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ORIGINAL RESEARCH

The Real-World Prevalence of Esophagogastric Varices, Bleeding, Emergency Room Visits, and Hospitalization Among Patients with Advanced Hepatocellular Carcinoma in the United States: A Retrospective Cohort Study

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Purpose: Esophagogastric varices (EGV) and upper gastrointestinal bleeding are common and potentially fatal complications in patients with advanced hepatocellular carcinoma (aHCC). We aimed to evaluate the real-world prevalence of EGV among the aHCC population in the United States.

Patients and Methods: This retrospective cohort study utilized IQVIA's PharMetrics Plus Health Plans Claims database between January 1, 2016, and July 31, 2021 (study period). Adult patients with an aHCC diagnosis who initiated systemic therapies were included, while those with any secondary malignancies or prior liver transplant at baseline were excluded. The date of therapy initiation was the index date; baseline characteristics, prior procedures, and clinical events of interest were captured during the 12-month pre-index (baseline) period. Patients were followed for clinical outcomes (EGV- or bleeding-related emergency room [ER] visits or hospitalization) during the 6-month post-index period. Logistic regression was conducted to identify key predictors of post-index EGV- or bleeding-related ER visit or hospitalization.

Results: 904 patients with aHCC were included in the study (mean age: 61.3 years; 75.3% male). Sorafenib (423 patients, 46.8%) was the most prescribed aHCC treatment. During the entire study period, 458 patients (50.7%) underwent an esophagogastroduodenoscopy (EGD), of whom 209 (45.6%) had post-index EGV. Among 327 patients (36.2%) with a baseline EGD, 175 (53.5%) were diagnosed with EGV and 50 (15.3%) had variceal bleeding; 141 patients (15.6% of all patients) experienced ≥1 EGV- or bleeding-related ER visit or hospitalization post-index.

Conclusion: There is a high prevalence of EGV in patients with aHCC. The presence of EGV, gastrointestinal bleeding, and portal hypertension–related comorbidities was associated with an increased risk of subsequent EGV- or bleeding-related ER visits or hospitalizations in patients with aHCC. Assessment and stratification of varices should be considered in patients with aHCC before initiating systemic therapies to inform treatment decisions.

Keywords: advanced hepatocellular carcinoma, esophagogastric varices, esophagogastroduodenoscopy, healthcare utilization, variceal bleeding

Introduction

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related death worldwide and accounts for the vast majority of liver cancer cases.[1] The high mortality associated with HCC is, in part, due to the competing risk associated with concomitant cirrhosis, which is present in over 80% of patients in the United States (US).[2,3] The prognosis of advanced HCC

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(aHCC) is poor, with 1-year survival rates of 14%.[4] Further, aHCC is associated with substantial healthcare resource utilization in the US with an estimated median annual direct cost of $176,456 per patient (2013 dollars).[5]

Among patients with aHCC and cirrhosis, esophagogastric varices (EGV) resulting from portal hypertension (PH) are a major complication that increase the risk of mortality.[6,7] PH develops in patients with HCC through multiple mechanisms, including 1) increased vascular resistance from morphological changes in the liver parenchymal architecture that are linked to chronic inflammation and angiogenesis, and 2) direct portal vascular invasion of HCC causing elevation in portal pressures.[6,7] Complications of PH, including EGV and EGV-related bleeding, ascites, hepatic encephalopathy, and hepatorenal syndrome carry a significant risk of morbidity and mortality in these patients.[6,7] Certain systemic therapies, including vascular endothelial growth factor receptor (VEGFR) inhibitors (eg, bevacizumab, sorafenib), may increase the risk of bleeding. Consequently, esophagogastroduodenoscopy (EGD), the gold standard for diagnosing EGV, is recommended prior to initiation of selected systemic treatments for HCC.[6–9] However, the prevalence of EGV among the aHCC population in the US is not well understood, nor are the predictors of EGV- or bleeding-related complications for patients who are on systemic therapies for aHCC.

Real-world studies detailing the prevalence of EGV and subsequent bleeding risk in patients with aHCC receiving systemic therapies are lacking. We aimed to evaluate clinical outcomes, including EGV and bleeding events, in a real-world cohort of patients diagnosed with aHCC. The primary objective was to evaluate the prevalence of EGV and bleeding events, as well as potential pre-index factors that may predict EGV- or bleeding-related ER visits or hospitalizations.

Materials and Methods

Study Design

This retrospective cohort analysis was conducted utilizing IQVIA's PharMetrics® Plus Health Plans Claims database. PharMetrics® Plus comprised longitudinal, adjudicated administrative claims data for more than 150 million unique health plan members across the US at the time of the study.[10] Data included inpatient and outpatient diagnoses and procedures, retail and mail order prescription records, pharmacy and medical benefit information, inpatient stay and provider details, demographic variables, product type, payer type, health plan enrollment dates, and payments.[10]

Patients with aHCC with ≥1 claim for bevacizumab, cabozantinib, lenvatinib, ramucirumab, regorafenib, sorafenib, ipilimumab, nivolumab, pembrolizumab, or atezolizumab from January 1, 2017 through July 31, 2021 were selected for inclusion in the study (Figure 1); the date of the first qualifying prescription claim was considered the index date.

Study Population

As illustrated in Figure 2, patients with ≥1 claim for bevacizumab, cabozantinib, lenvatinib, ramucirumab, regorafenib, sorafenib, ipilimumab, nivolumab, pembrolizumab, or atezolizumab from January 1, 2017 through January 31, 2021 who met the following criteria were included in the study: 1) continuous enrollment for ≥12 months immediately preceding the index date (pre-index or baseline period); 2) continuous enrollment for ≥6 months starting on and following the index date (post-index or follow-up period) (applicable only to patients who were alive for ≥6 months from index date); 3) ≥1 claim

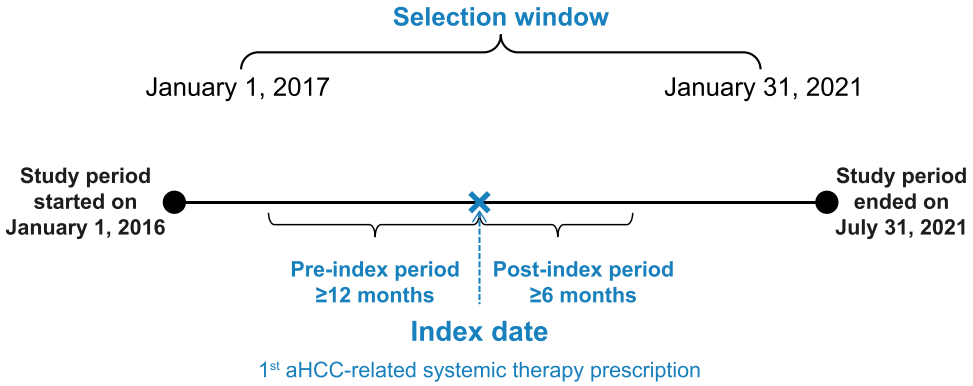

Figure 1 Study Design.
Abbreviation: aHCC, advanced hepatocellular carcinoma.

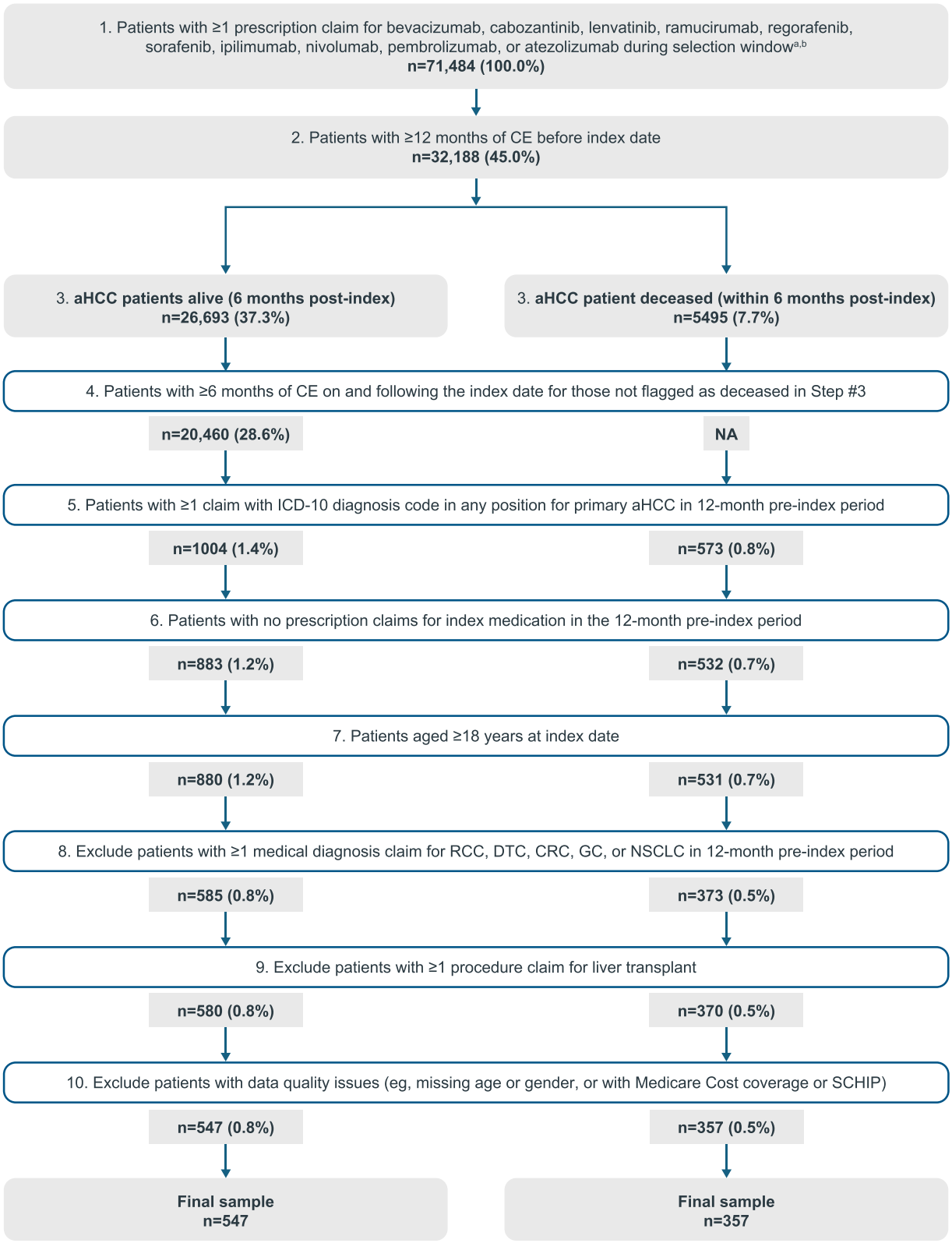

Figure 2 Study Attrition of aHCC Cohort by Survival Status Within 6 Months Post-index. [a]Selection window: January 1, 2017, through January 31, 2021. [b]Date of first such prescription serves as the index date.

Abbreviations: aHCC, advanced hepatocellular carcinoma; CE, continuous enrollment; CRC, colorectal cancer; DTC, differentiated thyroid carcinoma; GC, gastric cancer; ICD, International Classification of Diseases; NSCLC, non-small cell lung carcinoma; RCC, renal cell carcinoma; SCHIP, State Children's Health Insurance Program.

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with an International Classification of Diseases (ICD)-10 diagnosis code in any position for primary aHCC in the 12-month baseline period; 4) no prescription claims for any qualifying index medication in the 12-month baseline period; and 5) age ≥18 years on index date. Patients were excluded if they met any of the following criteria: 1) ≥1 medical diagnosis claim for any of the following malignancies in the 12-month baseline period: renal cell carcinoma, differentiated thyroid carcinoma, colorectal cancer, gastric cancer, non-small cell lung carcinoma; 2) liver transplant recipient; 3) patients with incomplete data or data quality issues (eg, missing gender, region, or health plan enrollment dates, or patients with Medicare Cost coverage or the State Children's Health Insurance Program).

A death proxy algorithm developed for claims-based analyses was employed to identify overall mortality, as well as the subset of deaths attributable to bleeding events within 6 months after the index date. For all patients, we identified claims that included any primary aHCC diagnosis with a mortality claim and flagged the date of the last mortality claim (A). Thereafter, we identified all medical claims with aHCC diagnosis after the date of the last mortality claim and flagged the date of the last medical claim (B). If the date of the last mortality claim (A) was equal to the date of the last medical claim (B), then the date was flagged as the approximate death date. If the patient had no medical claims >30 days from A to the end of the study period or the end of insurance coverage, then flag B was considered to be the approximate death date. If ≥30 days had transpired from A to the end of the study period or the end of eligibility, a mortality flag was not attached to the patient.

Study Measures

Among all patients, baseline patient demographics were measured as of their respective index date, and included age, gender, geographic region, payer type, health plan type, and year of index date. Baseline clinical characteristics (comorbidities and prior medication exposure) were measured over the 12-month baseline period, as were clinical events of interest (EGD, EGV, and variceal and non-variceal bleeding events), which were based on claims with applicable ICD-10, CPT-4, National Drug Code (NDC), and Healthcare Common Procedure Coding System (HCPCS) codes.

The incidence of bleeding events was reported among all patients with EGD during the baseline period, as well as among patients with EGV during baseline. Time from these clinical events to the date of index medication (mean, standard deviation [SD], median) was also reported. Prophylaxis for varices, including banding and non-selective beta-blocker use (carvedilol, propranolol, nadolol), was evaluated among patients with baseline EGV. Among the subset of patients whose index medication was atezolizumab, the proportion of patients with ≥1 prescription for bevacizumab (n, %) was reported, as the combination of atezolizumab and bevacizumab carries an increased risk of gastrointestinal bleeding.[11]

Outcome Events

Outcome events of interest included EGV, bleeding events (variceal or non-variceal), and EGV- or bleeding-related emergency room (ER) visits or hospitalization, which were reported over the 6-month follow-up period (including the index date) for the overall cohort, except for EGV which was reported only for patients with pre- or post-index EGD. Event-specific ER visits and hospitalizations were defined as claims with a diagnosis code for the clinical event in any position for inpatient or outpatient claims. Post-index EGD was not reported as this procedure was not part of clinical practice post-treatment initiation at the time of the study. A composite endpoint of post-index EGV- or bleeding-related ER visit or hospitalization was evaluated in multivariate analysis to identify potential pre-index factors associated with post-index clinical outcomes.

Statistical Analysis

Descriptive analyses were used to examine baseline demographics and clinical patient characteristics, as well as post-index clinical outcomes. All categorical variables were summarized with frequency and percentage. All continuous variables were summarized and reported with mean, SD, and median. Continuous variables were also categorized into appropriate intervals as relevant.

Logistic regression was conducted to identify the key predictors of EGV- or bleeding-related ER visit or hospitalization during the follow-up period. The dependent variable was evidence of ≥1 bleeding-related ER visit or hospitalization in the 6-month follow-up period. Covariates considered for inclusion into the models included a priori designated demographic and clinical variables. Collinearity among the variables of interest was evaluated during model development via association reports. A backwards stepwise approach for variable selection was used (P<0.10 for inclusion and

retention). Results for the model were presented in terms of odds ratios (exponentiated beta coefficients) along with corresponding 95% confidence intervals (CIs). All tests were conducted assuming a two-tailed test of significance, and a P value <0.05 was considered statistically significant for all analyses of outcome measures. A Cox proportional hazards model was used to identify predictors of survival among patients with aHCC.

Analyses were conducted using SAS® Release 9.4 (SAS, Cary, NC).

Results

Cohort Characteristics

A total of 904 patients with aHCC met study eligibility criteria and were included in the study cohort, 357 (39.4%) of whom were deceased within 6 months of their index date (Figure 1). The mean age of the cohort was 61.3 years (SD: 8.6), and 84.3% were aged 55 or older, 75.3% were male, and 45.9% were located in the South US region. For insurance payer profile, 61.9% of patients had commercial insurance and 26.9% were self-insured (Table 1).

Table 1 Baseline Demographics and Patient Characteristics for the Overall aHCC Cohort

Characteristics	aHCC Cohort (N=904)	
	n	%
Age		
Mean (SD)	61.3 (8.6)	
Median	62	
Age group		
18–34	10	1.1%
35–44	26	2.9%
45–54	106	11.7%
55–64	504	55.8%
≥65	258	28.5%
Gender		
Female	223	24.7%
Male	681	75.3%
Geographic region		
Northeast	165	18.3%
Midwest	206	22.8%
South	415	45.9%
West	118	13.1%
Payer type		
Commercial	560	61.9%
Medicaid	10	1.1%
Medicare Risk	86	9.5%
Self-insured	243	26.9%
Other/Unknown	5	0.6%
Health plan type		
Consumer-directed health care	26	2.9%
Health maintenance organization (HMO)	229	25.3%
Indemnity	6	0.7%
Point-of-service (POS)	54	6.0%
Preferred provider organization (PPO)	584	64.6%
Other/Unknown	5	0.6%

(*Continued*)

Table 1 (Continued).

Characteristics	aHCC Cohort (N=904)	
	n	%
Index year		
2017	233	25.8%
2018	227	25.1%
2019	196	21.7%
2020	228	25.2%
2021	20	2.2%

Abbreviations: aHCC, advanced hepatocellular carcinoma; SD, standard deviation.

Baseline Clinical Characteristics

The most common comorbidities at baseline are shown in Figure 3, and included liver cirrhosis (77.8%), hypertension (66.8%), and chronic viral hepatitis C (41.3%). Systemic therapy used by the patients at the index date is shown in Figure 4. Nearly half of the patients (46.8%, n=423) were prescribed sorafenib at their index date. Other prescribed index medications included lenvatinib (16.2%, n=146), nivolumab (13.7%, n=124), pembrolizumab (7.9%, n=71), atezolizumab and bevacizumab combination therapy (7.1%, n=64), atezolizumab (3%, n=27), and nivolumab and ipilimumab combination therapy (2.4%, n=22). Among the 27 patients whose index medication was atezolizumab, 4 (14.8%) had ≥1 prescription(s) of bevacizumab at a later point.

During the entire study period, 458/904 patients (50.7%) with aHCC underwent an EGD. During the baseline period, 327/904 aHCC patients (36.2%) underwent an EGD, at a mean (SD) and median of 132.1 (111.7) and 96 days, respectively, prior to initiating the index medication.

Among the 327 patients with baseline EGD, 175 (53.5%) had EGV, 50 (15.3%) had variceal bleeding, and 19 (5.8%) had non-variceal bleeding during the baseline period (Table 2). Patients with a variceal bleeding event during baseline had a longer time until their index medication than patients with a non-variceal bleeding event (mean/median 149.8/128 and

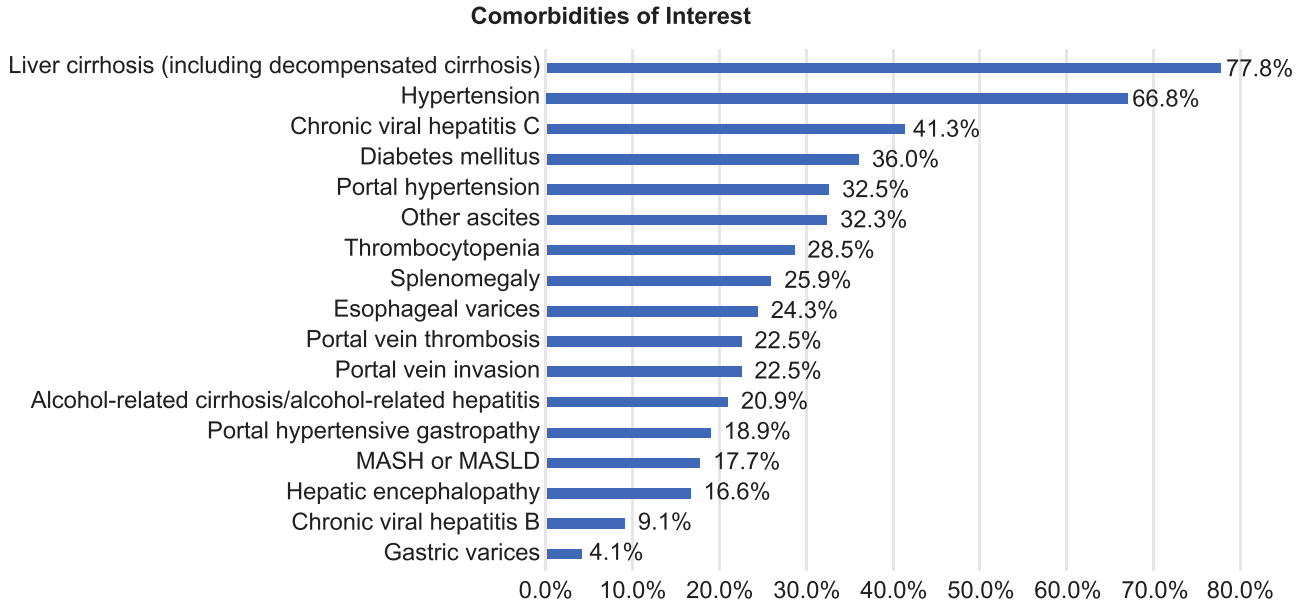

Figure 3 Prevalence of Baseline Comorbidities of Interest of the aHCC Cohort, by Condition.
Abbreviations: aHCC, advanced hepatocellular carcinoma; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease.

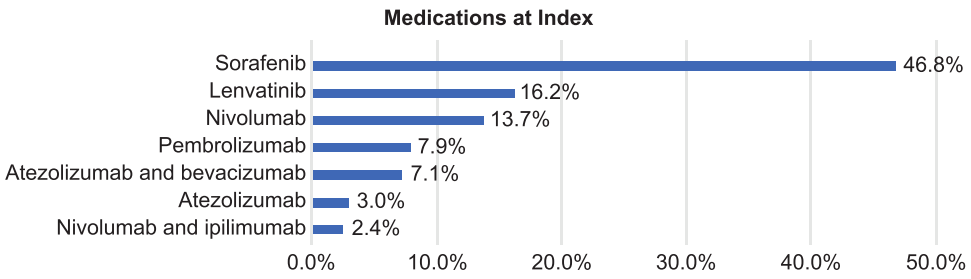

Figure 4 Distribution of Index Medication Use Profile of the aHCC Cohort. The medications that were used less than 1% as the index medication were excluded from the chart.
Abbreviation: aHCC, advanced hepatocellular carcinoma.

121.4/56 days, respectively). Among the 175 patients with EGV during the baseline period, the most common prophylactic or therapeutic treatments were non-selective beta-blockers (83/175 patients; 47.4%) and banding (69/175 patients; 39.4%).

Outcomes

In total, 96/904 patients (10.6%) overall had a post-index bleeding event, of whom 77 (80.2%) had undergone EGD (pre- or post-index) prior to post-index bleeding. Overall, 28 patients (3.1%) had a non-variceal bleeding event, including 17 patients (60.7%) with prior EGD. Of the 458 patients who underwent EGD during the entire study period, 209 (45.6%) had EGV during the post-index period and, of these, 73/209 (34.9%) had a variceal bleeding event. Patients had an average of 1.4 clinical encounters with an EGV diagnosis and 1.3 variceal bleeding events during the 6-month follow-up

Table 2 Prevalence of Clinical Events During Baseline in the aHCC Cohort

Clinical Events	**EGD Cohort (n=327)**	
	n	**%**
Patients with EGV	175	53.5%
Time from EGV to index medication, in days Mean (SD) Median	166.5 (122.7) 160	
Patients with bleeding events: variceal	50	15.3%
Time from variceal bleeding event to index medication, in days Mean (SD) Median	149.8 (117.8) 128	
Patients with bleeding events: non-variceal	19	5.8%
Time from non-variceal bleeding event to index medication, in days Mean (SD) Median	121.4 (124.9) 56	
Clinical Events	**EGV Cohort (n=175)**	
	n	**%**
Patients with bleeding events: variceal	50	28.6%
Time from variceal bleeding event to index medication, in days Mean (SD) Median	149.8 (117.8) 128	

(*Continued*)

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Table 2 (Continued).

Clinical Events	EGV Cohort (n=175)	
	n	%
Patients with bleeding events: non-variceal	12	6.9%
Time from non-variceal bleeding event to index medication, in days		
Mean (SD)	158.3 (144.2)	
Median	98	
Prophylaxis for varices		
Banding	69	39.4%
Non-selective beta-blockers (carvedilol, propranolol, nadolol)	83	47.4%
TIPS procedure	3	1.7%

Abbreviations: aHCC, advanced hepatocellular carcinoma; EGD, esophagogastroduodenoscopy; EGV, esophagogastric varices; SD, standard deviation; TIPS, transjugular intrahepatic portosystemic shunt.

period (Table 3). There was no statistically significant difference in time to death between patients with and without EGV (mean [SD] 81.9 [49.4] vs 73.8 [47.5] days; P=0.16) or with and without bleeding events (mean [SD] 81.0 [52.5] vs 75.4 [47.6] days; P=0.51). During the post-index period, 141/904 patients (15.6%) had ≥1 EGV- or bleeding-related ER visit or hospitalization. Among the different clinical events of interest, EGV-related ER visits and hospitalizations were most common, reported in 2.7% and 13.6% of patients, respectively. Bleeding-related ER visits and hospitalizations were reported in 1.0% and 7.0% of patients, respectively. Among all patients, 173/904 (19.1%) used non-selective beta blockers (carvedilol, propranolol, or nadolol) in the post-index period.

Multivariate Analysis

In the adjusted logistic regression analysis, having baseline EGV without bleeding (odds ratio: 3.1, 95% CI 1.94–4.93) and baseline bleeding with or without EGV (odds ratio: 4.5, 95% CI 2.56–8.03) were associated with having a post-index EGV- or a bleeding-related ER visit or hospitalization when compared with patients without those baseline risk factors. The baseline presence of PH–related comorbidities was associated with 3.1 times greater odds (95% CI: 1.55–6.12) of having a post-index outcome. The predictors of post-index EGV- or bleeding-related ER visit or hospitalization are shown in Table 4.

In the Cox proportional hazards model to identify the predictors of survival among patients with aHCC, no association was found between risk of death and gender, presence of comorbidities, use of bevacizumab, or baseline EGV/bleeding composites (Table 5).

Table 3 Number of Clinical Events per Patient During the Follow-up Period in the aHCC Cohort

Clinical Events, n per Patient	aHCC cohort (N=904)	
	Mean (SD)	Median
Clinical encounter with EGV	1.4 (2.7)	0
Any bleeding event	1.1 (2.0)	0
Any bleeding event subsequent to EGD	1.1 (1.9)	0
Any bleeding event in the absence of EGD	0.7 (1.0)	0
Bleeding events – variceal	1.3 (2.1)	0
Bleeding events – non-variceal	0.6 (1.1)	0

Abbreviations: aHCC, advanced hepatocellular carcinoma; EGD, esophagogastroduodenoscopy; EGV, esophagogastric varices; SD, standard deviation.

Table 4 Predictors of Post-Index EGV- or Bleeding-Related ER Visit or Hospitalization in the aHCC Cohort in the Logistic Regression Model[a]

Variable	Odds Ratio	Standard Error	Wald 95% Confidence Limits		*P* value
			Lower Limit	Upper Limit	
Age group, years (ref: ≥65)					
18–34	<0.001	36,684.9	<0.001	NA[c]	1.000
35–44	2.026	0.594	0.633	6.483	0.234
45–54	1.364	0.354	0.682	2.730	0.380
55–64	1.524	0.238	0.956	2.430	0.077
Gender (ref: male)					
Female	0.732	0.251	0.447	1.197	0.213
Comorbidities of interest (ref: absent)					
Any portal hypertension–related comorbidity[b]	3.082	0.350	1.552	6.119	0.001
Baseline EGV/bleeding composite (ref: no EGV or bleeding)					
EGV without bleeding	3.096	0.238	1.944	4.932	<0.0001
Bleeding with or without EGV	4.532	0.292	2.557	8.034	<0.0001

Notes: [a]Variables selected based on the stepwise approach. [b]Comorbidities include portal hypertension, thrombocytopenia, splenomegaly, portal vein invasion, hepatic encephalopathy, other ascites, portal vein thrombosis, decompensated cirrhosis. [c]The upper confidence limit cannot be generated due to small sample size and high standard error.

Abbreviations: aHCC, advanced hepatocellular carcinoma; EGV, esophagogastric varices; ER, emergency room; NA, not applicable; ref, reference.

Table 5 Cox Proportional Hazards Model to Identify Potential Predictors of Survival Among Patients with aHCC[a]

Variable	Hazard Ratio	Standard Error	Wald 95% Confidence Limits		*P* value
			Lower Limit	Upper Limit	
Gender (ref: male)					
Female	0.960	0.135	0.736	1.252	0.763
Comorbidities of interest (ref: absent)					
Any portal hypertension–related comorbidity[b]	1.146	0.143	0.866	1.516	0.340
Any bevacizumab (including combinations) (ref: no bevacizumab)					
Any bevacizumab	1.153	0.233	0.731	1.819	0.540
Baseline EGV/bleeding composite (ref: no EGV or bleeding)					
EGV without bleeding	1.012	0.150	0.754	1.357	0.939
Bleeding with or without EGV	1.138	0.219	0.740	1.750	0.555

Notes: [a]Variables selected based on the stepwise approach. [b]Comorbidities include portal hypertension, thrombocytopenia, splenomegaly, portal vein invasion, hepatic encephalopathy, other ascites, portal vein thrombosis, decompensated cirrhosis.

Abbreviations: aHCC, advanced hepatocellular carcinoma; EGV, esophagogastric varices; ref, reference.

Discussion

Our study presents novel data regarding the prevalence and outcomes related to EGV among patients with aHCC in the US. We found a high prevalence of EGV in patients with aHCC and the presence of EGV and/or bleeding during the baseline period was associated with increased risk of post-index EGV- or bleeding-related ER visits or hospitalization. However, we did not find that EGV or bleeding events prior to the initiation of systemic therapy were associated with survival. Utilization of systemic therapy in patients with aHCC was aligned with clinical practice guidelines.

Atezolizumab combined with bevacizumab has emerged as a new standard of care in first-line HCC treatment after demonstrating clinically meaningful efficacy and acceptable safety.[8,12–14] Bleeding, however, is a known adverse event of bevacizumab.[12,13,15] In the registrational Phase 3 IMbrave150 trial, the incidence of gastrointestinal bleeding was 7% in patients treated with atezolizumab and bevacizumab, versus 4.5% in patients treated with sorafenib.[13] In line with these findings, consensus guidelines developed since the approval of first-line atezolizumab and bevacizumab, including those from the US, United Kingdom, and China, recommend variceal risk assessment prior to initiation of this combination treatment, in order to mitigate the risk of bleeding.[8,12,16,17] The incidence of gastrointestinal bleeding events may be higher in real-world settings since the IMbrave150 study required EGD before enrollment and excluded untreated or incompletely treated EGV.[13,14] Indeed, our study showed a GI bleeding incidence of 15.6% during the post-index period. Potential reasons for such differences could include the selection of lower risk patients in clinical trials, and the potential for worse liver function and the presence of PH in real-world cohorts. However, a retrospective study conducted in Hong Kong, in which patients underwent endoscopy prior to treatment initiation, reported no bleeding-related adverse events with atezolizumab and bevacizumab despite patients having poor baseline liver function, suggesting that bleeding risks can be managed even in those with suboptimal liver function if patients undergo routine EGD prior to treatment.[18]

We have shown an EGV prevalence of 45.6% among those receiving EGD in our cohort, which is consistent with similar real-world studies conducted outside the US. An Italian cohort study showed esophageal varices were found in 63.3% of patients with HCC, and patients with varices had significantly shorter survival compared with patients without varices. The presence of esophageal varices was specifically associated with a higher risk of death from gastrointestinal bleeding.[19] Another Italian cohort study included 150 patients who received sorafenib for a mean period of 4.6 months. Patients with medium/large esophageal varices and those with previous bleeding were treated with propranolol, and 8% of patients bled from esophageal varices during sorafenib treatment. The study reported that portal vein tumor thrombus was the strongest independent predictor of bleeding.[20] A retrospective study conducted in Taiwan investigated 990 treatment-naïve patients with HCC who received an EGD at the time of HCC diagnosis, of which 480 (48.5%) had EGV. Patients with EGV had a significantly lower cumulative 5-year survival rate than those without EGV (24.9% vs 46.4%, $P<0.001$).[21]

This study has inherent limitations due to its retrospective, observational nature, including the potential for selection bias given that patients with EGV risk factors may be more likely to undergo EGD and therefore more likely to be diagnosed with EGV. That outcomes were assessed only in patients who underwent an EGD also limits the conclusions that can be drawn with regard to the potential impact of risk stratification. Lastly, while claims data are valuable for the efficient and effective examination of health outcomes, such databases may lack generalizability because the claims are collected for the purpose of payment within the commercially insured population and not for clinical research.

Notwithstanding these limitations, our results are largely consistent with the published literature and support the importance of early detection, intervention, and personalized care for varices in aHCC that could enhance patient outcomes and reduce the potential burden of EGV and bleeding events on patients and healthcare resources. While attainment of EGD can be a barrier to care, accurate assessment of high-risk varices is essential in optimizing outcomes in this population. A recent analysis showed the promise of non-invasive assessment of high-risk varices, which could help in removing this barrier to care in patients with aHCC.[9]

Conclusion

EGV and bleeding events are common in patients with aHCC prior to the initiation of systemic therapies and during active treatment. Our study presents novel US-based data, demonstrating an EGV prevalence of 45.6% among those who have undergone an EGD, consistent with findings from similar studies conducted outside the US. The presence of bleeding, EGV, and PH-related comorbidities before treatment initiation was associated with increased post-treatment risk of EGV- or bleeding-related ER visits or hospitalization for these patients. Risk stratification of varices should be routinely conducted in patients with aHCC before the initiation of systemic therapies.

Ethics Statement

The PharMetrics Plus database is fully compliant with the Health Insurance Portability and Accountability Act (HIPAA) of 1996. All patient-level data were de-identified to preserve patient anonymity and confidentiality. The Office for Human

Research Protections under the US Department of Health and Human Services does not consider research involving fully de-identified or fully anonymized information to involve human subjects;[22] therefore, institutional review board approval and informed consent were not required for this study.

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Disclosure

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