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ORIGINAL RESEARCH

Venous Thromboembolism in Hospitalized Melanoma Patients: Analysis from the National Inpatient Sample Database

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Introduction: The association between cancer and hyper-coagulability is well known. However, the association between melanoma and venous thromboembolism (VTE) has not been identified.

Methods: We studied the national inpatient sample (NIS) which compromise 20% of US hospitalization to better characterize melanoma and VTE. We analyzed the data between 2010 and 2014 using ICD-9 codes.

Results: Melanoma patients were grouped into presence/absence of VTE. Multiple logistic regression was used to obtain the odds ratio (OR) to compare the mortality of the inpatient, total charges, length of stay (LOS), and disability at discharge. A total of 61,812 melanoma patients were identified, of which 5.2% were hospitalized for VTE. The presence of VTE was associated with a remarkable higher rate of discharge with a moderate to severe disability (57.5% vs 41.4%, P<0.001), in-hospital stroke (7.6% vs 4.9%, P<0.001), and in-hospital mortality (8.8% vs 5.1%, P<0.001). Costs of hospitalization (64,720$ vs 46,606, P<0.001) and LOS (5 vs 3 days, P<0.001) were significantly higher as well in the VTE group. After adjusting for common confounder, VTE was found to be an independent predictor of mortality (OR = 1.596, 95% CI [1.399–1.821], P<0.001).

Conclusion: In summary, melanoma patients with VTE had higher inpatient mortality, LOS, higher hospital cost, and a higher degree of disability upon discharge.

Keywords: melanoma, venous thromboembolism, VTE, coagulation

Introduction

Venous thromboembolism (VTE) is the second most major cause of mortality in patients with malignancy.[1] Statistics collected from patients' registries in the United States and Europe propose that around 20% of all VTE happens in patients with cancer.[2,3] This risk is maximized in patients diagnosed with metastatic disease at the initial presentation, especially cancers that are rapidly growing which carries a poor prognosis.[4] The site of cancer and its histologic subtype plays a major role in the risk of VTE, for instance, pancreatic and brain malignancies are found to have a frequent association with a higher risk of thromboembolism.[5] Multiple components are deemed to be accountable for the hypercoagulable state in malignancy. It has been demonstrated that continuous expression of Tissue Factor (coagulation factor III) and Cancer Procoagulant (CP) protein by the malignant cells and release of cytokines and microparticles by malignant cells can elicit thrombosis. Additionally, the direct physical contact among malignant cells and healthy cells

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can cause a localized platelet aggregation along with clotting activation therefore release of procoagulant cytokines from leukocytes.[6]

Melanoma is the fifth leading cancer in men and women in the United States. It is anticipated that approximately 100,350 new melanomas would be diagnosed in the United States by 2020.[7] About 6850 people are expected to die of melanoma.[7] Venous thromboembolism events in cancer patients are well described in literature and notably raises the mortality and morbidity of the cancer population, however, it is still under-reported in melanoma patients.[1] This probably could be due to the confinement of most melanoma to the superficial layers of the skin rather than being in close connection with the bloodstream compared to other types of cancer.[8] A retrospective study by Sparsa et al concluded the high incidence of VTE in metastatic stage IV melanoma with prevalence similar to gastrointestinal and pulmonary malignancies. Therefore, this study is designed to describe the prevalence of VTE amidst patients with established diagnosed with melanoma, the patient's demographics, and report the effect of VTE on in-patient outcome, mortality, and hospital length of stay (LOS) in melanoma patients with VTE. The study is operated through data from the Nationwide Inpatient Sample (NIS) database of the Agency of Healthcare Research and Quality (AHRQ).

Methods

Data Source

We utilized the AHRQ's NIS database, which was developed as part of the Healthcare Cost and Utilization Project (HCUP). The National (Nationwide) Inpatient Sample (NIS) is the largest publicly available all-payer inpatient care database in the United States, as it contains data seven million hospital stays or more. Its vast sample size is optimum for establishing national and regional estimates and permits analyses of rare conditions, unusual treatments, and special populations. It includes data from approximately 8 million patient hospital stays per year from over 1000 hospitals and is a representative sample of about 20% of non-federal hospitals in the United States.

Study Population

We captured the patient's data from 2010 to 2014. All patients who were 18 years or older with a diagnosis of melanoma were identified using the clinical classification software codes (CCS). CCS is a tool that is developed by the agency of healthcare research and quality (AHRQ) for grouping the international classification disease (ICD) code into a manageable number of clinical categories. CCS offers scientists to look at classifications without having to sort through thousands of codes. We used CCS-ICD9 for codes between 2010 and 2014. We selected patient with melanoma diagnosis (1720 1721 1722 1723 1724 1725 1726 1727 1728 1729). VTE ICD-9 codes were the following (451.11, 451.19, 451.81, 451.83, 453.40, 453.41, 453.42, 453.82, 453.84, 453.85, 453.86, and 453.87) and PE (PE (ICD-9: 415.11, 415.13, and 415.19)

Patient and Hospital Characteristics

Data extracted from NIS databases include age, gender, race, metastatic cancer status, hospital region (rural vs urban), hospital teaching status (teaching vs nonteaching), hospital bed size (small, medium, large), length of stay (LOS), total charge (those were adjusted to inflation in reference to 2016). Comorbidities were classified using the Elixhauser comorbidity index.[9] Discharge status was classified as 1. Routine discharge (for none to minimal disability) 2. Moderate to severe disability. Moderate to severe disability (defined as any beyond routine home discharge; ranging from short-term stay to skilled nursing facility to death upon discharge).

Outcomes

Outcome included were the trend of VTE in melanoma patients, demographics, inpatient mortality, LOS, cost of hospitalization, and disability at discharge.

Statistical Analysis

Data from the Nationwide Inpatient Sample (NIS) database of the Agency of Healthcare Research and Quality (AHRQ) were analyzed. NIS provides the largest all-payer inpatient databases which provide information on roughly 20% of all US hospital stays. Adults ≥18 years who were admitted to the hospital with melanoma during the period between 2010 and 2014 were identified utilizing the appropriate ICD-9 codes. Patients were sorted based on the absence/ presence of VTE. Demographic characteristics and in-hospital outcomes among Melanoma without and with VTE were compared. Multiple logistic regression was utilized to obtain risk-adjusted odds ratio (OR) to compare inpatient mortality, length of stay (LOS), total charges, and disability at discharge between Melanoma patients with and without VTE. The regression model was modified for sex, melanoma stage, age, race, and presence of comorbid conditions.

Results

Baseline Characteristics

A total of 61,812 melanoma patients were included in our analysis, among them 5.2% were admitted with a VTE. Mean age in the VTE group was similar 63.3 years vs 63.6 years in the non-VTE group (P-value 0.275). Most patients were white; 90.8% of the VTE group and 91.2% of the non-VTE group (P<0.01). Hispanic were second most common; 3.9% in the VTE group. Most patients with VTE had a metastatic melanoma (58.2%) whereas most patients without VTE had a non-metastatic melanoma (62.8%), P<0.001.

Most melanoma patients were males and 65.2% of patients with VTE were males. 66.7% of VTE group had 3 or more Elixhauser comorbidities Index compared to 53% in non-VTE group, P<0.001. Patients with VTE were more likely to have coagulopathy (10.6% vs 6.9%,

Table 1 Baseline Characteristics of Melanoma Patients with or Without VTE (n = 61,812)

Melanoma Patients	VTE, n (%)	No VTE, n (%)	P-value
Overall	3237 (100)	58,575 (100)	
Age (years) mean, SD	63.3 (15.2)	63.6 (16)	0.275
Sex			0.007
Males	2107 (65.2)	36,786 (62.8)	
Females	1125 (34.8)	21,767 (37.2)	
Race			0.01
White	2758 (90.8)	49,552 (91.2)	
Black	66 (2.2)	1081 (2)	
Asian or pacific islander	41 (1.3)	439 (0.8)	
Native American	10 (0.3)	99 (0.2)	
Hispanic	119 (3.9)	2232 (4.1)	
Others	45 (1.5)	927 (1.7)	
Melanoma stage			<0.001
Non-metastatic	1353 (41.8)	35,013 (59.8)	
Metastatic	1884 (58.2)	23,563 (40.2)	
Comorbidities			
Coagulopathy	344 (10.6)	4060 (6.9)	<0.001
Congestive heart failure	220 (6.8%)	3677 (6.3%)	0.234
Hypertension	1563 (48.3%)	29,234 (49.9%)	0.074
Dyslipidemia	867 (26.8)	16,644 (28.4)	0.048
Atrial fibrillation	430 (13.3)	7971 (13.6)	0.615
Chronic pulmonary disease	428 (13.2%)	7434 (12.7%)	0.372
Liver disease	55 (1.7%)	1063 (1.8%)	0.678
Renal failure	246 (7.6%)	5012 (8.6%)	0.062
Smoking	755 (23.3)	14,976 (25.6)	0.004
Obesity	334 (10.3%)	4775 (8.2%)	<0.001
Alcohol abuse	50 (1.5%)	1180 (2%)	0.073
Elixhauser comorbidities Index			<0.001
0	10 (0.3)	3246 (5.6)	
1	384 (11.9)	10,908 (18.6)	
2	684 (21.1)	13,329 (22.8)	
3 or more	2159 (66.7)	31,074 (53)	
Location/teaching status of the hospital			0.449
Rural	251 (7.8)	4745 (8.1)	
Urban non-teaching	879 (27.2)	15,331 (26.3)	
Urban teaching	2106 (65.1)	38,304 (65.6)	

P<0.001), and obesity (10.3% vs 8.2%, P<0.001), but less likely to have dyslipidemia (26.8% vs 28.4%, P = 0.048) and be smokers (23.3% vs 25.6%, P = 0.004). Other baseline comorbidities including congestive heart failure, hypertension, atrial fibrillation, chronic pulmonary disease, liver disease, renal failure, and alcohol abuse did not differ significantly between the two groups. Table 1 summarizes baseline characteristics in included patients.

Morbidity Outcome

The presence of VTE was associated with a significantly higher rate of discharge with a moderate to severe disability (57.5% vs 41.4%, P<0.001), in-hospital stroke (7.6% vs 4.9%, P<0.001), and in-hospital mortality (8.8% vs 5.1%, P<0.001). Costs of hospitalization (64,720$ vs 46,606, P<0.001) and length of stay (5 vs 3 days, P<0.001) were also significantly higher in the VTE group (Table 2).

Mortality Outcome

After adjustment for age, sex, race, melanoma stage, coagulopathy, congestive heart failure, hypertension, dyslipidemia, atrial fibrillation, chronic pulmonary disease, liver disease, renal failure, smoking, obesity, and alcohol abuse, the presence of VTE was shown to be an independent predictor of mortality (OR = 1.596, 95% CI [1.399–1.821], P<0.001) (Table 3). Mortality in males is higher compared to females OR 1.38, p<0.001.

Discussion

Patients with malignancy are at a high risk of venous thromboembolism (VTE), which contributes to morbidity and mortality, playing a significant role in healthcare utilization among oncology patients.[10] Due to the heterogeneity of cancers, variable incidence of VTE have been reported in patients with cancer, ranging from 0.6% to 7.8%.[11–13] Reaching as high as 15% as observed by Goodnough et al in patients with stage IV breast cancer receiving chemotherapy.[14] VTE risk in melanoma remains underreported in the literature.[15] Our study, involving 61,812 melanoma patients, is the first comprehensive study to date to examine the prevalence, demographics, hospital outcomes, and mortality in melanoma patients with VTE in the inpatient setting. We limited our inclusion criteria to patients for whom VTE significantly impacted the hospitalization, as evidenced by a VTE code listed in the top three diagnoses.

Approximately, 5.2% of patients with malignant melanoma in our analysis experienced VTE during hospitalization, this is comparable with the rates reported by previous studies of hospitalized patients with cancer irrespective of their metastatic status; which is reported as 2.0% to 4.1%.[11,16] In regard to baseline characteristics of patients who developed VTE, our study showed that metastatic disease appeared to be more prevalent in the VTE population. This supports the strong association between metastatic stage malignancy and VTE that was shown in previous studies.[17] Our study found that Patients with malignant melanoma with VTE had higher odds of mortality compared with those without VTE, Identifying VTE independent predictor of mortality regardless of cancer stage and metastatic status.

Other previous studies have shown an increased risk of VTE in women and the African American population.[11,18–20] In our study, more women and African Americans had VTE than other populations. Most of the patients with VTE were white which is not surprising as fair skin is an independent risk factor for melanoma.[21]

Table 2 Outcomes of Melanoma Patients with or Without VTE (n = 61,812)

Melanoma Patients	VTE, n (%)	No VTE, n (%)	P-value
Overall	3237 (100)	58,575 (100)	
Discharge type			<0.001
None to minimal disability	1371 (42.5)	34,230 (58.6)	
Moderate to severe disability*	1852 (57.5)	24,212 (41.4)	
Cost ($) mean, SD	64,720 (87,249)	46,606 (53,897)	<0.001
Bleeding	50 (1.5)	684 (1.2)	0.062
Stroke	246 (7.6%)	2893 (4.9%)	<0.001
In-hospital mortality	286 (8.8)	3004 (5.1)	<0.001
Length of stay (days) Median, IQR	5 (3–8)	3 (2–6)	<0.001

Notes: *Moderate to severe disability (defined as any beyond routine home discharge; ranging from short-term stay to skilled nursing facility to death upon discharge).

Table 3 Multivariate Logistic Regression for Prediction of in-Hospital Mortality in Melanoma Patients

	Odds Ratio (95% CI)	P-value
The presence of VTE (vs no)	1.596 (1.399–1.821)	<0.001
Age (in years)	1.005 (1.002–1.008)	<0.001
Female sex (vs male sex)	0.728 (0.671–0.789)	<0.001
Race (vs white)		
Black	0.928 (0.696–1.236)	0.609
Hispanic	1.499 (1.274–1.764)	<0.001
Asian or Pacific Islander	1.413 (0.995–2.007)	0.053
Native American	1.814 (0.939–3.506)	0.076
Other races	1.524 (1.195–1.944)	0.001
Metastatic melanoma (vs non-metastatic)	1.833 (1.701–1.976)	<0.001
Coagulopathy (vs no)	1.597 (1.399–1.821)	<0.001
Congestive heart failure (vs no)	1.543 (1.353–1.760)	<0.001
Hypertension (vs no)	0.770 (0.710–0.836)	<0.001
Dyslipidemia (vs no)	0.775 (0.707–0.850)	<0.001
Atrial fibrillation (vs no)	1.417 (1.278–1.570)	<0.001
Chronic pulmonary disease (vs no)	1.182 (1.060–1.319)	0.003
Liver disease (vs no)	1.807 (1.459–2.237)	<0.001
Renal failure (vs no)	1.452 (1.290–1.635)	<0.001
Smoking (vs no)	0.730 (0.665–0.800)	<0.001
Obesity (vs no)	0.765 (0.656–0.892)	0.001
Alcohol abuse (vs no)	0.580 (0.417–0.806)	0.001

We report an increase in hospitalizations, inpatient charges, and overall length of stay in melanoma patients with VTE when compared to melanoma patients without VTE, leading to an overall increase in total healthcare costs (64,720$ in our VTE cohort). This could be due to the complications of VTE leading to more investigations, treatment, and longer hospital stay. Adding more burdens to the patients and the healthcare system.

The strengths of this analysis include the large sample size used for powered analysis. The study is limited by the cross-sectional study design that does not allow to determine any causality. Second, NIS data lacks information regarding medications; hence, we could not account for the use of VTE prophylaxis and treatment that might have influenced the outcome. The NIS does not provide the cause of the admission rather than it lists the ICD-9 codes of the whole diagnoses of a particular patient both acute and chronic in that hospital stay. The NIS does not distinguish patients with multiple admissions, because it is based on unique admission rather than a unique patient. Therefore, it is possible that repeated admissions of the same patients were included, and thereby VTE rates were underestimated or overestimated.

Conclusion

Our study identifies VTE as a significant complication of malignant melanoma that exerts a considerable negative impact on patient outcomes and overall healthcare costs. Given that some VTEs are preventable, there may be a need for more strict compliance with prevention methods in the high-risk patient population. As some of previous surveys showed only 52% of the hospitalized patient with a high risk of VTE are receiving appropriate prophylaxis.[22] Our study highlights the need for more prospective studies to clarify the impact of VTE in malignant melanoma patients and identify effective strategies to improve the outcome observed in this population.

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Author Contributions

All authors contributed to drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval to the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

None of the authors declared a conflict of interest.

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