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IDH mutation status and the development of venous thromboembolism in astrocytoma patients

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ABSTRACT

Background: Venous thromboembolism (VTE) is a very common adverse event for astrocytoma patients, but validation of proposed risk biomarkers has been elusive. We examine whether the status of the isocitrate dehydrogenase (*IDH*) gene is a risk factor for the development of venous thromboembolism (VTE) in astrocytoma patients.

Methods: We conducted a retrospective chart review of 282 astrocytoma patients enrolled in the PROACTIVE (Prospective Assessment of Correlative Biomarker) study at MD Anderson Cancer Center (MDACC) from 9/1/2000 until 12/31/2013.

Results: We identified 282 astrocytoma patients consisting of 49 *IDH* mutant astrocytomas and 233 *IDH* wildtype astrocytomas. Glioblastoma was the initial histopathologic diagnosis in 30 (61.2%) of the *IDH* mutated astrocytomas compared to 227(97.4%) of the *IDH* wild type astrocytomas. VTE was identified in 52 (18.4%) of patients. VTE was diagnosed in 7 (14.3%) of the *IDH* mutated astrocytomas compared to 45(19.3%) of the *IDH* wild type astrocytoma s ($p = 0.4094$). Median time to VTE from diagnosis was 2.71 months. Median time to VTE from diagnosis was 2.6 months for *IDH* mutated astrocytomas compared to 3.06 months for the *IDH* wild type astrocytomas ($p = 0.8663$).

Conclusions: IDH gene status did not appear as a significant risk factor for the development of venous thromboembolism (VTE) in our cohort of astrocytoma patients. Further research into potential biomarkers for VTE may be warranted.

1. Introduction

Venous thromboembolism (VTE) is a common adverse event for astrocytoma patients, particularly those with higher grade tumors [1,2]. In patients with glioblastoma (GBM), the incidence has been reported to range from 24 to 30% [2–6]. Development of venous thromboembolism (VTE), was first described in the mid-nineteenth century by Trousseau and is thought to be caused by the release of cytokines, acute phase proteins, over-expression of tissue factors, and the activation of oncogenic pathways coupled with the loss of tumor suppressors, leading to an altered expression, activity, and release of coagulation factors. The discovery of molecular markers in gliomas has revolutionized the field and recently resulted in updated diagnostic criteria for central nervous system tumors including astrocytomas [7]. Isocitrate dehydrogenase (IDH) mutation status is now included as a necessary component of the diagnosis when available. IDH mutations are more common in lower

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grade 2 and 3 tumors (~70%) and are infrequently seen in newly diagnosed (~approximately 12%) glioblastoma [8,9]. Notably, IDH mutations are associated with younger age and better survival [10]. Recent studies have suggested that mutant IDH gliomas have potent antithrombotic activity within gliomas as well as throughout the peripheral circulation and are a powerful predictive marker for VTE [11]. The purpose of this study is to evaluate the relationship between IDH mutation status and VTE diagnosis in astrocytoma patients and examine if IDH mutation status is a risk factor for the development of VTE.

2. Methods

This retrospective chart review was performed at our center with institutional board (IRB) review approval. Patients were identified with a diagnosis of astrocytoma in the IRB approved Prospective Assessment of Correlative Biomarker (PROACTIVE) protocol at MD Anderson Cancer Center (MDACC) from 9/1/2000 until 12/31/2013. Clinical data, including patient-, tumor-, and treatment-related characteristics were extracted from the medical record. Karnofsky performance scale (KPS) at time of initial resection and time of VTE was determined by the treating physician and extracted from the medical record. Extent of surgical resection was determined based on contrast enhancing disease on immediate post-operative imaging. IDH mutation status was determined at time of surgical resection and was detected via immunohistochemistry and/or sequencing.

2.1. Statistical analysis

VTE is a time-to-event symptom, which is defined as the time from diagnosis to time of VTE occurrence. VTE after adjuvant therapy is defined as the time from starting adjuvant therapy (radiation and/or chemotherapy) to time of VTE occurrence, as low grade astrocytoma sometimes are monitored on surveillance alone following a surgical biopsy/resection. A patient was censored if he/she does not have this symptom until last follow-up time. Data was summarized using standard descriptive statistics such as mean, standard deviation, median and range for continuous variables; and frequency and proportion for categorical variables. Wilcoxon signed-rank test was used to examine the change on continuous variables from time of starting adjuvant therapy to time of VTE occurrence within group. Kaplan-Meier method is used to estimate median time to VTE. Univariate Cox regression models is applied to assess the demographic/clinical characteristics on VTE. All computations were carried out in SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

A total of 282 patients were identified with a diagnosis of astrocytic lineage, of which 233 patients were IDH wildtype and 49 were IDH mutant (Table 1). Median age at diagnosis was 54 years for all patients, however when divided by IDH status, median age for IDH-mutant patients was 38 years and IDH-wildtype patients was 57 years ($p < 0.0001$). Grade of tumor included grade 2 astrocytoma (11 patients, 3.9%), grade 3 astrocytoma (14 patients, 5%), gliosarcoma (8 patients, 2.8%), and GBM (249 patients, 88.3%). There were 176 men (62.4%) and 106 women (37.6%). 162 patients (57.4%) were able to undergo a gross total resection, while 77 patients (27.3%) received a subtotal resection, and 43 (15.2%) underwent a biopsy. The majority of patients (220 patients, 78%) were not on steroids at the time of starting adjuvant therapy.

52 patients (18.4%) did experience a VTE, with VTE in 7 (14.3%) of the IDH mutant astrocytomas compared to 45 (19.3%) of the IDH wildtype astrocytomas ($p = 0.4094$) (Table 2). 50% of patients with VTE had a DVT alone, while 30.8% had both a DVT and pulmonary embolism, and 19.2% had a pulmonary embolism alone. Median time to VTE from diagnosis was 2.71 months, with a median time to VTE from diagnosis of 2.6 months for IDH mutant astrocytomas compared to 3.06 months for the IDH wildtype astrocytomas ($p = 0.8663$).(Table 3). Twenty- seven (52%) of VTE occurred within the first 3 months of initial diagnosis. Five (71.4%) out of seven VTE in IDH Mutant tumors occurred with the first 6 months after diagnosis (all in the first 3 months) and 71.1% of VTE in IDH wildype tumors occurred in the first 6 months after diagnosis (22/45 in first 3 months and 10/45 three to six months after diagnosis).

Table 1
Summary of demographic & clinical characteristics.

Variables of Interest	Levels	Total	IDH		*p*-value
			Mutant	WT	
All Patients		282 (100%)	49 (100%)	233 (100%)	
Diagnosis	Astrocytoma Grade 2	11 (3.9%)	9 (18.4%)	2(0.9%)	<0.0001
	Astrocytoma Grade 3	14(5%)	10 (20.4%)	4(1.7%)	
	Glioblastoma	249 (88.3%)	30 (61.2%)	219 (94%)	
	Gliosarcoma	8(2.8%)	0(0%)	8(3.4%)	
Sex	Female	106 (37.6%)	17 (34.7%)	89 (38.2%)	0.6453
	Male	176 (62.4%)	32 (65.3%)	144 (61.8%)	
Extent of Resection	Biopsy	43 (15.2%)	6 (12.2%)	37 (15.9%)	0.5979
	GTR	162 (57.4%)	27 (55.1%)	135 (57.9%)	
	Partial Resection	77 (27.3%)	16 (32.7%)	61 (26.2%)	
KPS at time of starting ADJ	Unknown	3			
	50	2(0.7%)	0(0%)	2(0.9%)	0.0056
	60	6(2.2%)	3(6.1%)	3(1.3%)	
	70	20 (7.2%)	3(6.1%)	17 (7.4%)	
	80	49 (17.6%)	2(4.1%)	47 (20.4%)	
	90	112 (40.1%)	18 (36.7%)	94 (40.9%)	
	100	90 (32.3%)	23 (46.9%)	67 (29.1%)	
VTE	No	230 (81.6%)	42 (85.7%)	188 (80.7%)	0.4094
	Yes	52 (18.4%)	7 (14.3%)	45 (19.3%)	

It was noted that 30 patients (57.7%) were on treatment (radiation and/or chemotherapy) at the time of VTE, while 22 patients (42.3%) were not on treatment at the time of VTE. Four VTE (57%) in IDH mutated astrocytomas occurred during chemotherapy compared to 26 (58%) of the VTE IDH wildtype astrocytoma patients.

For the 30 patients developing VTE on treatment- 6 occurred during chemoradiation, 15 during adjuvant temodar, and 7 while receiving treatment for recurrence. For the 22 VTEs developing while not on treatment- 19 occurred post surgery before the start of any treatments, 2 occurred in between chemoradiation and start of adjuvant temodar, and 1 occurred while on surveillance (6 months since finishing adjuvant TMZ).

Of the patients on treatment at time of VTE, 63.3% were receiving temozolomide alone. KPS at the time of starting adjuvant therapy was 90–100 for 72.4% of patients, however a KPS of 90–100 was seen in only 39.3% of patients at time of VTE.

On univariate analysis IDH mutation status was not significantly associated with time to VTE in relation to diagnosis or treatment, and the use of steroids was not significantly associated as well. BMI > 37 was significant for development of VTE after adjuvant therapy ($p = 0.0319$), as was biopsy vs gross total resection (GTR) ($p = 0.0170$), with patients after biopsy 1.86 times more likely to have a VTE compared to patients

Table 2
VTE characteristics.

Variables of Interest	Levels	Total	IDH		p-value
			Mutant	Wildtype	
All VTE		52(100%)	7(100%)	45(100%)	
Type of VTE	Both	16(30.8%)	3(42.9%)	13(28.9%)	0.8659
	DVT	26(50%)	3(42.9%)	23(51.1%)	
	PE	10(19.2%)	1(14.3%)	9(20%)	
Treatment for VTE	Warfarin	4(7.7%)	0(0%)	4(8.9%)	
	Warfarin + IVC Filter	2(3.8%)	0(0%)	2(4.4%)	
	IVC Filter	9(17.3%)	2(28.6%)	7(15.6%)	
	IVC Filter + Xarelto	1(1.9%)	0(0%)	1(2.2%)	
	LMWH	29(55.8%)	3(42.9%)	26(57.8%)	
	LMWH + IVC Filter	3(5.8%)	0(0%)	3(6.7%)	
	Other	2(3.8%)	2(28.6%)	0(0%)	
	Xarelto	2(3.8%)	0(0%)	2(4.4%)	
Bleeding Complications of anticoagulation	Intracranial	1(1.9%)	1(14.3%)	0(0%)	0.2534
	None	50(96.2%)	6(85.7%)	44(97.8%)	
	Other	1(1.9%)	0(0%)	1(2.2%)	
On treatment during DVT	No	22(42.3%)	3(42.9%)	19(42.2%)	1.0000
	Yes	30(57.7%)	4(57.1%)	26(57.8%)	
Which chemo during DVT ($n = 30$)	Accutane	2(6.7%)	1(25%)	1(3.8%)	
	bevacizumab	1(3.3%)	0(0%)	1(3.8%)	
	bevacizumab, CCNU	3(10%)	1(25%)	2(7.7%)	
	bevacizumab, irinotecan	2(6.7%)	0(0%)	2(7.7%)	
	Sorafenib, Everolimus	1(3.3%)	0(0%)	1(3.8%)	
	temozolomide	19(63.3%)	1(25%)	18(69.2%)	
	temozolomide, Accutane	2(6.7%)	1(25%)	1(3.8%)	
KPS at VTE	Unknown	2			
	40	1(2%)	0(0%)	1(2.3%)	0.7672
	50	3(5.9%)	1(14.3%)	2(4.5%)	
	60	4(7.8%)	1(14.3%)	3(6.8%)	
	70	14(27.5%)	1(14.3%)	13(29.5%)	
	80	9(17.6%)	1(14.3%)	8(18.2%)	
	90	14(27.5%)	2(28.6%)	12(27.3%)	
	100	6(11.8%)	1(14.3%)	5(11.4%)	

Table 3
Time to VTE.

Time to VTE	All Patients			IDH					
				Mutant			WT		
	N	% Among $N = 52$	% Among $N = 282$	N	% Among $N = 7$	% Among $N = 49$	N	% Among $N = 45$	% Among $N = 233$
<3 months	27	52.0%	9.6%	5	71.4%	10.2%	22	48.9%	9.4%
3–6 months	10	19.2%	3.5%	0			10	22.2%	4.3%
6–12 months	0			0			0		
12–18 months	7	13.5%	2.5%	1	14.3%	2.0%	6	13.3%	2.6%
18–24 months	0			0			0		
24–30 months	1	1.9%	0.4%	0			1	2.2%	0.4%
30–36 months	4	7.7%	1.4%	0			4	8.9%	1.7%
4.7 years	1	1.9%	0.4%	1	14.3%	2.0%	1	2.2%	0.4%
9 years	1	1.9%	0.4%	0			1	2.2%	0.4%
10.3 years	1	1.9%	0.4%	0			1	2.2%	0.4%
Median Time to VTE (months)	2.71			2.60			3.06		
	95% CI: (1.28, 3.29)			95% CI: (0.43, 13.54)			95% CI: (1.18, 3.29)		

with GTR.

Comparison of overall survival in the IDH mutated cohort revealed no significant differences in survival in patients with VTE and without VTE ($p = 0.9494$) (Fig. 1) (Supplementary Table A). In the IDH wildtype group, univariate cox model shows that patients with VTE had increased hazard ratios (1.38 times) compared to patients without VTE ($p = 0.0642$). (Supplementary Table B). However, after adjusting for age at diagnosis, sex and BMI, there is no significant difference between patients with VTE and without VTE in the wildtype group as well ($p = 0.222$) (Supplementary Table C).

There was no significant difference in VTE rate between GBM versus lower grade astrocytomas. Out of a total of 257 GBM patients, 48 developed VTE compared to 25 lower grade patients, among them 4 developed VTE. (Fig. 2) A Chi-square test for GBM and lower grade astrocytomas versus VTE status was not significant ($p = 1.0$). We also looked into the association between VTE rate for GBM and lower grade astrocytomas by IDH mutation status. These associations are not significantly different for IDH mutated ($p = 0.4072$) and IDH wildtype ($p = 0.6019$) astrocytomas.

All patients who developed a VTE received management for the VTE with either an inferior vena cava (IVC) filter, anticoagulation, or a combination of both modalities (Table 2). IVC filter alone was given to nine patients (17.3%). Anticoagulation alone was given in 37 patients (71.1%). Low molecular weight heparin most commonly used for anticoagulation alone in 29 patients (55.8%). Warfarin was received by four patients (7.7%). Rivaroxaban was used in 2 patients (3.8%). A combination of IVC filter and rivaroxaban was used in 1 patient (1.9%), IVC filter and warfarin was used in 2 patients (3.8%) and an IVC filter and low molecular weight heparin was used in three patients (5.8%). After anticoagulation, one patient (1.9%) experienced an intracranial

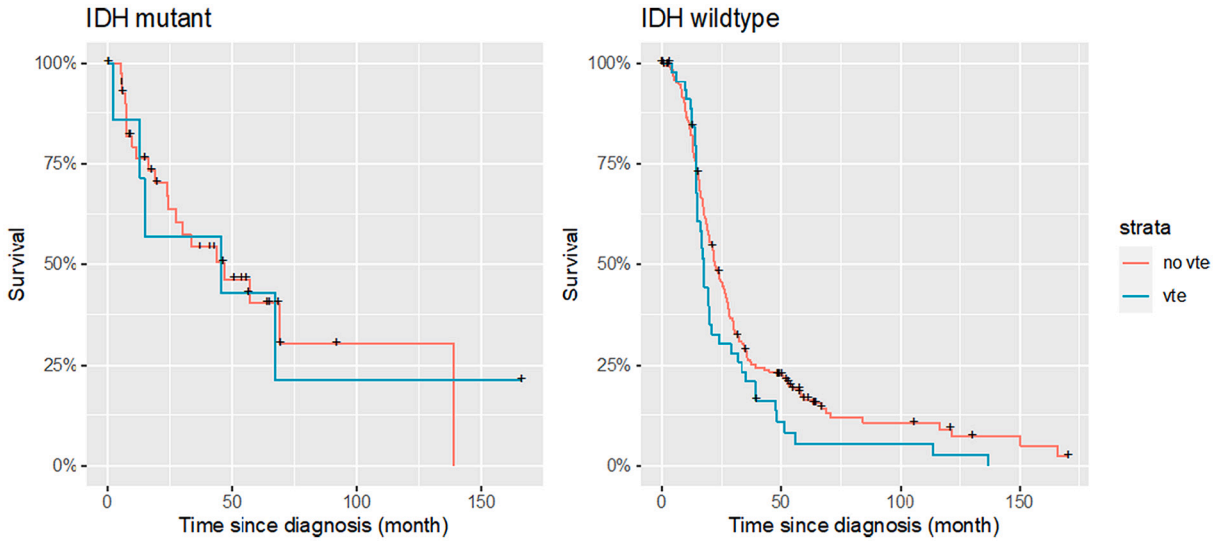

Fig. 1. Kaplan-Meier curve of overall survival for IDH mutant and IDH wildtype cohorts with or without VTE. Kaplan Meier curve presents patient survival (time since initial diagnosis to death time) compared for patients who developed vte and who did not develop vte. All patients who were still present at the end of the study are censored in the plot and in all survival analysis.

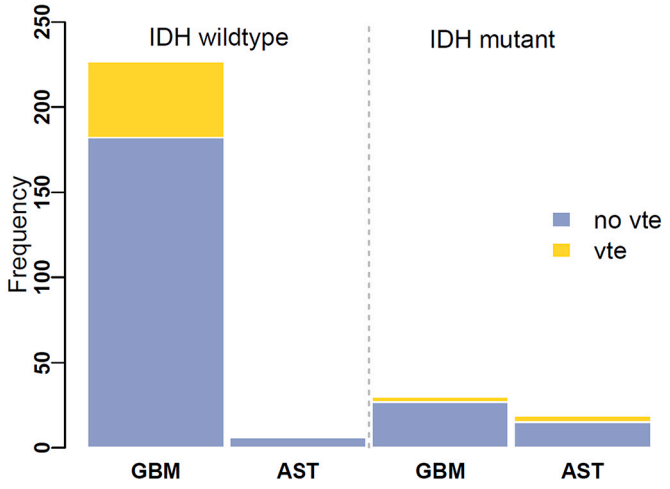

Fig. 2. Bar plot of Frequency of VTE (GBM = Glioblastoma, AST = lower grade astrocytomas).

hemorrhage.

4. Discussion

IDH mutation status was not a significant risk factor for development of VTE in our cohort of astrocytoma patients. Of the 282 patients examined, VTE was experienced by 52 patients (18.4%), of which 45 patients (86.5%) were IDH-wildtype. However, VTE was seen in 7 (14.3%) of the IDH mutant astrocytomas compared to 45 (19.3%) of the IDH wildtype astrocytomas. ($p = 0.4094$) Additionally, there was no difference in the median time to VTE from diagnosis between the two groups, with a median time to VTE from diagnosis of 2.6 months for IDH mutant astrocytomas compared to 3.06 months for the IDH wildtype astrocytomas ($p = 0.8663$).

The findings of our study are in contrast to a recent study that found that VTE occurred in 26–30% of patients with wild type IDH1 gliomas, but not in patients with mutant IDH1 gliomas (0%) [11]. This study also found that microthrombi were far less common within mutant IDH1 gliomas regardless of WHO grade (85–90% in wild-type versus 2–6% in mutant), and were an independent predictor of IDH1 wild-type status. Yet, a prior retrospective study examining 96 patients of which DVT developed in 30 (31.3%) patients found that there was no correlation between the number of microscopic thrombi and the subsequent development of DVT in patients with GBM [12]. Another recent retrospective from Schiff et al. found that 8.7% of IDM mutant patients developed a VTE [11,13]. This study reported that in WHO grade II–IV glioma patients, absence of an IDH mutation was associated with a threefold increase in VTE risk when compared to IDH-mutant patients (hazard ratio 3.06, 95% confidence interval 2.03–4.64) [13]. However, the competing-risks regression for time to VTE in patients in lower grade glioma patients did not show a statistically significant increase risk of VTE in IDH wildtype patients compared to both IDH mutant, 1p/19-codeleted and IDH mutant, 1p/19q-intact patients, (IDH wildtype vs IDH mutant, 1p/19q-codeleted, subdistribution HR [SHR] 1.67, 95% CI 0.59–4.72, $p = 0.56$; IDH wildtype vs IDH mutant, 1p/19q-intact, SHR 1.87, 95% CI 0.54–6.53, $p = 0.55$) [13]. In contrast to our cohort, this study included a large proportion of oligodendrogliomas (1p/19q co-deleted tumors) making up 37.5% of their lower grade gliomas and 17.8% of their entire cohort. Additionally, Schiff et al. found that for grade 4, IDH mutant tumors 24% (4/17) developed VTE. However, their IDH mutant cohort only had 8% Grade 4, IDH mutant tumors (17/208) and our cohort of IDH mutant astrocytomas was composed of over 60% Grade 4, IDH mutant tumors (30/49) [13].

Subsequent studies have suggested *IDH1* and podoplanin are joint prognostic markers and that using the combination of the two may be beneficial, but our cohort was retrospective in nature and podoplanin expression testing was not performed. [14,15] A notable difference in our retrospective study was that all patients were symptomatic leading to clinical testing whereas the Wanatbe et al. study used D-dimer levels as a cut off leading to a CT scan which resulted in 95.4% (42/44) of the VTE seen in asymptomatic patients [15].

Cytokine levels could potentially contribute to VTE production in glioma [16]. In a recent study, patients with glioma were observed for development of VTE over a two year period, or until development of confirmed VTE. Nine cytokines were measured in the serum at each timepoint. 13.2% of patients developed VTE during follow-up. Evaluation of the serum indicated that chemokine C—C motif ligand 3 (CCL3) levels were inversely associated with risk of VTE, and there was no association between the risk of VTE and serum levels of interleukin (IL)-1β, IL-4, IL-6, IL-8, IL-10, IL-11, tumor necrosis factor (TNF)-α and vascular endothelial growth factor (VEGF). Of note, when examining systemic

CCL3 levels and risk of glioma-associated VTE in multivariable cox regression analyses adjusted for IDH1 mutation status the inverse association of serum CCL3 levels with risk of glioma-associated VTE remained (CCL3: adjusted HR per double increase: 0.412, 95% CI: 0.174–0.975, $p = 0.044$). IDH status was not statistically significant (IDH1 mutation vs. IDH1 wildtype: adjusted HR: 0.450, 95% CI: 0.056–3.636, $p = 0454$) [16].

In addition to IDH-1, podoplanin and cytokine expression, prior studies have examined potential predictive biomarkers of VTE in glioma patients including AB blood group, D-dimer, prothrombin fragment 1 + 2, Factor VIII, and circulating microparticles/Tissue factor often with conflicting results [17–21]. A retrospective review of 130 glioma patients found that ABO blood group was a risk factor for VTE among patients with malignant gliomas, with blood group AB being particularly high risk for thrombosis [17]. However, a subsequent multicenter prospective trial found that patients with an elevated factor VIII activity (>147%) were 2.1-fold more likely to develop VTE, but ABO blood group, D dimer and thrombin generation were not associated with VTE in this study [19]. Alternatively, another prospective study of 821 patients with newly diagnosed cancer or progression of disease, who did not recently receive chemotherapy, radiotherapy, or surgery (where the VTE cohort was 29% (18/62) high grade glioma), concluded that elevated D-dimer and Prothrombin fragment 1 + 2 levels independently predict occurrence of VTE in patients with cancer [18]. Additionally, a study looking at 61 GBM patients of which 11 developed a VTE found that tissue factor bearing microparticles were significantly higher in 11 GBM patients who developed VTE than in those who did not (p 0.04). However, a different study examining 119 brain cancer patients of which 19 developed VTE concluded that microparticle-associated tissue factor activity was not associated with a future VTE [20,22].

Distinctive risk prediction models have been established to distinguish cancer patients at high risk of developing cancer associated thrombosis who may benefit from thromboprophylaxis [23]. Yet, when validated in independent cohorts, these risk models using previously established biomarkers and clinical parameters often perform poorly [6,23,24]. Identification of new and more accurate biomarkers are necessary. Recently, genome-wide association studies (GWAS) have contributed to the identification of novel VTE-associated single-nucleotide polymorphisms (SNPs) which constitute potential prognostic and predictive biomarkers that may allow for better management of cancer patients at risk for VTE development [25]. However, these SNPS will require further investigation and validation in future prospective studies.

Our study is limited by its retrospective nature and that it involves patients seen at a single institution. However, the incidence of VTE in our population is consistent with prior published studies suggesting the generalizability of the data. While there was not a statistical difference between VTE occurrences in IDH wildype versus IDH mutated astrocytoma, our study was limited by a relatively small sample size. It is also noted that general screening was not routinely done on patients who did not exhibit symptoms of VTE, and thus asymptomatic patients may not have been diagnosed which may have led to an underestimation of events. Glioblastoma was the initial diagnosis in a high rate of IDH mutated astrocytomas in this study which we speculated is likely due to MDACC status as a tertiary referral center.

In conclusion, *IDH* gene status did not appear as a significant risk factor for the development of venous thromboembolism (VTE) in our cohort of astrocytoma patients. Due to the high rate of occurrence in brain cancer patients and the potential associated morbidity and mortality of VTE, further research examining potential biomarkers for VTE is warranted.

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Declaration of Competing Interest

No known conflict of interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2021.117538.

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