의학석사 학위논문

간세포암종에 대해 아테졸리주맙-베바시주맙 및 렌바티닙 치료를 받는 환자의 정맥류 출혈의 위험도 평가

Risk of Variceal Bleeding in Patients Receiving Atezolizumab-Bevacizumab and Lenvatinib Treatment for Hepatocellular Carcinoma

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이 논문을 의학석사 학위 논문으로 제출함

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Abstract

Background and aims: There is limited real-world data on the actual risk of variceal bleeding (VB) in patients receiving atezolizumab–bevacizumab (Atezo–Bev) or lenvatinib treatment. This study was aimed to assess the risk of VB in patients with advanced hepatocellular carcinoma (HCC) receiving two treatments and to construct a predictive model for VB.

Methods: This retrospective study included 585 patients with HCC who underwent endoscopy before Atezo–Bev (n = 476) or lenvatinib (n = 109) treatment at two hospitals in Korea. The primary outcome was the occurrence of VB. Non-VB event was considered as a competing event.

Results: Of the 585 patients, 31 developed VB (4.7% at 6 months, 6.2% at 12 months), without significant difference in the risk of VB between the two treatments. The median follow-up was 6.1 months. No patient died from VB. In multivariable analysis, factors associated with an increased risk of VB were portal vein invasion (PVI, subdistribution hazard: 3.30, 95% confidence interval [CI]: 1.44–7.58), platelet <100,000 mm^3 (SHR: 2.59, 95% CI: 1.23–5.45), and varices needing treatment (VNT, SHR: 3.79, 95% CI: 1.76–8.17). We built a prediction model PV100 consisting of PVI, low platelet count, VNT, and history of bleeding.

Conclusion: A low platelet count, PVI, and VNT increased the risk of VB after Atezo–Bev or lenvatinib treatment for HCC. Our model PV100 can predict and assess the risk of VB risk in

real-world settings.

Keywords: Hepatocellular carcinoma; Lenvatinib; Bevacizumab; Bleeding

Contents

Introduction

Since the IMbrave 150 trial, atezolizumab–bevacizumab (Atezo–Bev) has been the standard of care for advanced hepatocellular carcinoma (HCC), owing to overall and progression-free survival significantly higher than sorafenib alone.(1-4) However, the risk of gastrointestinal (GI) bleeding following Atezo–Bev treatment for HCC has raised concerns primarily due to the antiangiogenic effect of bevacizumab.(5) Due to combined liver cirrhosis, most patients with HCC are prone to bleeding, particularly to life-threatening variceal bleeding (VB).

The IMbrave 150 trial included only patients without a history of VB and excluded those with a high risk of varices. Nevertheless, the frequency of VB was higher among patients with main portal vein invasion (PVI) or varices who were treated with Atezo–Bev than those who were treated with sorafenib.(1, 2) Furthermore, a phase 2 trial for HCC treatment, bevacizumab increased the risk of GI bleeding.(6) Therefore, in clinical practice, the risk of GI bleeding, especially VB, remains a significant concern with Atezo–Bev treatment administered to patients with a history of GI bleeding, a high risk of varices, and an impaired liver function. Hence, for patients who are not eligible for Atezo–Bev, lenvatinib treatment is recommended as an alternative first-line systemic treatment. Despite the lack of head-to-head comparison randomized trial between the two treatments, lenvatinib has comparable efficacy to Atezo–Bev treatment.(7)

Real-world data on the actual risk of VB after Atezo–Bev or lenvatinib administration are limited.(8-10) PVI, severe esophageal varices (EV) on pretreatment esophagogastroduodenoscopy (EGD), and a history of GI bleeding are associated with increased risk of GI bleeding.(8-10) However, these studies evaluated a small number of patients and include a part of those who underwent pretreatment EGD. Thus, the association between the presence or severity of EV prior to Atezo–Bev or lenvatinib treatment and the risk of VB was not elucidated.

Therefore, the present study was aimed to assess the risk of VB in patients treated with Atezo–Bev or lenvatinib for HCC in a multicenter real-world cohort and to identify the risk factors for VB. In addition, we sought to develop a prediction model for VB following Atezo–Bev or lenvatinib treatment for HCC.

PATIENTS AND METHODS

Study population

The source population for this study comprised consecutive patients treated with Atezo–Bev or lenvatinib for HCC at the Asan Medical Center and Severance Hospital, Seoul, Republic of Korea, between 2018 and 2023. Of the 585 patients included, 537 (91.8%) patients were from Asan Medical Center and 48 (8.2%) were from Severance Hospital. The inclusion criteria were as follows: (1) confirmatory diagnosis of HCC histologically or radiologically according to international guidelines for HCC,(11, 12) (2) Barcelona Clinic Liver Cancer (BCLC) stage B or C, (3) receiving at least one dose of Atezo–Bev or lenvatinib, and (4) presence of EGD results at least within 1 year before the first dose of Atezo–Bev or lenvatinib. The exclusion criteria were Atezo–Bev for adjuvant setting in clinical trials, BCLC stage D, not undergoing EGD within 1 year before Atezo–Bev or lenvatinib treatment, or Child–Pugh class C.

This study was approved by the Institutional Review Board of Asan Medical Center (IRB No. 2023-0076), and the need for informed consent was waived by the IRB.

Data collection, definitions, and treatment

Clinical, laboratory, and tumor characteristics were evaluated from the electronic medical

records of the two hospital's clinical database. PVI was classified into two categories: branch vascular invasion (presence of PVI in the first- or second-order branches) and main or bilateral vascular invasion (main trunk PVI or extension to the contralateral PV). All patients underwent EGD within 1 year before the start of Atezo–Bev or lenvatinib administration. The presence of EV was divided into three classes based on EGD findings proposed by the Japanese Society of Portal Hypertension.(13) Primary or secondary prophylaxis using endoscopic variceal ligation (EVL) or beta-blockers to prevent VB was performed before Atezo–Bev or lenvatinib administration at the physician's discretion. Varices needing treatment (VNT) defined as EV grade ≥2, or small varices with stigmata of recent hemorrhage such as red wale signs, fibrin clot, or active bleeding.(14)

Patients were treated with atezolizumab (1,200 mg) and bevacizumab (15 mg/kg) every 3 weeks based on the IMbrave 150 trial.(1) Lenvatinib was administered based on the dosage described in the REFLECT trial.(15) Patients were assessed for disease progression every 2–3 cycles of Atezo–Bev treatment or every 6–8 weeks of lenvatinib treatment using follow-up CT or MR images.

Primary outcome

The primary outcome of this study was the occurrence of VB, which was defined as either confirmed active VB on EGD or suspected VB accompanied by clinical symptoms of

gastrointestinal bleeding, such as hematemesis, melena, and a decrease in hemoglobin level of ≥2 g/dL from the baseline value followed by EVL. All patients were observed from the date of the first dose of Atezo–Bev or lenvatinib administration to the date of documented VB or the final date of Atezo–Bev or lenvatinib administration. EGD or colonoscopy findings, when EGD failed, were used to evaluate the etiology of GI bleeding. Any other causes of VB bleeding were categorized as non-VB and were considered a competing event to the primary outcome.

Statistical analysis

A prediction model for VB was constructed according to the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) guidelines.(16) First, we analyzed the entire patient cohort, summarizing baseline characteristics and outcomes for Atezo–Bev and lenvatinib treatment groups. Between-group comparisons were made using t-test or Chi-square test, with a significance threshold set at p-value < 0.05 (two-tailed).

The primary event of interest was VB, while the competing events were non-VB events, deaths, or treatment interruptions unrelated to VB. The incidence of VB was estimated using the cumulative incidence function, and the cumulative incidence rates were compared for groups with potential risk factors. The prediction horizon time was set at 6 months, and the

Fine–Gray subdistribution hazard model was utilized as the foundation model.(17) The entire cohort was used for prediction modeling, and the complete-case method was used to handle missing data. Initially, univariate Fine–Gray models were fitted to VB, identifying potential risk factors with p-values below 0.2. Subsequently, several multivariable models were fitted to select the final prediction model. The ultimate choice of the prediction model was based on both clinical and statistical significance. Consequently, factors such as PVI, low platelet levels (<100,000 mm^3), varices requiring treatment, and a history of GI bleeding were incorporated into the final model.

The performance of our competing risks survival model was evaluated in terms of both discrimination and calibration. Discrimination was assessed using the time-dependent area under the curve (AUC), while calibration ability was measured using a calibration curve, comparing predicted risk for the 6-month VB event with the observed event rate. Additionally, the overall performance of the prediction model was quantified using the Brier score, which represents the weighted average of squared distances between observed event status and predicted VB event probability. A lower Brier score indicates a superior predictive model. However, a biased assessment occurs when the final model is directly assessed in the sample where it is derived from. Therefore, bootstrap validation was performed to remove the biased optimistic assessment. A total of 1,000 bootstrapped samples were generated, and the patients were divided into three risk groups according to the estimated 6-month VB risk using the final

prediction model: low (<1.5%), intermediate (1.5–4.0%), and high-risk (≥4.0%) group. R software (version 4.1.2) was employed for all data analyses. The R packages crr and riskRegression were utilized to fit the Fine–Gray model and evaluate the performance of our final prediction model. An interactive and user-friendly web calculator (https://pv100.shinyapps.io/pv100/) was used to facilitate easy clinical application.

RESULTS

Baseline characteristics of the study population

Table 1 presents the baseline characteristics of the study population of 585 patients. The mean age was 60.1 years, and 82.9% of the patients were male. Of the 174 (29.7%) patients with EV on pretreatment EGD, 61 were classified as VNT. Of the 24 patients (12 for VB and 12 for non-VB) with a history of GI bleeding, 14 (2.9%) in the Atezo–Bev group and 11 (10.1%) in the Lenvatinib group experienced GI bleeding before treatment. The time span between their prior VB and the initiation of treatment (6 in the Atezo–Bev group and 6 in the Lenvatinib group) ranged from 3 to 63 months in 12 patients with a history of VB. The remaining 12 patients experienced other causes of GI bleeding (peptic ulcer bleeding, gastric antral vascular ectasia, and hemobilia).

Compared with the Lenvatinib group, the Atezo–Bev group was significantly older and had a lower prevalence of main PVI and extrahepatic metastasis (Table 1). The Lenvatinib group showed a significantly higher proportion of patients with previous GI bleeding, EV with red color signs, and VNT.

Table 1. Baseline characteristics of study population

Characteristics	Total (N = 585)	Atezolizumab /Bevacizumab (N = 476)	Lenvatinib (N = 109)	P value
Demographics				
Age, years [mean ± SD]	60.1 ± 10.8	60.9 ± 11.0	56.8 ± 9.7	<0.001
Male sex	485 (82.9)	391 (82.1)	94 (86.2)	0.377
Etiology of liver disease				<0.001
Hepatitis B virus	409 (69.9)	339 (71.2)	71 (64.2)	
Hepatitis C virus	28 (4.8)	21 (4.4)	7 (6.4)	
Alcoholic or others	148 (25.3)	116 (24.4)	31 (29.4)	
Laboratory findings				
Median ALT, [IQR]	26.0 [17.0–44.0]	24.0 [16.0–40.5]	36.0 [21.0–63.0]	<0.001
Median albumin, [IQR]	3.4 [3.0–3.8]	3.4 [3.1–3.8]	3.2 [2.9–3.7]	0.014
Median platelet, ×1000/mm^3 [IQR]	143.0 [98.0–212.0]	141.5 [100.5–209.5]	149.0 [96.0–227.0]	0.523
Platelet count <100,000/mm^3	151 (25.8)	118 (24.8)	33 (30.3)	0.290
Median PT, INR [IQR]	1.1 [1.0–1.2]	1.1 [1.0–1.2]	1.1 [1.0–1.2]	0.004
Median total bilirubin, mg/dL [IQR]	0.7 [0.5–1.1]	0.7 [0.5–1.1]	0.9 [0.6–1.5]	0.012
Median creatinine, mg/dL [IQR]	0.8 [0.7–0.9]	0.8 [0.7–0.9]	0.8 [0.7–1.0]	0.293
Child–Pugh class				0.351
A	379 (64.8)	314 (66.0)	65 (59.6)	
B	206 (32.1)	162 (34.0)	44 (40.4)	
ALBI, [IQR]	−0.4 [−0.6–−0.3]	−0.4 [−0.6–−0.3]	−0.5 [−0.6–−0.3]	0.380
MELD, [IQR]	7.4 [6.8–8.0]	7.4 [6.8–8.1]	7.3 [6.8–7.9]	0.287
Tumor characteristics				
BCLC stage				0.101
B	68 (11.6)	56 (11.8)	12 (11.0)	
C	517 (88.4)	420 (88.2)	97 (89.0)	
Macrovascular invasion, present	312 (53.3)	248 (52.1)	64 (58.7)	0.253
PV invasion				<0.001
None	293 (50.1)	244 (51.3)	49 (45.0)	
Branch vascular invasion	112 (19.1)	103 (21.6)	9 (8.3)	
Main or bilateral	180 (30.8)	129 (27.1)	51 (46.8)	
Extrahepatic metastasis, present	308 (52.6)	229 (48.1)	79 (72.5)	<0.001
Endoscopic findings				
History of gastrointestinal bleeding	25 (4.3)	14 (2.9)	11 (10.1)	0.002
EV, present	174 (29.7)	132 (27.7)	42 (21.1)	0.035
Grade 1	120 (20.5)	97 (20.4)	23 (21.1)	
Grade 2	39 (6.7)	28 (5.9)	11 (10.1)	
Grade 3	15 (2.6)	7 (1.5)	8 (7.3)	
EV with red color signs	44 (7.5)	29 (6.1)	15 (13.8)	0.011
Varices needing treatment	61 (10.4)	40 (8.4)	21 (19.3)	0.002
Prophylaxis with beta-blocker	84 (14.4)	69 (14.5)	15 (13.8)	0.010
Previously performed EVL	41 (7.0)	31 (6.5)	10 (9.2)	0.439

Presented as number (proportions) or median [interquartile range]

Abbreviation: ALT, alanine aminotransferase; BCLC, Barcelona clinic liver cancer; EV, esophageal varices; EVL, esophageal variceal ligation; IQR, interquartile range; INR, international normalized ratio; PT, prothrombin time; PV, portal vein; SD, standard deviation; VNT, varices needing treatment

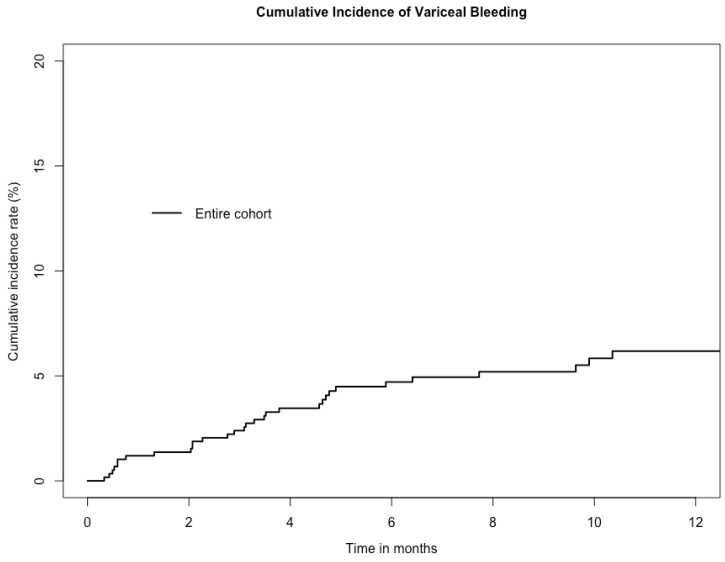
Variceal bleeding after Atezo–Bev and lenvatinib treatment

During the median follow-up of 6.1 months (interquartile range [IQR], 3.7–10.3), 31 (5.3%) developed VB after Atezo–Bev and lenvatinib treatment. The median time from the first dose of treatment to VB was 3.1 months (IQR, 1.5–4.0). The cumulative VB rates in the entire study population were 2.4%, 4.7%, 5.2%, and 6.2% at 3, 6, 9, and 12 months, respectively (Figure 1A). All 31 patients with VB were successfully treated with EVL and conservative treatment without mortality. VB occurred in 23 patients in the Atezo–Bev group and 8 patients of the Lenvatinib group. The risk of VB was not significantly different between the Atezo–Bev and Lenvatinib group (P=0.500, Figure 1B).

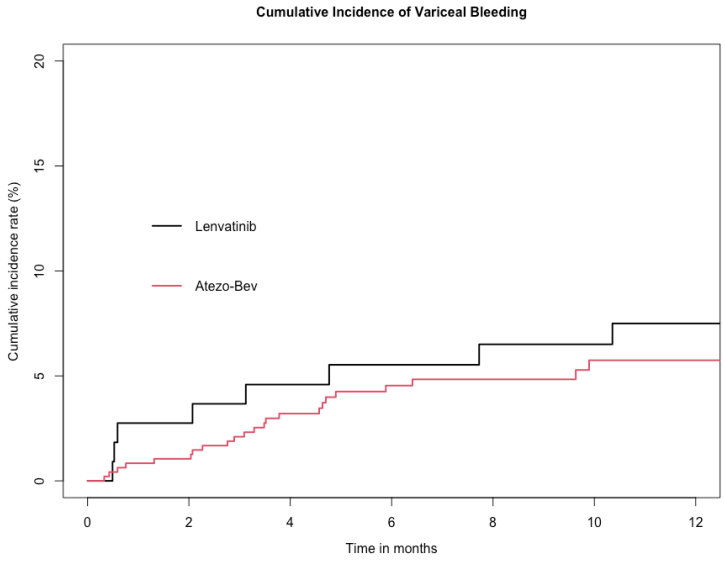
The frequency of VB was significantly higher in patients with PVI (n=24, 8.2%) than in those without PVI (n=7, 2.4%, P=0.002; Figure 1C). Patients with lower platelet <100,000/mm3 showed a significantly higher incidence of VB than those with platelet ≥100,000/mm3 (P=0.002, Figure 1D). Of the 61 patients with VNT, 11 (18.0%) developed VB, showing a significantly higher incidence of VB than those without VNT (n=20, 3.8%, P<0.001; Figure 1E). Of the 25 patients with a history of GI bleeding, 5 (20.0%) developed VB, showing a significantly higher incidence of VB than 560 patients without previous GI bleeding (4.6% of VB, Figure 1F).

Figure 1

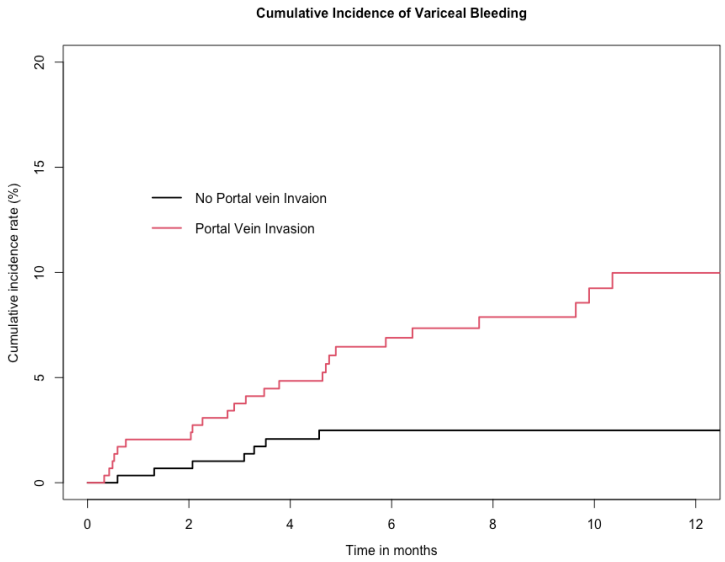
(A) Entire cohort



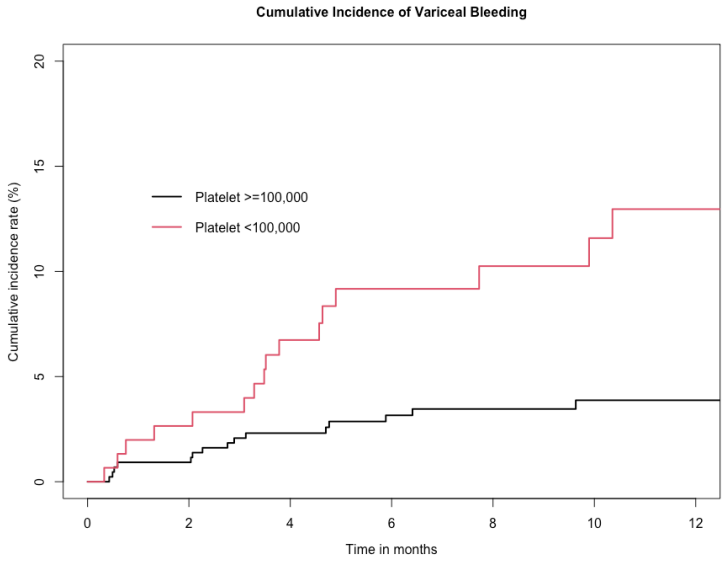
(B) According to treatment regimen



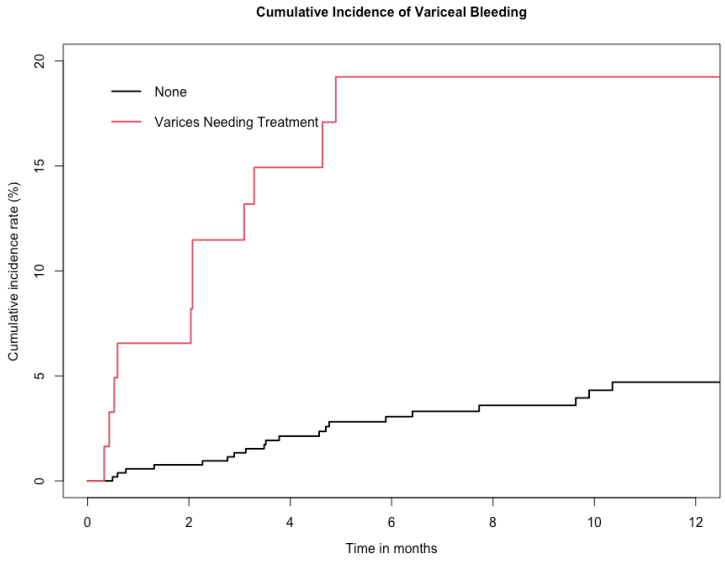
(C) According to presence of portal vein invasion



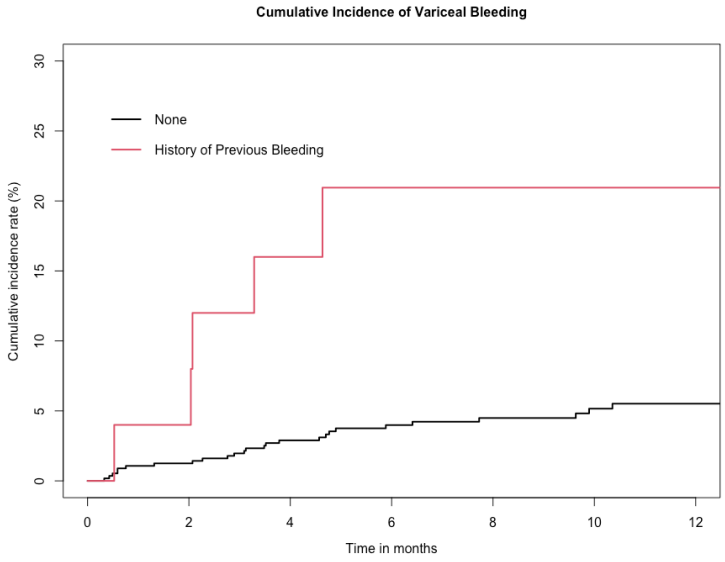
(D) According to platelet count



(E) According to varices needing treatment



(F) According to presence of prior gastrointestinal bleeding history



Non-variceal bleeding events

A total of 10 non-VB events occurred during the follow-up period. Most common cause of the non-VB was peptic ulcer bleeding (n=5), followed by lower GI bleeding (n=3), stomach bleeding directly from the left lobe of the HCC invasion (n=1), and stomach bleeding from the stent insertion site (hepato-gastrostomy stent, n=1). No patient died from these non-VB events.

Prophylaxis for variceal bleeding

Of the 174 patients identified EV on pretreatment EGD, 84 (48.3%) received prophylaxis either beta-blocker (n = 43), EVL (n=25), or both treatment (n=16) prior to the initiation of systemic treatment (Table 2). Propranolol (n=45) and carvedilol (n=14) were used for prophylactic beta-blocker. Of the 61 patients with VNT, 45 (73.4%) patients received prophylaxis for VB (beta-blocker in 16 patients, EVL in 16 patients, and both treatment in 13 patients). VB occurred in 10 (22.2%) in 45 patients with prophylaxis for VNT and 1 (6.3%) in 16 patients without prophylaxis for VNT. Among the 113 patients with EV but not classified as VNT, 7 (17.9%) of 39 patients with prophylaxis and 3 (4.1%) of 74 patients without prophylaxis experienced VB.

Table 2. Details about prophylaxis for variceal bleeding

	Esophageal varices (n = 174)				**No varices (n = 411)**	
	N		VB		N	VB
Prophylaxis	84 (48.3%)		17 (20.2%)			
No prophylaxis	90 (51.7%)		4 (4.4%)		411	10 (2.4%)
	VNT (+, n = 61)		**VNT (–, n = 113)**			
	N	VB	N	VB		
Prophylaxis	45 (73.4%)	10 (22.2%)	39 (34.5%)	7 (17.9%)		
No prophylaxis	16 (26.6%)	1 (6.3%)	74 (65.5%)	3 (4.1%)		

Abbreviation: VB, variceal bleeding

Predictors of variceal bleeding and construction of a risk prediction model

In the multivariable analysis, factors associated with an increased risk of VB were PVI (adjusted subdistribution hazard ratio [aSHR]: 3.30, platelet <100,000 mm3 (aSHR: 2.59), and VNT (aSHR: 3.79) (Table 3). History of GI bleeding was incorporated into the final model for its clinical significance. Given the number of VB event, it seems appropriate for the final prediction model to have four variables. Figure 2A provides the calibration plot as well as the AUC and the Brier score in the entire cohort. The calibration plot appeared to align closely with the 45° line, suggesting an effective calibration capability. Moreover, the discrimination ability and overall performance of the prediction model are suitable (AUC=77.0%, Brier=4.1%). In the results of the bootstrap validated sample, the AUC was slightly lower (74.2%), and the Brier scores were lower (4.4%) (Figure 2B). The calibration ability of the prediction model deteriorates in the bootstrap validated sample.

Utilizing the final prediction model PV100, the patients were categorized based on the estimated 6-month VB risk: low (<1.5%), intermediate (1.5–4.0%), and high risk (≥4.0%) (Figure 3). In the high-risk group, the cumulative VB rates at 3, 6, 9, and 12 months were 6.0%, 11.0%, 12.2%, and 15.1%, respectively.

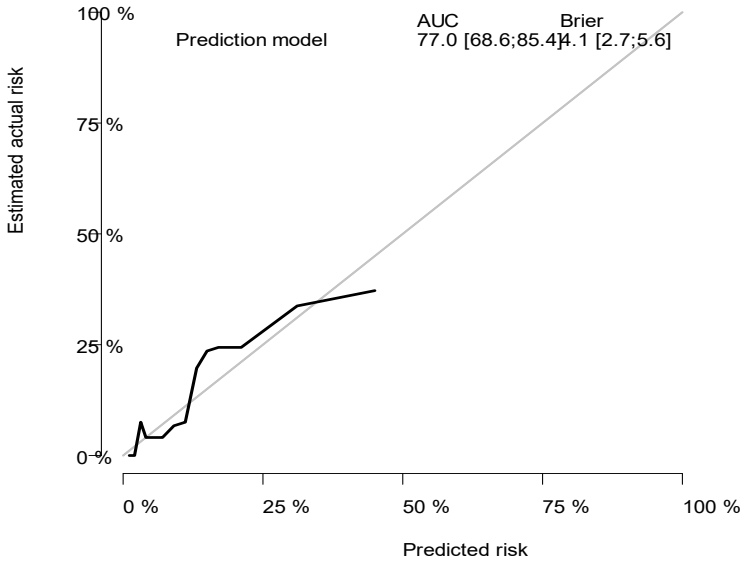
Table 3. Factors associated with variceal bleeding during the treatment with Atezolizumab/Bevacizumab or Lenvatinib

Variables	Univariate analysis			Multivariable analysis		
	SHR	95% CI	P	Adjusted SHR	95% CI	P
Treatment group			0.42			
Atezolizumab/Bevacizumab	1	Reference				
Lenvatinib	1.39	0.62–3.10				
Age, per 1 year increase	0.96	0.93−0.98	0.001			
Sex, male	1.40	0.49–4.00	0.535			
Portal vein invasion	3.54	1.52–8.22	0.003	3.30	1.44–7.58	0.005
Platelet, <100,000	3.21	1.59–6.48	0.001	2.59	1.23–5.45	0.012
Albumin	0.52	0.29–0.94	0.031			
PT, INR ≥1.3	2.66	1.09–6.53	0.032			
MELD, per 1 increase	1.28	1.06–1.56	0.012			
History of GI bleeding	4.84	1.84–12.75	0.002	1.65	0.58–4.70	0.347
BCLC stage			0.77			
B	1	Reference				
C	1.17	0.41–3.33				
Extrahepatic metastasis	1.12	0.55–2.26	0.76			
Varices needing treatment	5.40	2.58–11.33	<0.001	3.79	1.76–8.17	0.001

Abbreviation: BCLC, Barcelona clinic liver cancer; CI, confidence interval; HR, hazard ratio; INR, international normalized ratio; PT, prothrombin; PVI, portal vein invasion; SHR: subdistribution hazard ratio

Figure 2

(A) Entire cohort



(B) Bootstrap cross-validation sample

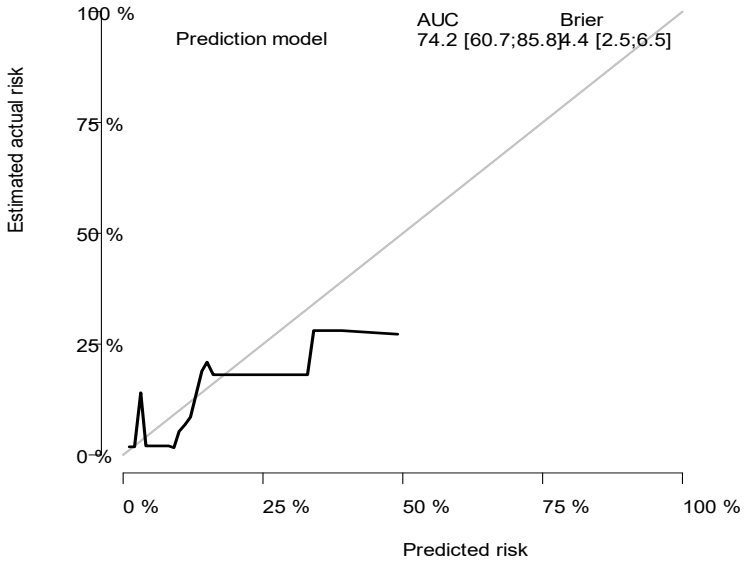
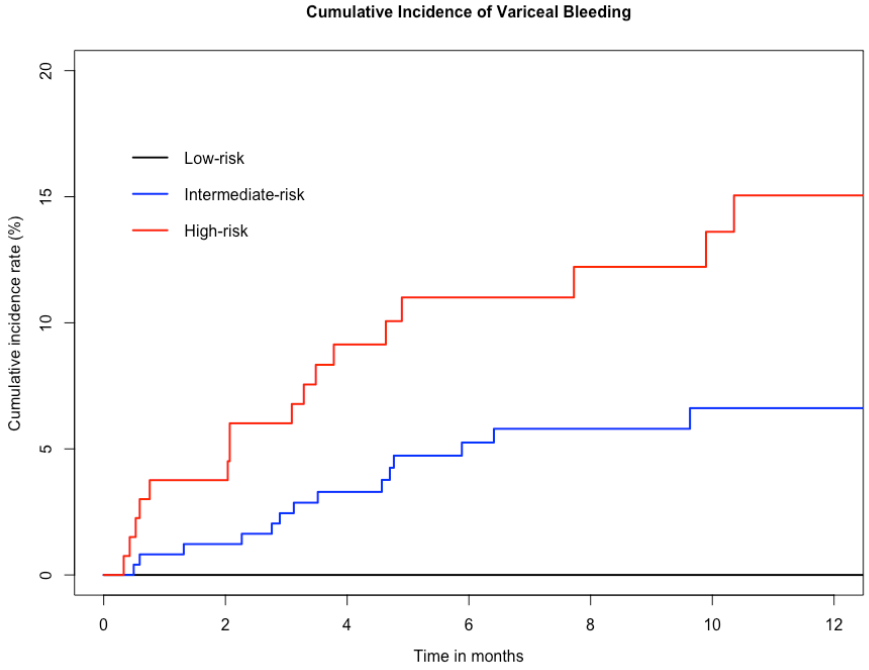


Figure 3


Cumulative Incidence of Variceal Bleeding
Low-risk
Intermediate-risk
High-risk
Cumulative incidence rate (%)
0
5
10
15
20
0
2
4
6
8
10
12
Time in months

Application of the predictive model

To test our PV100 model, it was applied to actual patients. For example, a 54-year-old male patient with advanced HCC was scheduled to administrative Atezo–Bev treatment. He had a main PVI and his platelet count was 130,000/mm3. He did not have a high risk of varices on pretreatment EGD without any history of bleeding. According to the PV100 model, his risk of developing VB was 9.2%. Our PV100 model can be readily used on the website (https://pv100.shinyapps.io/pv100/).

DISCUSSION

In this study on 585 patients who received Atezo–Bev or lenvatinib treatment for advanced HCC, VB occurred in 31 (5.3%) patients and was successfully managed without mortality. Low platelet count, PVI at baseline, and VNT on pretreatment EGD were significantly associated with an increased risk of VB. With these three factors, we developed a new model, PV100, with a strong predictive performance for estimating the risk of VB during Atezo–Bev or lenvatinib treatment.

The IMbrave 150 trial revealed 2.4% of VB in the Atezo–Bev group after excluding patients with a high risk of varices or history of GI bleeding. In our study, the incidence rate of VB was 4.8% among those treated with Atezo–Bev regimen, which was greater than those reported in the IMbrave 150 trial because our study included data from real-world practice. Another retrospective study involving 102 Korean patients receiving Atezo–Bev reported a VB rate of 4.1%(9) and that main PVI and EV grade ≥ 2 on pretreatment EGD were associated with an elevated risk of VB in the univariate analysis; however, due to the small number of bleeding events, multivariable analysis was not performed. These findings are consistent with our findings. However, D'Alessio et al. found a larger incidence of bleeding (14%) than our study(10), but the incidence of GI bleeding grade ≥3 was only 6% and did not find any

association between EV on pretreatment EGD and GI bleeding. However, only 53% of the included patients were examined using EGD before receiving Atezo–Bev treatment; therefore, this conclusion should be interpreted with caution.(10)

Of the 109 patients who received lenvatinib, 8 (7.3%) experienced VB during treatment, which was higher than that in patients treated with Atezo–Bev (4.8%). However, the risk of VB after statistical adjustment was not significantly different between these two treatments. This may suggest that Atezo–Bev treatment does not further increase the risk of VB compared to lenvatinib treatment in real-world practice. Therefore, concerns regarding the increased risk of bleeding from Atezo–Bev regimen should not preclude choice other systemic therapy regimen instead of Atezo–Bev.

In the present study, 10 patients experienced VB despite the absence of EV on pretreatment EGD. All these patients had PVI at baseline, with 8 having main PVI and 2 having branch PVI. Thus, EV may develop and progress independent of the findings of pretreatment EGD, and portal hypertension may worsen due to HCC itself or deterioration of liver function. In a study from France, Atezo–Bev treatment did not increase EV size between baseline and 6 months of treatment, regardless of PVI.(8) However, in the present study, 4 (66.7%) of 6 patients who experienced VB during treatment showed an increase in EV size, indicating that the risk of VB can change during the course of treatment. Additionally, of these 10 patients who developed VB without EV on pretreatment EGD, four had a platelet <100,000/mm3, indicating

a risk of VB. This also emphasizes that if a patient carries risk factors that we identified, VB can occur during the treatment, despite the lack of EV on pretreatment EGD.

Appropriate prophylactic measures to prevent VB should be carried out during management of HCC given that most patients with HCC had underlying chronic liver disease, mostly liver cirrhosis. In the present study, 48.3% of the patients with EV on pretreatment EGD received prophylaxis, and 73.4% of the patients classified as VNT were managed with appropriate prophylactic measures. However, not all patients cannot receive beta-blockers or EVL as prophylaxis in real-world settings due to patient's intolerability or limited resources. Patients who receive prophylaxis for VB had a significantly higher risk of VB than those without prophylaxis. However, this does not mean that prophylaxis was not effective or that appropriate prophylaxis was not given to our patients. Currently, the indication of prophylaxis for VB is generally determined by the status of EV mostly from EGD, as in the present study. However, this recommendation is applicable to patients with liver cirrhosis, and not for patients with advanced HCC who may have additional risks for VB due to HCC itself. In the present study, patients receiving prophylaxis had a higher CP score and a higher proportion of PVI, platelet < 100,000/mm3, and a history of GI bleeding than those without prophylaxis (Table 4). This means that patients who received prophylaxis originally had a higher risk of VB than those without prophylaxis despite appropriate prophylaxis measure and that both the findings of EV from EGD and the patient characteristics (history of GI bleeding) and tumor

(PVI) and advanced liver disease (lower platelet count) can influence the actual risk of VB for these patients receiving Atezo–Bev or lenvatinib treatment. Thus, prophylaxis for VB might be indicated by the presence of EV on pretreatment EGD as well as patient or tumor characteristics prior to systemic treatment.

Table 4. Comparison of baseline characteristics between patients with and without prophylaxis with confirmed esophageal varices on pretreatment EGD

Characteristics	Prophylaxis (N=84)	Without prophylaxis (N=84)	*P*
Demographics			
Treatment Atezolizumab-Bevacizumab Lenvatinib	 69 (82.1) 15 (17.9)	 63 (70.0) 27 (30.0)	0.090
Age, years [mean ± SD]	58.3 ± 10.7	61.0 ± 9.8	0.079
Etiology of liver disease Hepatitis B virus Hepatitis C virus Alcoholic liver disease Others	 71 (84.5) 2 (2.4) 5 (6.0) 6 (7.1)	 63 (70.0) 9 (10.0) 6 (6.7) 12 (13.3)	0.078
Ascites, present	31 (36.9)	28 (31.1)	0.518
Laboratory findings			
Median ALT, [IQR]	32.0 [20.5–51.0]	30.0 [17.0–61.0]	0.871
Median albumin, [IQR]	3.2 [2.9–3.5]	3.3 [2.9–3.7]	0.086
Median platelet, ×1000/mm^3 [IQR]			
Median PT, INR [IQR]	1.2 [1.1–1.3]	1.1 [1.0–1.2]	0.000
Median total bilirubin, mg/dL [IQR]	1.0 [0.7–1.9]	0.8 [0.5–1.3]	0.005
Median creatinine, mg/dL [IQR]	0.8 [0.7–0.9]	0.8 [0.7–1.1]	0.298
Child-Pugh class A B	 49 (58.3) 28 (33.3)	 49 (54.4) 34 (37.8)	0.829
ALBI	-0.2[-0.4-0.0]	-0.4 [-0.6–-0.2]	0.003
MELD	8.1 [7.5–9.3]	7.4 [6.9–8.3]	0.000
Tumor characteristics			
Macrovascular invasion, present	55 (65.5)	55 (61.1)	0.660
Portal vein invasion, None Branch vascular invasion of PV Main or bilateral vascular	53 (63.1) 31 (36.9) 14 (16.7) 39 (46.4)	54 (60.0) 36 (40.0) 16 (17.8) 38 (42.2)	0.792
Extrahepatic metastasis, present	35 (41.7)	42 (46.7)	0.609
Endoscopic findings			
History of gastrointestinal bleeding	15 (17.9)	2 (2.2)	0.001
EV Grade 1 Grade 2/3	84 (100.0) 42 (50.0) 42 (50.0)	90 (100.0) 78 (86.7) 12 (13.3)	0.000
EV with red color signs	35 (41.7)	9 (10.0)	0.000
Varices needing treatment	45 (53.6)	16 (17.8)	0.000
Prophylaxis with beta-blocker	59 (70.2)	0 (0.0)	0.000

Importantly, the median duration of VB after the first dose of Atezo–Bev was 3.1 months in our study, which corresponds to 5–6 cycles of Atezo–Bev treatment. Given that the progression-free survival in the updated IMbrave 150 trial was 6.9 months, VB may interrupt the early course of Atezo–Bev treatment, despite its efficacy against HCC. This also highlights the significance of appropriate prophylaxis for VB, and clinicians should constantly be made aware of the potential risk of VB during the treatment period.

Our simple prediction model PV100 had four elements and accurately predicted the probability of VB based on patients' baseline characteristics. Patients in our model' low-risk group may not need to be concerned about VB during the treatment given the incidence of VB was almost zero. However, the incidence of VB in the intermediate- and high-risk groups was 5.3% and 11.0%, respectively, at 6 months. This suggests that patients in these groups should consider appropriate prophylaxis for VB prior to first-line systemic treatment. Additionally, patients in the high-risk group should carefully consider treatment regimen to alleviate the risk of VB as low as possible with appropriate choice of treatment regimen which is less vulnerable for bleeding, such as tremelimumab.(15, 18, 19)

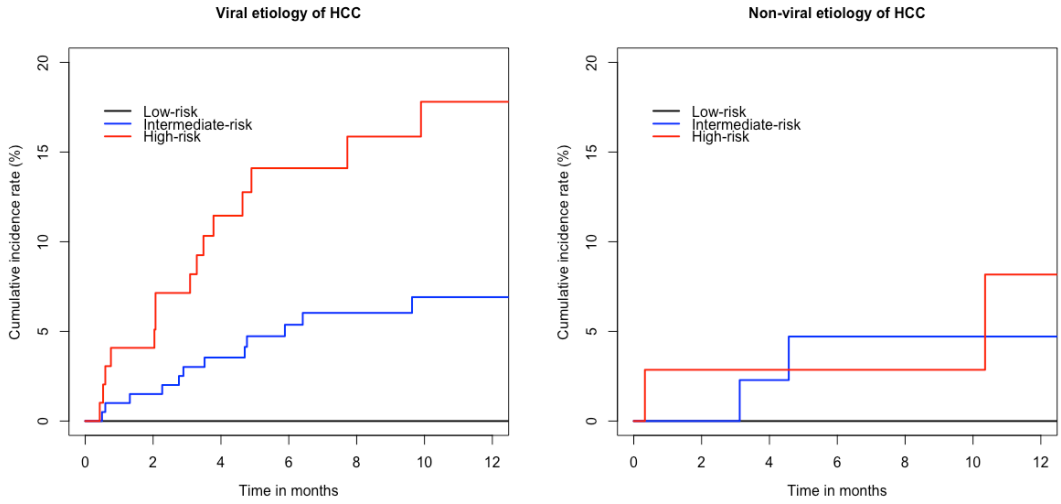
Our study has several strengths. First, we included patients with available data on pretreatment EGD, which allowed evaluation of the association between pretreatment EGD findings and VB risk. Second, to the best of our knowledge, we have the largest sample size of 585 patients from actual clinical practice on this topic. Third, before initiating Atezo–Bev

or lenvatinib treatment, we proposed a simple and readily applicable model (PV100) to predict the risk of VB. Finally, the risk of VB was compared between patients receiving Atezo–Bev and lenvatinib treatment, both widely used regimen as the first-line systemic treatment for advanced HCC. The risk of VB was not significantly different between groups, suggesting that patient's and tumor characteristics are more important that treatment regimen itself to determine the risk of VB.

Our study has some limitations. First, due to its retrospective nature, selection bias was unavoidable. However, we attempted to minimize bias by including consecutive patients receiving Atezo–Bev or lenvatinib treatment, which allowed us to replicate real-world clinical practice. Second, the decision to administer prophylaxis for VB was based on physicians' discretion rather than uniformed protocol as we aimed to gather real-world data. Additionally, our study population was predominantly composed of patients with HBV infection, who had a higher risk of VB following Atezo–Bev treatment than those without HBV infection. Our predictive model demonstrated better performance in patients with HBV infection than those without HBV infection (Figure 3). However, due to the small number of patients experiencing VB in the non-HBV population, the predictive performance of our model may be attenuated in this subgroup. Further studies are needed and should involve a large number of HCC patients with different etiologies. Lastly, we did not investigate possible association between

the tumor response and the risk of VB. If the tumor is responded from the Atezo–Bev or lenvatinib treatment, the risk of VB may decrease by alleviating portal hypertension.

Figure 3. Cumulative incidence of variceal bleeding based on the PV100 model and the etiology of hepatocellular carcinoma



Conclusion

In conclusion, low platelet count, PVI, and VNT on pretreatment EGD were associated with an increased risk of VB following Atezo–Bev or lenvatinib treatment for advanced HCC. We proposed a simple and easily applicable web model to predict the risk of VB following Atezo–Bev or lenvatinib treatment according to the patients' characteristics at baseline. Thus, for safer systemic treatment for advanced HCC, prophylaxis and regular monitoring of VB should be emphasized.

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국문요약

배경 및 목적: 아테졸리주맙-베바시주맙 또는 렌바티닙 치료를 받는 간세포암 환자에서 정맥류 출혈의 실제 위험에 관한 데이터는 제한적이다. 이 연구는 아테졸리주맙-베바시주맙 또는 렌바티닙 치료를 받는 진행성 간세포암 환자의 정맥류 출혈의 위험을 평가하고, 정맥류 출혈에 대한 예측 모델을 구축하기 위해 수행되었다.

방법: 이 연구는 후향적 연구로 2018 년에서 2023 년까지 서울아산병원, 세브란스병원에서 아테졸리주맙-베바시주맙(476 명) 또는 렌바티닙(109 명)치료 전 위내시경을 시행한 585 명의 간세포암 환자를 대상으로 하였다. 일차 평가변수는 임상적으로 확인된 정맥류 출혈이다.

결과: 585 명의 환자 중 31 명에서 정맥류 출혈이 발생했으며 (6 개월에 4.7%, 12 개월에 6.2%), 두 치료 간 정맥류 출혈의 위험에는 유의한 차이가 없었다. 평균 추적 기간은 6.1 개월이었다. 정맥류 출혈로 사망한 환자는 없었다. 다변량 분석에서 정맥류 출혈 위험 증가와 관련된 요인은 간문맥 침범(PVI, subdistribution hazard ratio: 3.30, 95% confidence interval [CI]: 1.44-7.58), 혈소판 <100,000 mm^3 (SHR: 2.59, 95% CI: 1.23-5.45) 및 치료가 필요한 정맥류(VNT, SHR: 3.79, 95% CI: 1.76-8.17)로 나타났다. 우리는 간문맥 침범,

낮은 혈소판 수, 치료가 필요한 정맥류 및 출혈 병력으로 구성된 PV100 이라는 예측 모델을 개발하였다.

결론: 간문맥 침범, 낮은 혈소판 수, 치료가 필요한 정맥류는 간세포암 환자에게 아테졸리주맙-베바시주맙 또는 렌바티닙 치료 후 정맥류 출혈의 위험을 증가시키는 요인으로 확인되었다. PV100 모델은 정맥류 출혈의 실제 위험을 예측하고 평가할 수 있다.