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Risk of Bleeding in Hepatocellular Carcinoma Patients Treated with Atezolizumab/Bevacizumab: A Systematic Review and Meta-Analysis

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Keywords
Meta-analysis · Bleeding · Variceal bleeding

Abstract

Introduction: The combination of atezolizumab/bevacizumab has emerged as an effective first-line treatment for advanced hepatocellular carcinoma (HCC). However, this therapy is potentially associated with bleeding complications, warranting a comprehensive analysis of their incidence and severity. This meta-analysis aims to synthesize available evidence from clinical trials and observational studies to quantify the prevalence of bleeding following atezolizumab/bevacizumab administration. ***Methods:*** This meta-analysis focused on HCC treatment using atezolizumab/bevacizumab, particularly examining bleeding complications. It determined the prevalence of bleeding post-administration and compared the risk ratio with tyrosine kinase inhibitors (sorafenib or lenvatinib). Risk factors for bleeding complications were also evaluated. ***Results:*** From 28 studies involving 3,895 patients, the pooled prevalence of bleeding side effects was 8.42% (95% CI: 5.72–11.54). Grade III or IV bleeding occurred in 4.42% (95% CI: 2.64–6.10) of patients, with grade V bleeding observed in 2.06% (95% CI: 0.56–4.22). Gastrointestinal bleeding, predominantly variceal, was the most common, with a prevalence of 5.48% (95% CI: 3.98–7.17). Subgroup analysis indicated variability in bleeding rates based on study design and geographical location. Atezolizumab/bevacizumab treatment exhibited a 2.11 times higher prevalence of bleeding compared to tyrosine kinase inhibitors (95% CI: 1.21–3.66). Meta-regression identified high body mass index (BMI) and higher proportion of albumin-bilirubin (ALBI) grade 3 as significant risk factors for bleeding complications. ***Conclusion:*** Atezolizumab/bevacizumab therapy for advanced HCC carries a heightened risk of gastrointestinal bleeding, exceeding that of tyrosine kinase inhibitors. High BMI and higher ALBI grade are key predictors of bleeding complications, emphasizing the need for cautious patient selection and monitoring.

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer globally, posing a significant health burden with a rising incidence [1]. Late diagnosis and

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limited treatment options make advanced HCC challenging, often leading to poor outcomes [2]. However, targeted therapies and immunotherapies offer hope for improved survival and quality of life in these patients [3].

The combination of atezolizumab, a programmed death-ligand 1 (PD-L1) inhibitor, with bevacizumab, a vascular endothelial growth factor inhibitor, has emerged as a groundbreaking first-line treatment for advanced HCC [4]. This combination capitalizes on synergistic effects, enhancing immune response against tumor cells while inhibiting tumor angiogenesis. Clinical trials have demonstrated its efficacy in extending overall survival and delaying disease progression compared to the previously standard sorafenib therapy, establishing it as a superior treatment modality for this patient population [4, 5].

However, the clinical implementation of this promising combination therapy faces challenges [6]. Bleeding events, a notable adverse effect linked to atezolizumab and bevacizumab, raise concern due to bevacizumab's anti-angiogenic action, which can compromise vascular integrity and heighten the risk of hemorrhage [7]. These complications, varying from minor mucosal bleeds to life-threatening hemorrhages, present significant management dilemmas and affect the treatment regimen's safety profile [8].

Considering the critical nature of these adverse events, it is imperative to conduct a comprehensive analysis of the incidence and severity of bleeding associated with atezolizumab/bevacizumab therapy in patients with advanced HCC. This meta-analysis aims to synthesize available evidence from clinical trials and observational studies to quantify the bleeding risk, elucidate potential risk factors, and offer a balanced perspective on the safety and efficacy of this combination therapy.

Methods

We conducted systematic review and meta-analysis in strict compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) checklist. Prior to commencement, it was registered with the International Prospective Register of Systematic Reviews, PROSPERO, under the registration number CRD42024519451.

Inclusion Criteria, Exclusion Criteria, and Study Outcomes

Our study encompassed randomized controlled trials (RCTs), prospective and retrospective cross-sectional or cohort studies detailing bleeding complications following atezolizumab/bevacizumab administration in HCC patients. We included studies examining both primary and secondary line therapies involving atezolizumab/bevacizumab, including combinations with other treatments like transarterial chemoembolization. Exclusions comprised case reports, case series with fewer than 5 patients, review articles, and studies lacking specific bleeding complication rates. Our primary aim was to determine bleeding complication incidence post-atezolizumab/-bevacizumab therapy. Subgroup analyses scrutinized variables such as study design, geographical location, and publication year. We also compared bleeding side effects incidence from tyrosine kinase inhibitors (TKIs) (sorafenib or lenvatinib) to atezolizumab/bevacizumab therapy. Additionally, we aimed to identify bleeding complication risk factors by aggregating factors mentioned across studies for meta-regression analysis.

Search Strategy

The research methodology involved a comprehensive search strategy incorporating keywords relevant to HCC, the atezolizumab/bevacizumab treatment regimen, and bleeding incidents. We identified and utilized synonyms for these keywords to ensure thoroughness in our search. Organized around the Patient/Problem, Intervention, Comparison, and Outcome (PICO) framework, our search strategy employed specific terms outlined in the online supplementary materials (for all online suppl. material, see https://doi.org/10.1159/000539423). We conducted searches across multiple databases, including MEDLINE (PubMed), Embase, Cochrane Library, Web of Science, and KoreaMed, utilizing Medical Subject Headings to locate studies published in English between January 1, 2018, and October 31, 2023. Detailed accounts of the search strategies employed and results obtained from each database are available in the methodology section and online supplementary materials. All search-related tasks were carried out by a professional librarian, EAJ.

Study Selection and Data Extraction

Two authors independently scrutinized titles and abstracts, while two reviewers (Y.G.S. and K.M.Y.) separately assessed the full-text articles for their relevance to the research. In cases of disagreement among the reviewers, JJY facilitated resolution through discussion. Additionally, both investigators independently conducted a risk of bias assessment for each included study. They also consistently recorded the characteristics and outcomes of these studies.

Methodological Quality and Risk of Bias Assessment

The assessment of bias risk was tailored to match the characteristics of each study under review. For RCTs, we used the Cochrane Collaboration's risk of bias tool. Conversely, for non-randomized studies such as cohort studies, we employed the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool. Detailed descriptions of these bias risk assessments are available in the online supplementary materials under the risk of bias section. Any discrepancies in opinion between the authors (Y.G.S. and K.M.Y.) were resolved through discussion. Additionally, funnel plots were utilized to assess the presence of publication bias.

Statistical Analysis

The overall prevalence rate was calculated using a random-effects model, with variance between studies estimated by the DerSimonian-Laird technique. Heterogeneity among studies was assessed using the I^2 statistic, which measures the percentage of total variation across studies attributable to heterogeneity rather than random chance, alongside the p value from the Cochran Q test. I^2 values range from 0% (indicating no heterogeneity) to 100%

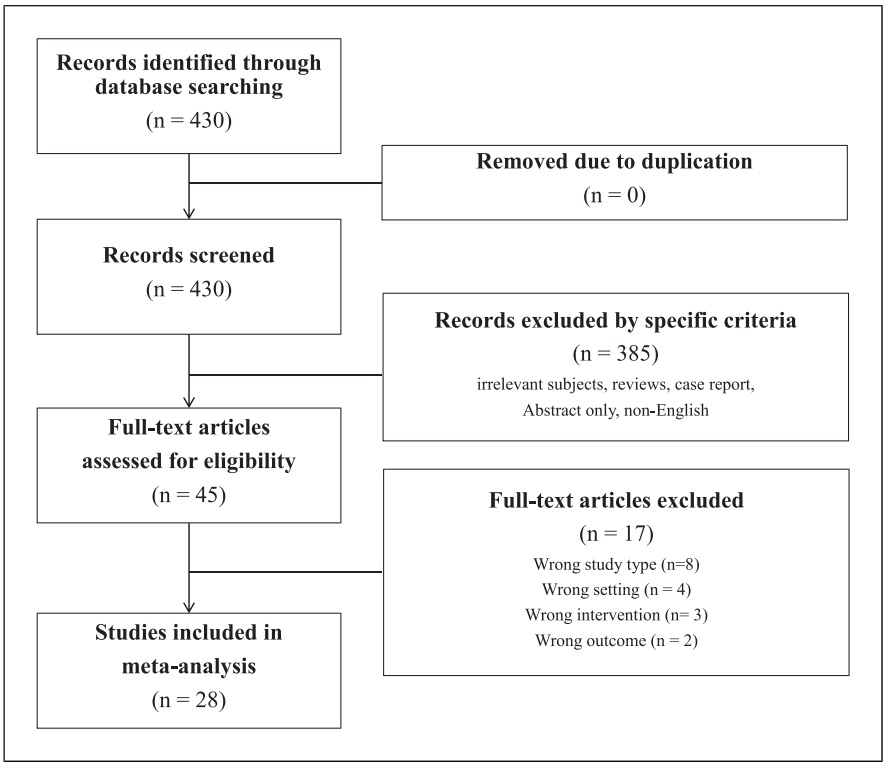

Fig. 1. Flowchart.

(indicating maximum heterogeneity). To assess publication bias, AS-Thompson's test was employed. Statistical analyses were conducted using RevMan 5 from the Cochrane Library and the "meta" package in R software (version 4.1.0, R Foundation for Statistical Computing, Vienna, Austria).

Results

Characteristics of the Included Studies

In the end, 28 studies were selected for analysis (Fig. 1). Details regarding the enrolled patients are presented in Table 1, totaling 3,895 study subjects. Among these, 6 were prospective studies, and 22 were retrospective studies. Of the 28 studies, 17 were conducted in Eastern regions, 7 in Western regions, and the remaining 4 were mixed. Patient ages ranged from 52.8 to 74 years on average, with a predominant male representation in most studies. Eighteen studies performed upper endoscopy before atezolizumab/bevacizumab treatment and provided prophylactic treatment for high-risk varices identified during the procedure (online suppl. Table 1). Other detailed characteristics of individual studies such as etiology, albumin-bilirubin (ALBI) grade, presence of portal hypertension, and proportion of macrovascular invasion are listed in online supplementary Table 1.

Prevalence of Bleeding Complication after Atezolizumab/Bevacizumab

The number of patients with bleeding, location of bleeding, and bleeding grade in individual studies are listed in Table 2. Analyzing 28 studies involving 3,895 patients, we found that the prevalence of bleeding side effects was 8.42% (95% CI: 5.72–11.54) (Table 3). Among these, the prevalence of grade III–IV and grade V bleeding was 4.42% (95% CI: 2.64–6.10) and 2.06% (95% CI: 0.56–4.22), respectively.

When examining the site of bleeding, we observed that gastrointestinal bleeding had a prevalence of 5.48% (95% CI: 3.98–7.17). Notably, variceal bleeding accounted for a substantial portion, with a prevalence of 4.31% (95% CI: 2.42–6.63), suggesting that the majority of gastrointestinal bleeding cases were variceal. In comparison, non-gastrointestinal bleeding was relatively less frequent, with a prevalence of 4.27% (95% CI: 1.99–7.24). The sites of non-gastrointestinal bleeding are described in Table 2.

Subgroup Analysis in Various Situations

We conducted a subgroup analysis to assess the bleeding rate following atezolizumab/bevacizumab across various subgroups (Table 4). First, when categorized by study type, the prevalence of bleeding in RCTs, prospective cohort studies, and retrospective cohort studies was 15.26%,

Table 1. Demographics and characteristics of the studies included in the systematic review and meta-analysis

Study	Year	Study design	Country	Number of patients	Age, years	Male, %
Cao et al. [9]	2023	Retrospective cohort	Chinese	139	52.8	84.4
Chaibi et al. [10]	2023	Retrospective cohort	France	57	63.0	83.0
Charonponguntorn et al. [11]	2022	Prospective cohort	Thailand	30	58.1	90.0
Cheng et al. [5]	2022	RCT	Multinational	329	NA	NA
Cheon et al. [12]	2023	Retrospective cohort	South Korea	169	62.0	61.6
Cheon et al. [13]	2022	Retrospective cohort	South Korea	121	61.0	83.5
Chon et al. [14]	2022	Retrospective cohort	South Korea	121	63.0	100
D'alessio et al. [15]	2022	Retrospective cohort	Multinational	202	69.0	85.0
Castro et al. [16]	2022	Retrospective cohort	Multinational	147	69.1	82.4
Finn et al. [4]	2020	RCT	Multinational	336	64.0	82.0
Giovannini et al. [17]	2023	Prospective cohort	Italy	34	NA	88.0
Haghnejad et al. [18]	2023	Retrospective cohort	France	50	65.0	76.0
Hatanaka et al. [19]	2022	Retrospective cohort	Japan	426	73.0	80.4
Hayakawa et al. [20]	2022	Retrospective cohort	Japan	52	73.0	80.8
Ha et al. [21]	2023	Retrospective cohort	South Korea	194	62.1	86.6
Jost-brinkmann et al. [22]	2023	Retrospective cohort	Germany	100	67.0	87.0
Kim et al. [23]	2022	Retrospective cohort	South Korea	86	62.0	81.4
Kulkarni et al. [24]	2023	Retrospective cohort	India	67	61.0	86.5
Larrey et al. [25]	2022	Prospective cohort	France	43	65.0	79.1
Lee et al. [26]	2023	Retrospective cohort	South Korea	37	60.7	94.6
Manzar et al. [27]	2022	Retrospective cohort	USA	21	68.0	81.0
Qin et al. [28]	2021	RCT	China	132	57.0	87.2
Su et al. [29]	2023	Retrospective cohort	Taiwan	46	61.2	82.6
Tada et al. [30]	2023	Retrospective cohort	Japan	506	74.0	77.4
Teng et al. [31]	2022	Retrospective cohort	Taipei	89	NA	NA
Vithayathil et al. [32]	2022	Retrospective cohort	Multinational	191	68.4	84.3
Yao et al. [33]	2022	Retrospective cohort	China	136	58.0	84.6
Zhao et al. [34]	2023	Retrospective cohort	China	34	55.0	85.3

NA, not available.

12.59%, and 7.19%, respectively. Second, when classified by the geographical region of the study, those conducted in the East exhibited lower bleeding rates compared to those in the West or mixed regions (4.88% vs. 13.32%, 17.78%). Among studies published from 2020 to 2022, the prevalence of bleeding was 9.84%, while in those published in 2023, it slightly decreased to 6.70%. Lastly, when analyzing 18 studies on upper endoscopy surveillance and prophylactic treatment for varices prior to atezolizumab/bevacizumab, the prevalence of bleeding was 10.41%.

Comparison of Bleeding Prevalence between Atezolizumab/Bevacizumab and TKIs

We conducted an analysis comparing bleeding incidences between atezolizumab/bevacizumab and TKIs (Table 5). A total of 7 studies reported comparisons of side effects between TKIs (sorafenib, lenvatinib) and atezolizumab/bevacizumab. In comparison to TKIs, atezolizumab/bevacizumab exhibited a 2.11 times higher bleeding prevalence (95% CI: 1.21–3.66) regarding any grade of bleeding. When individually compared with sorafenib and lenvatinib, the bleeding risk associated with atezolizumab/bevacizumab treatment was 3.83 times (95% CI: 0.77–19.09) and 1.80 times (95% CI: 0.54–6.01) higher, respectively. Regarding grade 3–4 bleeding, atezolizumab/bevacizumab had a 1.38 times higher risk than TKI (95% CI: 0.79–2.41) but was not statistically significant.

Risk Factors for Bleeding Complication

Finally, we conducted a meta-regression analysis to identify risk factors associated with bleeding complications following atezolizumab/bevacizumab treatment (Table 6). Our analysis considered 13 potential risk factors: age, sex, body mass index (BMI), proportion of hepatitis B virus patients, proportion of hepatitis C virus patients, proportion of patients with metabolic associated fatty liver disease, proportion of alcoholic hepatitis patients, proportion of Child-Pugh class B patients, ALBI grade, macrovascular invasion, presence of portal hypertension, endoscopic surveillance before atezolizumab/

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Table 2. Bleeding outcome of individual studies

Study	Group	Total, *n*		Grade, *n*		Bleeding site, *n*			
		patients	bleeding event	grade 3–4	grade 5	gastrointestinal bleeding	variceal bleeding	non-gastrointestinal bleeding	site of non-gastrointestinal bleeding
Cao et al. [9]	Ate/beva	77	0			0			Only GI bleeding is mentioned
Cao et al. [9]	TACE + ate/beva	62	2			2			Only GI bleeding is mentioned
Chaibi et al. [10]	Albumin	15	2			2	2		Only GI bleeding is mentioned
Chaibi et al. [10]	No albumin	42	7			7	7		Only GI bleeding is mentioned
Charonponguntorn et al. [11]		30	6	6		6			Only GI bleeding is mentioned
Cheng et al. [5]		329	100	28	6			37	Epistaxis (37)
Cheon et al. [12]	Child-Pugh class A	133	4	1		4			Only GI bleeding is mentioned
Cheon et al. [12]	Child-Pugh class B	36	6	6		6			Only GI bleeding is mentioned
Cheon et al. [13]		121	7	4		7	7		Only GI bleeding is mentioned
Chon et al. [14]		121	7	5		6		1	ICH (1)
D'alessio et al. [15]		202	28	12		25		3	Epistaxis (1), HCC rupture (1), duodenal ulcer bleeding (1)
Castro et al. [16]	ImBrave IN	74	11	11	7	6	3	5	Tumor bleeding (3), ICH (1), other areas are not described
Castro et al. [16]	ImBrave OUT	73	10	10		5	3	5	Tumor bleeding (3), ICH (1), other areas are not described
Finn et al. [4]		336	54		5	20	8	34	Epistaxis (34)
Giovannini et al. [17]		34	2			2			Only GI bleeding is mentioned
Haghnejad et al. [18]		50	5	1		3		2	Epistaxis (2)
Hatanaka et al. [19]	Training set	255	4	2		4			Only GI bleeding is mentioned

Table 2 (continued)

Study	Group	Total, *n*		Grade, *n*		Bleeding site, *n*			
		patients	bleeding event	grade 3–4	grade 5	gastrointestinal bleeding	variceal bleeding	non-gastrointestinal bleeding	site of non-gastrointestinal bleeding
Hatanaka et al. [19]	Validation set	171	2	2		2			Only GI bleeding is mentioned
Hayakawa et al. [20]		52	8	1					Epistaxis, subcutaneous hemorrhage, however, specific numbers are not provided
Ha et al. [21]		194	12			12	8		Only GI bleeding is mentioned
Jost-brinkmann et al. [22]		100	24			9	9		Only GI bleeding is mentioned
Kim et al. [23]		86	6	4		5		1	ICH (1)
Kulkarni et al. [24]		67	3	2		2	2	1	Epistaxis (1)
Larrey et al. [25]		43	6			6	6		Only GI bleeding is mentioned
Lee et al. [26]		37	2	2		2	2		Only GI bleeding is mentioned
Manzar et al. [27]		21	3		1	3			Only GI bleeding is mentioned
Qin et al. [28]		132	5	3	1	5			Only GI bleeding is mentioned
Su et al. [29]		46	6	3	1	3	2	3	Epistaxis (3)
Tada et al. [30]	Non-EGV	355	7	4		7	2		Only GI bleeding is mentioned
Tada et al. [30]	EGV	151	3	2		3	2		Only GI bleeding is mentioned
Teng et al. [31]		89	6	4		4	3	2	Epistaxis (2)
Vithayathil et al. [32]		191	20						NA
Yao et al. [33]		136	9	7		9			Only GI bleeding is mentioned
Zhao et al. [34]		34	4	1		4			Only GI bleeding is mentioned

GI, gastrointestinal; ICH, intracranial hemorrhage; HCC, hepatocellular carcinoma; EGV, esophago-gastric varices; NA, not available.

Table 3. Prevalence of bleeding event after atezolizumab/bevacizumab in HCC patients

Outcome	No. of studies	Prevalence,%	95% CI	I^2	*p* for heterogeneity
Any type of bleeding	28	8.42	5.72–11.54	89	<0.01
Grade of bleeding					
Grade III–IV bleeding	19	4.42	2.64–6.10	76	<0.01
Grade V bleeding	6	2.06	0.56–4.22	58	0.04
Bleeding site					
Gastrointestinal bleeding	26	5.48	3.98–7.17	69	<0.01
Variceal bleeding	12	4.31	2.42–6.63	72	<0.01
Non-gastrointestinal bleeding	10	4.27	1.99–7.24	80	<0.01

CI, confidence interval.

Table 4. Prevalence of bleeding across various subgroups

Outcome	Studies, *n*	Prevalence, %	95% CI	I^2	*p* for heterogeneity
Study type					
RCT	3	15.26	4.18–31.44	96	<0.01
Prospective cohort	3	12.59	5.71–21.39	29	0.24
Retrospective cohort	22	7.19	4.96–9.75	81	<0.01
Region					
East	17	4.88	3.22–6.82	70	<0.01
West	7	13.32	9.14–18.08	40	0.11
Mixed	4	17.78	11.34–25.28	86	<0.01
Publication year					
2020–2022	16	9.84	5.98–14.47	91	<0.01
2023	12	6.70	3.61–10.52	81	<0.01
Prior endoscopy before starting treatment	18	10.41	6.82–14.62	90	<0.01

CI, confidence interval.

bevacizumab, and presence of baseline varices. Among these factors, BMI and the proportion of ALBI grade 3 were found to be associated with bleeding complications. Specifically, the prevalence of bleeding significantly increased in patients with a higher BMI (beta coefficient 0.019, 95% CI: 0.019–0.095, $p = 0.003$) and higher proportion of ALBI grade 3 (beta coefficient 0.002, 95% CI: 0.001–0.008, $p = 0.020$).

Discussion

In this meta-analytical study, we rigorously synthesized available evidence to quantitatively assess the hemorrhagic risk associated with the administration of atezolizumab and bevacizumab in patients diagnosed with HCC. Our findings reveal a significant incidence of bleeding complications, with a reported pooled prevalence of 8.42% (any grade) highlighting a considerable risk in the therapeutic landscape of HCC.

Among bleeding complications, clinical significance varies based on the grade and location of the bleeding. High-grade bleeding events are not only life threatening but also necessitate immediate and aggressive intervention. Grade 4 bleeding events, such as esophageal varices, are particularly concerning due to their high mortality risk and the complex management required. In our study, the pooled prevalence of grade 3–4 bleeding was 4.42%, mostly gastrointestinal bleeding and a few intracranial hemorrhage.

A key finding of our study is that the hemorrhagic risk associated with the atezolizumab/bevacizumab therapeutic regimen significantly exceeds that associated with established TKIs such as sorafenib or lenvatinib. This observation holds clinical significance, delineating a distinct adverse

Table 5. Comparison of bleeding between atezolizumab/bevacizumab and sorafenib or lenvatinib

Group	Studies, *n*	Patients, bleeding/ total (ate/ beva), *n*	Patients, AE/ total (control), *n*	RR (M-H, random)	95% CI	I^2	*p* for heterogeneity
Any grade							
Atezolizumab/ bevacizumab versus sorafenib or lenvatinib	7	199/1,063	51/676	2.11	1.21–3.66	47	0.08
Atezolizumab/ bevacizumab versus sorafenib	3	159/797	30/370	3.83	0.77–19.09	71	0.03
Atezolizumab/ bevacizumab versus lenvatinib	3	16/166	11/226	1.80	0.54–6.01	53	0.12
Grade 3-4							
Atezolizumab/ bevacizumab versus sorafenib or lenvatinib	5	39/627	18/440	1.38	0.79–2.41	0	0.86
Atezolizumab/ bevacizumab versus sorafenib	2	31/461	11/214	1.33	0.68–2.58	0	1.00
Atezolizumab/ bevacizumab versus lenvatinib	3	8/166	7/226	1.51	0.53–4.29	0	0.54

RR, risk ratio; CI, confidence interval.

Table 6. Meta-regression analysis of risk factors for bleeding after atezolizumab/bevacizumab

Variable	Coefficient (95% CI)	*p* value
Age	0.001 (−0.007 to 0.007)	0.965
Male (%)	0.003 (−0.003 to 0.010)	0.350
BMI (kg/m^2)	0.019 (0.019 to 0.095)	**0.003**
Proportion of HBV etiology (%)	0.000 (−0.002 to 0.001)	0.733
Proportion of HCV etiology (%)	0.001 (−0.005 to 0.005)	0.923
Proportion of MAFLD etiology (%)	0.002 (−0.009 to 0.001)	0.061
Proportion of alcohol etiology (%)	0.002 (−0.004 to 0.007)	0.650
Child-Pugh class B (%)	0.001 (−0.003 to 0.004)	0.293
ALBI grade 1 (%)	0.001 (−0.004 to 0.001)	0.364
ALBI grade 2 (%)	0.002 (−0.004 to 0.004)	0.902
ALBI grade 3 (%)	0.002 (0.001 to 0.008)	**0.020**
Macrovascular invasion (%)	0.001 (−0.001 to 0.004)	0.080
Presence of portal hypertension (%)	0.002 (−0.002 to 0.003)	0.671
Endoscopy before treatment (%)		
Presence of baseline varices	0.001 (−0.002 to 0.004)	0.710

CI, confidence interval; BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; MAFLD, metabolic associated fatty liver disease; ALBI, albumin-bilirubin.

profile for the immunotherapy-angiogenesis inhibitor combination and emphasizing the importance of an informed and judicious patient selection process. Regarding the severity of bleeding, in RCTs comparing TKIs with atezolizumab/bevacizumab, no significant difference in grade 3–4 bleeding events was reported between the groups. In our study, the incidence of grade 3–4 bleeding appeared to be higher in the atezolizumab/bevacizumab group, although this difference was not statistically significant (risk ratio 1.38, 95% CI: 0.79–2.41). This finding aligns with

outcomes from the IMbrave150 trial [35], where high-grade bleeding events similarly demonstrated significant clinical impact. Particularly, events like esophageal varices, noted both in our analysis and in the IMbrave150 study, are of grave concern due to their high mortality risk and the complex, urgent care they require. This comparison underscores the need for vigilant monitoring and proactive intervention strategies tailored to the severity and location of bleeding in patients treated with atezolizumab/bevacizumab.

Another particularly notable finding from our study was the prevalence of gastrointestinal, particularly variceal, bleeding among the spectrum of hemorrhagic complications observed. Despite rigorous pre-treatment endoscopic evaluations aimed at excluding patients with a high baseline risk for variceal hemorrhage, the incidence of such events remains concerning. This highlights a potential limitation in current pre-treatment screening protocols and suggests that existing guidelines, which recommend preventive strategy such as endoscopic variceal ligation or non-selective β-blockers before initiating atezolizumab/bevacizumab therapy, may not adequately mitigate the risk of severe bleeding [21, 36]. In preventive variceal management, in general, variceal ligation is recommended for patients with high-risk or previously bleeding varices, while non-selective β-blockers are used to reduce portal hypertension and prevent initial bleeding in patients with smaller varices or those unsuitable for band ligation. However, there are no specific studies or guidelines on choosing between band ligation and non-selective β-blockers as varix prevention therapy prior to atezolizumab/bevacizumab treatment.

Moreover, our meta-analysis identified specific patient populations at an increased risk for bleeding complications, notably individuals with elevated BMI and higher proportion of ALBI grade 3. This insight is crucial for refining patient selection and monitoring strategies, thereby optimizing the balance between therapeutic efficacy and safety [37]. Interestingly, no significant variation in bleeding risk was observed in patients with portal hypertension of presence of varices before atezolizumab/bevacizumab. We believe that this potentially suggests the effectiveness of pre-treatment risk stratification, with exclusion and prophylactic treatment of varices, which was successful with atezolizumab/bevacizumab therapy.

It is essential to acknowledge the inherent limitations of our study, including the heterogeneity among included studies and the potential for publication bias, which may impact the generalizability of our findings. Thus, these factors necessitate a cautious interpretation of our conclusions within the broader context of HCC management. Future research endeavors should aim to further delineate the risk factors for bleeding complications in the context of atezolizumab/bevacizumab therapy and explore the clinical efficacy of alternative therapeutic strategies or modifications, such as the potential discontinuation of bevacizumab, to mitigate the identified risks.

In conclusion, our meta-analysis offers compelling quantitative evidence of the heightened hemorrhagic risk linked with atezolizumab/bevacizumab therapy in HCC, underscoring the critical significance of meticulous patient selection, proactive management strategies, and exploration of alternative treatments for high-risk cohorts. Further investigation is imperative to deepen our understanding and refine our approach to managing these risks, with the ultimate aim of enhancing patient outcomes in advanced HCC.

Statement of Ethics

This study protocol was reviewed and the need for approval was waived by the Institutional Review Board of Soonchunhyang University Bucheon Hospital. The need for informed consent was waived by the Institutional Review Board of Soonchunhyang University Bucheon Hospital.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Study concept and design and data analysis and interpretation: Jeong-Ju Yoo, Young-Gi Song, and Kyeong-Min Yeom; provision of study materials or patients: Young-Gi Song, Kyeong-Min Yeom, and Eun-Ae Jung; collection and assembly of data: Sang Gyune Kim and Young Seok Kim; Manuscript writing: Jeong-Ju Yoo; and final approval of manuscript: all authors.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author upon reasonable request.

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