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BRIEF COMMUNICATION

Correlates, Trends, and Short-Term Outcomes of Venous Thromboembolism in Hospitalized Patients with Hepatocellular Carcinoma

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Abstract

Background and Aim The incidence and overall mortality of hepatocellular carcinoma (HCC) in the US have been increasing over the past decade. Venous thromboembolism (VTE) is a leading cause of morbidity and mortality in cancer patients. This study aims at examining the epidemiology, risk factors, and short-term outcomes of VTE in hospitalized patients with HCC.

Methods We utilized the National Inpatient Sample for the years 2008–2013. Using the International Classification of Diseases codes, ninth edition, we identified hospitalized adult patients with a prior diagnosis of HCC who were diagnosed with VTE. Weighted multivariate logistic regression models were used to examine the effect of patients' sociodemographic and clinical characteristics on the occurrence of VTE, and to evaluate the impact of VTE on in-hospital mortality and length of hospital stay.

Results We identified a total of 54,275 hospitalized patients with a prior diagnosis of HCC. The prevalence of VTE in the study cohort was 2.8% (2.5% in 2008 to 3.0% in 2013, a statistically significant increase).

Older age, African American ethnicity, history of metastasis, and higher Elixhauser comorbidity index were associated with higher odds of VTE. However, having a prior diagnosis of cirrhosis, hepatitis C, or diabetes mellitus were associated with lower odds of VTE in HCC patients. Furthermore, development of VTE was associated with longer hospital stay and increased in-hospital mortality.

Conclusion Our work highlights significant age, racial, and comorbid factors in the development of VTE in hospitalized patients with HCC in the US. These findings can help in stratification of HCC patients according to their VTE risk. Patients at higher risk of VTE may benefit from more aggressive pharmacologic prophylaxis, an area for future investigation.

Keywords Hepatocellular carcinoma · Venous thromboembolism · Health outcomes research · In-hospital mortality · Length of stay

Background and Aim

The incidence and overall mortality of hepatocellular carcinoma (HCC) in the United States (US) have been increasing over the past decade. Venous thromboembolism (VTE) is a leading cause of morbidity and mortality in cancer patients [1]. Identifying risk factors that predict an increased risk of VTE in cancer patient has been the focus of an increasing number of studies [1–6]. Data related to the VTE risk in patients with HCC are limited.

This study aims at examining the epidemiology, risk factors, and short-term outcomes of VTE in hospitalized patients with HCC.

Methods

We utilized the National Inpatient Sample (NIS) for the years 2008–2013. The NIS database is the largest publicly available all-payer inpatient care database in the US, containing data on more than seven million hospital stays each year. This database is publicly available and contains deidentified patient

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data; therefore, the study was deemed exempt by the Institutional Review Board.

Using the International Classification of Diseases codes, ninth edition, we identified hospitalized adult patients with a prior diagnosis of HCC who were diagnosed with VTE, including deep venous thrombosis and pulmonary embolism, and excluding intra-abdominal thrombosis such as hepatic, portal, splenic, and mesenteric venous thrombosis. Weighted multivariate logistic regression models were used to examine the effect of patients' sociodemographic and clinical characteristics on the occurrence of VTE, and to evaluate the impact of VTE on in-hospital mortality and length of hospital stay.

Results

We identified a total of 54,275 hospitalized patients with a prior diagnosis of HCC. The prevalence of VTE in the study cohort was 2.8% (2.5% in 2008 to 3.0% in 2013, a statistically significant increase).

Weighted multivariate analysis (Table 1) indicated that patients aged ≥ 65 versus 18–64 years (OR 1.23, 95% CI 1.10–1.38), African American versus White ethnicity (OR 1.20, 95% CI 1.03–1.39), history of metastasis versus no metastasis (OR 2.11, 95% CI 1.85–2.40), and higher Elixhauser comorbidity index (OR = 1.26, 95% CI 1.23–1.30) were associated with higher odds of VTE. Having a prior diagnosis of cirrhosis (OR 0.59, 95% CI 0.53–0.67), hepatitis C (OR 0.70, 95% CI 0.62–0.79), or diabetes mellitus (OR 0.76, 95% CI 0.67–0.85) was associated with lower odds of VTE in HCC patients. Furthermore, development of VTE was associated with longer hospital stay (OR 2.05, 95% CI 1.84–2.29) and increased in-hospital mortality (OR 1.38, 95% CI 1.19–1.61) (Table 2).

Discussion

Venous thromboembolism is a leading cause of morbidity and mortality in cancer patients [5]. Patients with active malignancies have a four- to sevenfold increased risk of VTE compared to non-cancer patients [2]. The cumulative prevalence of VTE in our study cohort was 2.8%. This has demonstrated a statistically significant increase from 2.5% in 2008 to 3% in 2013. This could be the result of an increased incidence of VTE in HCC patients or increased recognition with wider utilization of imaging tests. These figures are lower than those previously reported in the literature which ranged between 3 and 6.7% [7–9]. A possible explanation for this discrepancy would be exclusion of patients with intra-abdominal venous thrombosis (such as portal venous thrombosis and Budd Chiari syndrome) from our cohort. In addition, our cohort did not include HCC patients who were diagnosed and treated for VTE on an outpatient basis.

Table 1 VTE rates and weighted multilevel logistic regression predicting the occurrence of VTE in hepatocellular carcinoma patients, Nationwide Inpatient Sample, 2008–2013

Characteristics	VTE %	OR (95% CI)[a]	P value
Overall	2.8	-	-
Sex			
Male	1.9	0.95 (0.85 – 1.06)	0.3811
Female	0.9	1.00 [Reference]	
Age (yr.)			
>=65	1.4	1.23 (1.10 – 1.38)	0.0004
<65	1.4	1.00 [Reference]	
Race/ethnicity			
Black	0.49	1.20 (1.03 – 1.39)	0.0184
Hispanic	0.39	0.92 (0.79 – 1.08)	0.3166
Other	0.33	0.90 (0.75 – 1.08)	0.2403
White	1.61	1.00 [Reference]	
Insurance status			
Insured	2.55	0.70 (0.58 – 0.84)	0.0002
Uninsured	0.26	1.00 [Reference]	
Presence of metastasis			
Yes	6.7	2.11 (1.85 – 2.40)	<.0001
No	5.4	1.00 [Reference]	
Presence of cirrhosis			
Yes	6.7	0.59 (0.53 – 0.67)	<.0001
No	5.4	1.00 [Reference]	
Hepatitis B infection			
Yes	6.7	1.18 (0.96 – 1.44)	0.1147
No	5.4	1.00 [Reference]	
Hepatitis C infection			
Yes	6.7	0.70 (0.62 – 0.79)	<.0001
No	5.4	1.00 [Reference]	
Diabetes Mellitus			
Yes	6.7	0.76 (0.67 – 0.85)	<.0001
No	5.4	1.00 [Reference]	
Household income			
First quartile	0.87	1.15 (0.99 – 1.35)	0.0748
Second quartile	0.68	1.15 (1.98 – 1.34)	0.0881
Third quartile	0.70	1.16 (1.00 – 1.36)	0.554
Fourth quartile	0.57	1.00 [Reference]	
Hospital region			
Northeast	0.61	1.03 (0.89 – 1.18)	0.7369
Midwest	0.53	1.05 (0.90 – 1.23)	0.5441
West	0.70	1.01 (0.87 – 1.16)	0.9369
South	0.98	1.00 [Reference]	
Elixhauser comorbidity index	-	1.27 (1.23 – 1.30)	<.0001

Abbreviations: VTE, venous thromboembolism; OR, odds ratio; CI, confidence interval

[a] The model was weighted and adjusted for patients' clinical and sociodemographic characteristics, tumor characteristics, and hospital level factors

Table 2 Rates of VTE in hepatocellular carcinoma patients who experienced in-hospital mortality and prolonged hospital stay, and weighted multilevel hierarchal regression examining the association between VTE and in-hospital mortality and prolonged hospitalization in patients with hepatocellular carcinoma, Nationwide Inpatient Sample, 2008–2013

Outcome variable	No VTE	VTE		
	%[a]	%[a]	OR (95% CI) [b]	P value
In-hospital mortality	9.6	14.3	1.38 (1.19–1.61)	<.0001
Prolonged hospital stay	1.22	23.00	2.05 (1.84–2.29)	<.0001

Abbreviations: VTE, venous thromboembolism; OR, odds ratio; CI, confidence interval

[a] Weighted rate

Based on the multivariate analysis, age of 65 years and older and African American ethnicity were associated with higher odds of development of VTE in hospitalized HCC patients as compared with age less than 65 years old and White ethnicity, respectively. These findings are in line with previous reports exploring age, African American ethnicity, and metastasis as risk factors for VTE in patients with active malignancies [1, 6, 10, 11].

HCC patients with underlying cirrhosis had significantly lower odds of VTE compared to HCC patients without a prior diagnosis of cirrhosis. Despite the associated coagulopathy based on laboratory testing, patients with cirrhosis have been shown to have an increased risk of VTE [12–14]. The complex mechanisms behind the hemostatic dysregulation in patients with cirrhosis affect the balance of both pro-coagulant and anti-coagulant factors [15]. We speculate that the superimposed development of hepatocellular carcinoma may potentially shift the hemostatic balance toward an anticoagulated state.

Hospitalized patients with HCC secondary to chronic hepatitis C virus (HCV) infection had significantly lower odds of developing VTE when compared to HCC patients without a history of HCV infection. In contrast, two recent meta-analyses suggested that HCV-infected patients, without a prior diagnosis of HCC, may exhibit an increased risk of VTE [16, 17]. The exact mechanism is yet to be determined but possible explanations include chronic inflammation and hyperviscosity secondary to cryoglobulin production [17]. Although no prior studies have evaluated the risk of VTE in HCV-infected patients with HCC, our findings can be potentially explained by alterations in the homeostatic balance induced by HCC that would favor an anti-coagulated state.

Similarly, a history of diabetes mellitus (DM) was associated with significantly lower odds of developing VTE when compared to HCC patients without a history of DM. Although initial studies reported a slightly increased risk of VTE in diabetic patients, further studies and meta-analyses have found no significant association between DM and the risk of VTE [18–20].

In our cohort, development of VTE in hospitalized HCC patients was associated with a prolonged hospital stay and increased in-hospital mortality. These results are in line with prior studies that evaluated these endpoints in hospitalized patients with malignancy-associated VTE [6].

Our work highlights significant age, racial, and comorbid factors in the development of VTE in hospitalized patients with HCC in the US. These findings can help in stratification of HCC patients according to their VTE risk. Patients at higher risk of VTE may benefit from more aggressive pharmacologic prophylaxis, an area for future investigation. In light of the recent trends of increasing incidence of HCC and VTE, prevention of VTE will likely continue to be an emerging issue and a preventable cause of morbidity and mortality in this population.

Author Contributions AMA, GWK, and BNT created the study concept and design. KAM worked on data acquisition and statistical analysis. All authors have participated in the interpretation of data and drafting of the manuscript. The final version of this manuscript was reviewed and approved by all authors prior to submission.

Compliance with Ethical Standards

Research Data Statement The datasets generated during the current study are available from the corresponding author upon request.

Conflict of Interest The authors declare that they have no conflict of interest.

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