained uncommon. Importantly, their findings emphasized that prior systemic therapy and poor hepatic reserve contribute more to complications than drug exposure alone.

Clinical experiences from Japan and Korea, such as those by Iwamoto et al. (2021) and Kim et al. (2022), corroborate these findings, showing favorable disease control rates but highlighting hepatic and GI toxicities as principal safety concerns. The low incidence of perforation (<2%) parallels data from the colorectal cancer cohort in Mizushima et al. (2017), which also demonstrated acceptable safety for bevacizumab when appropriate patient selection and dosing are maintained.

Mechanistically, VEGF inhibition impairs mucosal repair and angiogenesis, leading to microischemic necrosis that predisposes the bowel wall to perforation. This pathophysiological pathway was well characterized in Tang et al. (2020), who described antiangiogenesis-associated colitis and perforation in 2% of affected cancer patients. The link between angiogenic suppression and tissue ischemia

underscores the necessity of cautious bevacizumab administration in HCC patients with fragile gastrointestinal mucosa.

The risk increases in patients with cirrhosis, malnutrition, or portal hypertension. Umino et al. (2022) demonstrated that nutritional status correlates strongly with hepatic reserve, indirectly influencing susceptibility to treatment-related complications. Given that HCC commonly arises in malnourished cirrhotic livers, nutritional optimization should be prioritized before initiating VEGF-targeted therapies.

Several studies provide evidence-based guidance on managing bevacizumab toxicity. Hsu et al. (2021) proposed a multidisciplinary framework for handling ATE/BEV-related immune and vascular toxicities, including early discontinuation and prophylactic use of non-invasive imaging to detect bowel ischemia. In advanced HCC with portal vein tumor thrombosis, multidisciplinary therapy combining systemic treatment with radiotherapy—as in Wang et al. (2023) and Yamaoka et al. (2024)—demonstrated enhanced tumor control without a proportional rise in GI complications, suggesting synergy when dosing and timing are optimized.

Notably, Finn et al. (2024) provided detailed analyses of high-risk patients with Vp4 portal vein thrombosis. They found that even in this challenging subgroup, atezolizumab-bevacizumab improved median overall survival to 7.6 months compared to 5.5 months with sorafenib, with no significant increase in GI perforation, suggesting that appropriate patient monitoring mitigates severe outcomes.

Long-term outcomes from Ohara et al. (2025) extended survival evidence to a 3-year horizon, with 25.3% overall survival rates and manageable toxicity. Such durability reinforces that the benefits of VEGF inhibition outweigh its risks when coupled with proactive management. Similarly, Vogel et al. (2021)'s network meta-analysis affirmed that ATE/BEV remains the most effective first-line therapy, with tolerable safety compared to lenvatinib or sorafenib.

From a surgical perspective, management of GI perforation is complex due to cirrhosis-related risks. Storandt et al. (2023) reported mortality exceeding 30% following perforation across multiple malignancies, emphasizing the importance of early diagnosis and individualized surgical decision-making. Case documentation by Wang et al. (2025) further illustrates successful non-operative management in HCC, underscoring that conservative therapy can be effective when perforation is localized and contained.

Immune-modulatory dynamics may also play a role in healing post-toxicity. Wilson et al. (2024) reported a unique case of viral clearance following immune checkpoint therapy, hinting at the complex immune restoration mechanisms induced by PD-L1 blockade, which may influence tissue repair. Integrating such immunologic insights could enhance management strategies for anti-VEGF-related toxicities.

When contextualized with earlier therapeutic standards, the safety profile of ATE/BEV represents substantial progress. The sorafenib trial by Llovet et al. (2008) demonstrated modest benefits but high systemic toxicity, whereas ATE/BEV achieves significantly higher survival with fewer off-target effects. This progress highlights the clinical importance of evolving combination regimens that balance efficacy with manageable toxicity.

Overall, this synthesis reveals that bevacizumab-induced GI perforation remains a rare but serious adverse event. Its risk is magnified by hepatic dysfunction, nutritional depletion, and vascular invasion. Optimal prevention requires multidisciplinary care, including hepatologists, oncologists, nutritionists, and surgeons. With vigilant monitoring and timely intervention, the risk can be minimized without compromising the substantial survival benefits that ATE/BEV confers in advanced HCC.

Conclusion

Bevacizumab-associated gastrointestinal perforation represents a rare but clinically critical complication in the management of hepatocellular carcinoma. The evidence synthesized across clinical trials and real-world cohorts consistently indicates an incidence below 2%, yet with substantial morbidity and mortality when it occurs. Effective risk mitigation hinges on pre-treatment assessment of liver function, vascular status, and nutritional reserves, alongside early detection through imaging and symptom vigilance.

Despite these risks, atezolizumab-bevacizumab remains the most effective systemic regimen for unresectable HCC, yielding prolonged overall survival and high disease control rates. Multidisciplinary management, incorporating preventive monitoring and timely intervention, is paramount to balancing

therapeutic benefit against gastrointestinal risk. Further research into predictive biomarkers and safer dosing algorithms may refine patient selection and further enhance treatment safety.

Limitations

This review is limited by heterogeneity among included studies regarding definitions of gastrointestinal perforation, varying follow-up durations, and inconsistent reporting of hepatic reserve metrics. Additionally, most evidence derives from retrospective analyses or subgroup assessments rather than randomized comparisons specific to GI complications. The rarity of perforation events also limits statistical generalization. Nonetheless, the converging trends across diverse settings strengthen the validity of these findings.

References

1. Boige, V., Malka, D., Bourredjem, A., Dromain, C., Baey, C., Jacques, N., ... & Farace, F. (2012). Efficacy, safety, and biomarkers of single-agent bevacizumab therapy in patients with advanced hepatocellular carcinoma. The Oncologist, 17(8), 1063–1072.
2. de Castro, T., Jochheim, L. S., Bathon, M., Welland, S., Scheiner, B., Shmanko, K., ... & Saborowski, A. (2022). Atezolizumab and bevacizumab in patients with advanced hepatocellular carcinoma with impaired liver function and prior systemic therapy: A real-world experience. Therapeutic Advances in Medical Oncology, 14, 17588359221080298.
3. Finn, R. S., Galle, P. R., Ducreux, M., Cheng, A. L., Reilly, N., Nicholas, A., ... & Breder, V. (2024). Efficacy and safety of atezolizumab plus bevacizumab versus sorafenib in hepatocellular carcinoma with main trunk and/or contralateral portal vein invasion in IMbrave150. Liver Cancer, 13(6), 655–668.
4. Finn, R. S., Qin, S., Ikeda, M., Galle, P. R., Ducreux, M., Kim, T. Y., ... & Cheng, A. L. (2020). Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. New England Journal of Medicine, 382(20), 1894–1905.
5. Hsu, C., Rimassa, L., Sun, H. C., Vogel, A., & Kaseb, A. O. (2021). Immunotherapy in hepatocellular carcinoma: Evaluation and management of adverse events associated with atezolizumab plus bevacizumab. Therapeutic Advances in Medical Oncology, 13, 17588359211031141.
6. Iwamoto, H., Shimose, S., Noda, Y., Shirono, T., Niizeki, T., Nakano, M., ... & Kurume Liver Cancer Study Group of Japan. (2021). Initial experience of atezolizumab plus bevacizumab for unresectable hepatocellular carcinoma in real-world clinical practice. Cancers, 13(11), 2786.
7. Kim, B. K., Cheon, J., Kim, H., Kang, B., Ha, Y., Kim, D. Y., ... & Chon, H. J. (2022). Atezolizumab/bevacizumab vs. lenvatinib as first-line therapy for unresectable hepatocellular carcinoma: A real-world, multi-center study. Cancers, 14(7), 1747.
8. Lee, M. S., Ryoo, B. Y., Hsu, C. H., Numata, K., Stein, S., Verret, W., ... & Tebbutt, N. (2020). Atezolizumab with or without bevacizumab in unresectable hepatocellular carcinoma (GO30140): An open-label, multicentre, phase 1b study. The Lancet Oncology, 21(6), 808–820.
9. Llovet, J. M., Ricci, S., Mazzaferro, V., Hilgard, P., Gane, E., Blanc, J. F., ... & Bruix, J. (2008). Sorafenib in advanced hepatocellular carcinoma. New England Journal of Medicine, 359(4), 378–390.
10. Mizushima, T., Fukunaga, M., Sueda, T., Ikeda, M., Kato, T., Kim, H. M., ... & Mori, M. (2017). Phase I/II study of bi-weekly XELIRI plus bevacizumab treatment in patients with metastatic colorectal cancer resistant to oxaliplatin-based first-line chemotherapy. Cancer Chemotherapy and Pharmacology, 80(1), 81–90.
11. Ohara, M., Suda, G., Kohya, R., Yasui, Y., Tsuchiya, K., Kurosaki, M., ... & Sakamoto, N. (2025). Three-year overall survival in unresectable hepatocellular carcinoma treated with atezolizumab plus bevacizumab. Hepatology International, 1–11.
12. Pan, C., Deng, D., Wei, T., Wu, Z., Zhang, B., Yuan, Q., ... & Yin, P. (2022). Metabolomics study identified bile acids as potential biomarkers for gastric cancer: A case control study. Frontiers in Endocrinology, 13, 1039786.
13. Siegel, A. B., Cohen, E. I., Ocean, A., Lehrer, D., Goldenberg, A., Knox, J. J., ... & Schwartz, J. D. (2008). Phase II trial evaluating the clinical and biologic effects of bevacizumab in unresectable hepatocellular carcinoma. Journal of Clinical Oncology, 26(18), 2992–2998.

14. Storandt, M. H., Tran, N. H., Ehret, C. J., Hanna, M., Jochum, J., Moynagh, M. R., & Jatoi, A. (2023). Gastrointestinal perforation after bevacizumab: A multi-site, single-institution study with a focus on survival. World Journal of Surgical Oncology, 21(1), 177.
15. Tang, T., Abu-Sbeih, H., Ma, W., Lu, Y., Luo, W., Foo, W. C., ... & Wang, Y. (2020). Gastrointestinal injury related to antiangiogenesis cancer therapy. Clinical Colorectal Cancer, 19(3), e117–e123.
16. Umino, R., Kobayashi, Y., Akabane, M., Kojima, K., Okubo, S., Hashimoto, M., & Shindoh, J. (2022). Preoperative nutritional score predicts underlying liver status and surgical risk of hepatocellular carcinoma. Scandinavian Journal of Surgery, 111(1), 14574969211061953.
17. Vogel, A., Rimassa, L., Sun, H. C., Abou-Alfa, G. K., El-Khoueiry, A., Pinato, D. J., ... & Merle, P. (2021). Comparative efficacy of atezolizumab plus bevacizumab and other treatment options for patients with unresectable hepatocellular carcinoma: A network meta-analysis. Liver Cancer, 10(3), 240–248.
18. Wang, K., Xiang, Y. J., Yu, H. M., Cheng, Y. Q., Liu, Z. H., Zhong, J. Y., ... & Cheng, S. Q. (2023). Intensity-modulated radiotherapy combined with systemic atezolizumab and bevacizumab in treatment of hepatocellular carcinoma with extrahepatic portal vein tumor thrombus: A preliminary multicenter single-arm prospective study. Frontiers in Immunology, 14, 1107542.
19. Wang, Y. J., Hsu, K. F., Liao, G. S., & Fan, H. L. (2025). Bevacizumab related gastrointestinal perforation in hepatocellular carcinoma patient: A case report. Case Reports in Oncology.
20. Wilson, H., Macdonald, D., & Bryce, K. (2024). Clearance of hepatitis C virus following immune checkpoint inhibitor therapy for hepatocellular carcinoma: Case report. Case Reports in Gastroenterology, 18(1), 347–351.
21. Yamaoka, K., Kawaoka, T., Fujii, Y., Uchikawa, S., Fujino, H., Nakahara, T., ... & Oka, S. (2024). Multidisciplinary treatment for patients with advanced hepatocellular carcinoma complicated by Vp4 portal vein tumor thrombosis: Combination of atezolizumab and bevacizumab after hepatic arterial infusion chemotherapy and radiotherapy: A case series. Medicine: Case Reports and Study Protocols, 5(6), e00325.*