

Research Article

Role of perioperative plasma D-dimer in intracerebral hemorrhage after brain tumor surgery: A prospective study

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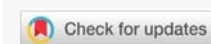
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Keywords: D-dimer; Intracerebral hemorrhage; Tumor; Neurosurgery Coagulation; Biomarker; Bleeding; Intracranial hypertension

Abbreviations: APTT: Activated Partial Thromboplastin Time; CT: Computerized Tomography; Fb: Fibrinogen; FP: Frozen Plasma; G6PDD: Glucose-6-Phosphate Dehydrogenase Deficiency; Hb: Hemoglobin; Ht: Hematocrit; ICH: Intracranial Hemorrhage; IH: Intracranial Hypertension; INR: International Normalized Ratio; P: Platelets; PA: Prothrombin Activity; PCR: Prothrombin Complex; PP: Pooled Platelets; RBC: Red Blood Cells; TXA: Tranexamic Acid



Abstract

Background: Intracerebral hemorrhage (ICH) is one of the most feared complications after brain tumor surgery. Despite several factors being considered to influence bleeding, an increasing number of clinical studies emphasize that hemostatic disorders, developed during surgical aggression and tumor status, could explain unexpected ICH. The objective of this prospective study was to evaluate the influence of perioperative D-dimer levels on ICH after brain tumor surgery.

Methods: This prospective, observational, 18-month study, at a single third-level hospital, included all consecutive adults operated on brain tumors and postoperative stay in an intensive care unit. Three blood samples evaluated D-dimer levels (A-baseline, B-postoperative and C-24 hours after surgery). The normal range considered was 0-500 ng/ml. ICH, as a primary outcome, was defined as bleeding that generates radiological signs of intracranial hypertension either by volume or by mass effect on the routine CT scan 24 hours after surgery. Other tumor features and hemostasis variables were analyzed. Chi-squared and Fisher's exact test were used in the inferential analysis for qualitative variables and Wilcoxon and T-Test for quantitative ones. *P*-value < 0.05 was considered significant for a confidence interval of 95%.

Results: A total of 109 patients operated on brain tumor surgery were finally included, 69 male (63,30%) and 40 female (36,70%), with a mean age of 54,60 ± 14,75 years. ICH was confirmed in 39 patients (35,78%). Their average of DDimer was A-1.526,70 ng/dl, B-1.061,88 ng/dl, and C-1.330,91 ng/dl (A p0.039, B p0,223 C p0.042, W-Wilcoxon test). The male group was also associated with ICH (p0,030 X² test). Of those 39 patients with ICH, 30 in sample A (76,9%), 20 in sample B (51,28%) and 35 in sample C (89,74%) had a D-dimer > 500 ng/dl (p0,092, p1, p0,761 X² test) and the relative risk of developing a postoperative hematoma in this patients was increased 0,36-fold presurgery, 0,25-fold postsurgery and 0,40-fold 24 hours after surgery. D-dimer variation, had no statistical significance (p0,118, p0,195, p0,756 T-test). Platelets and prothrombin activity were associated with D-dimer levels only in sample A (p 0,02 and p 0,20, W Wilson).

Conclusion: High levels of perioperative D-dimer could be considered a risk marker of ICH after brain tumor surgery. However, more studies would be worthwhile to confirm this association and develop primary prevention strategies for stroke.



Background

Cancer incidence is increasing globally, being a leading cause of death worldwide [1-3]. Though brain tumors are uncommon, they cause morbidity and mortality disproportionate to their incidence [4,5]. Despite individualized management and optimal surgical measures, a removal of a brain tumor carries a higher risk of intracerebral hemorrhage (ICH) [6,7]. Multifactorial and sometimes unexplained, it is likely the most feared complication leading to poor functional prognosis, even risk of death [8,9].

Functional integrity of the hemostatic system and normal standard coagulation tests are both required for safe neurosurgical procedures, but other specific acquired hemostatic disorders, not routinely measured, could be developed during cancer surgery and increase or predict bleeding risk [10-12].

D-dimer, a fibrinogen compound with high molecular weight, formed during activation of the coagulation system, derived from the degradation of crosslinked fibrinogen when the dissolution of a fibrin clot, at the end of the coagulation cascade. Its activity is a global reflection of clot formation and lysis. It can't be generated in vitro conditions after blood collection so, that formation is considered a reflection of in vivo hemostatic activity. So, it is appeared to be one of the most valuable parameters in thrombosis research [13,14].

Until a few years ago, plasma D-dimer variation was explained by prothrombotic and inflammatory tumoral state, insufficient control of an antiinflammatory response, multifactorial coagulopathy, surgery, or biological conditions. In spite of that, plasma measurement of D-dimer has become essential in clinical to exclude deep vein thrombosis, pulmonary embolism and disseminated intravascular coagulation. It is considered a biomarker of worse-outcome in cardiovascular disease, with a convincing evidence of association with ischemic stroke, but conflicting and potentially more complex with ICH, until now [15-18].

Poor neurological outcome and high disability scores after ICH have lately increased the interest to determine new biomarkers of bleeding. The recent literature suggested that D-dimers can be used to evaluate and predict clinical prognosis in neurosurgical patients, including after subarachnoid hemorrhage, ICH, ischemic stroke, trauma, dural arteriovenous fistula and intracerebral neoplasms [19-23].

Increasing incidence and morbi-mortality of brain tumors conducted this study to evaluate perioperative plasma D-dimer as risk biomarker of bleeding after brain tumor surgery.

It should be noted during the COVID-19 pandemic, early and effective predictors of clinical outcomes were urgent needed for risk stratification. It has been reported COVID-19 was associated with hemostatic abnormalities and elevated D-dimer levels were observed in non-survivors. It was

considered, with a nonwell established optimal cut-off, the earliest and most helpful biomarker to predict poorer outcomes and improve management. Thanks to the pandemic, the relevance of D-dimer was considered again [24-27].

Methods

A prospective, observational, 18-month study (July 2013-December 2014) was conducted in the Neurointensive Care Unit (N-ICU) at Miguel Servet University Hospital, a single third-level center in Spain. The study included all consecutive adults operated on elective brain tumor surgery by trained and experienced neurosurgeons with postoperative stay in the N-ICU. Dead people in the operating room, incomplete coagulation test (by lost or mistake) or nontumor tissue were exclusion criteria.

Two blood samples were drawn from a jugular central venous catheter placed prior to surgery (A-presurgery or baseline, B-postsurgery and C-24 hours after surgery). The cut-off value of D-dimer was < 500 mg/dl. D-Dimer was immediately measured with two autoanalyzers ACL-TOP 500 y 700 CTS by latex particle immunoassay. Competence and quality management of medical laboratory was accredited by ISO 15189: 2012 certification. Patients did not receive any prophylaxis or hemostatic therapy.

ICH, as a primary outcome, was defined as bleeding that generates radiological signs of intracranial hypertension (IH) either by volume or by mass effect on the routine head computerized tomography (CT) scan 24 hours after surgery. All CT scans were assessed by a committee of neuroradiologists and neurosurgeons. Other filiation data were collected (age, gender, previous coagulopathy, origin and tumor tissue, routine hemostasis and hemogram parameters). Perioperative management of antiplatelet and antiacoagulant agents was properly considered.

Categorical variables were presented as frequencies and percentages. The association between qualitative variables was determined by Pearson Chisquared test (X^2) or Fisher's exact test. Wilconxon-test and T-Test were considered to stablish correlation between quantitative variables. *P* - value < 0.05 was significant for confidence interval of 95%.

Data collection worksheets were stored and analyzed by SPSS® Statistic Software 21.0.0. Each participant was assigned a registration number to to data anonymization. Ethical approval for this study was obtained from Ethics Committee of Clinical Investigation in Aragon (CEICA, nº CP14/2013).

Results

A total of 120 patients were operated on neurosurgery during 18 months. But finally 12 of them were excluded, 10 due to incomplete blood sample and two due to absence of tumor tissue in the histopathological analysis. From 109 patients, 69 were male (63,30%) and 40 female (36,70%)



with a mean age of 54,60 ± 14,75 years; 34 patients (31,2%) were < 50 years old.

Primary tumor resection (68,80%) was more common than recurrent tumor (21,10%) and metastases (10,09%). There were different histological types of brain tumor, being high-grade glioma the most prevalent (39,44%) followed by meningioma (27,52%). The least common was mesenchymal (4,58%). Volume were < 30 ml in most of them (64%) and subtotal removal (≥ 90% of volumen) was possible in more than 85%. Most patients (71,5%) did not have postoperative neurological complications: focal neurologic deficit 24,77% was the most prevalent, followed by headache (5,5%). Only eleven patients (10%) suffered from critical care complication, 8 of them sepsis. According to hemostasis and bleeding disorders, one patient had unexplained preoperative anemia 8,9 g/dl and another one a previous inherited condition (glucose-6phosphate dehydrogenase deficiency G6PDD).

Fifteen units of blood products were transfused, 12 of 14 were intraoperative red blood cells (RBC) and also, intraoperative, 1 pooled platelets (PP). 5 patients needed TXA and 1 prothrombin complex (PC). Noone needed neither frozen plasma (FP) nor FVIIa.

The average length of stay in ICU was 3,34 ± 2,77 days. All patients, except two who died due to massive ICH, were discharged from ICU to neurosurgery hospital floor (Table 1).

Most of patients suffered from minimal disorders in routine hemostasis and hemogram parameters (hemoglobin (Hb), hematocrit (Ht) platelets (P), international normalized ratio (INR), activated partial thromboplastin time (APTT), Prothrombin Activity (PA) and fibrinogen (Fb)) but within normal ranges (Tables 2-4). It should be highlighted that antiplatelet and anticoagulant therapy were both adequately stopped. Despite normal routine and specific baseline hemostasis and coagulation, male with G6PDD suffered from ICH and needed 2 intraoperative RBC.

ICH was finally confirmed in 39 patients (35,78%). The average of D-dimer in those patients was A-1.526,70 ng/dl, B-1.061,88 ng/dl and C-1.330,91 ng/dl. HDD-dimer levels were lower in patients without ICH A-543,97 ng/dl, B-572,02 ng/dl and C-965,23 ng. Maximum value of D-dimer in sample A was 15.053 ng/dl and minimum 39 ng/dl, 5.043 ng/dl and 46 ng/dl in B and 5.494 ng/dl and 36 ng/dl in C respectively (Table 5).

Inferential analysis determined that none of the clinical and tumor data analyzed were statistically associated with ICH, except male group (p0,030 X² test) and ICU stay (< 0,01 W Wilconxon) (Table 1).

Increased levels of D-dimer A and C were associated with ICH (A p0.039, B p0,223 and C p0.042 W-Wilconxon test) (Table 6), but not in patients without ICH. No differences also in D-dimer variation (A-B p0,118, A-C p0,195, B-C p0,756 T-test) (Table 7).

Table 1: Clinical and tumor data and ICH.

		ICH	No ICH	p value
Age	< 50 y.o	12	22	0,73
	> 50 y.o	27	48	
Gender	Male	30	39	0,03
	Female	9	31	
Tumor origin	Primary	25	50	0,25
	Recurrent or Metastasis	14	20	
Histopathology	Meningioma	9	21	0,22
	Glioma	21	32	
	Others	1	14	
	Metastasis	8	3	
Tumor volume NMR	< 29 ml	23	47	0,06
	≥ 30 ml	26	23	
% Tumor removal	≥ 90%	31	8	0,47
	< 89%	62	8	
Postoperative complications	Seizures	0	1	> 0,1
	Hydrocephalus	0	1	
	Headache	2	4	
	Ischemia	2	2	
	Neurologic Deficit	13	14	
	Sepsis	5	3	
Transfusion	Red cells	6	8	> 0,1
	Platelets	1	0	
	Frozen plasma	0	0	
	FVII	0	0	
	Protrombin complex	1	0	
	Tranexamic acid	4	1	
ICU stay (mean days)	3,34 ± 2,77	1,88 ± 1,31		< 0,01
Death	Death	2	0	0,06
	No death	37	70	

Table 2: Routine hemogram and hemosthesis. A- Sample.

	Minimum	Maximum	Mean	SD
Hb	8,90	17,40	13,34	1,66
Ht	26,80	53,50	39,53	4,69
P	90000	310000	180729,73	52838,67
INR	0,40	1,16	0,97	0,098
APTT	17,40	39,70	26,49	4,14
PA	32	162	102,06	16,70
Fb	0,90	8	3,04	1,27

Table 3: Routine hemogram and hemosthesis. B-Sample.

	Minimum	Maximum	Mean	SD
Hb	8,10	16,40	12,50	1,45
Ht	19,20	47,40	37,30	4,69
P	59000	196000	184784,95	192237,39
INR	0,84	9,20	1,08	0,82
APTT	11,00	86,6	26,85	7,91
PA	42,00	136,00	101,58	13,48
Fb	1,10	8,80	3,19	1,32

Postoperative D-dimer levels were extremely elevated in the two patients who suffered from ICH associated with ischemic stroke and also in the three blood samples in those who died. -It should be noted that among patients with ICH, 30 of them (76,9%), in sample A, 20 (51,28%) in sample B and 35 (89,74%) in sample C had D-dimer levels > 500 ng/dl, compared with D-dimer levels < 500 ng/dl (p0,092, p1, p0,761 X² test).



The relative risk of developing a postoperative hematoma was increased 0,36-fold presurgery, 0,25-fold postsurgery and 0,40-fold 24 hours after surgery in patients with D-dimer > 500 ng/dl, respectively.

Regression analysis showed plasma D-dimer levels were statistically associated only with baseline P and PA (p0,02, p0,20, Pearson correlation) (Tables 8-10). Significant association between standard coagulation and ICH was demonstrated only with baseline APTT and postoperative P (p0,020, p0,033 Wilconxon test) (Tables 11-13).

Table 4: Routine hemogram and hemostasis. C- Sample.

	Minimum	Maximum	Mean	SD
Hb	7,90	15,85	12,25	1,45
Ht	24,20	47,90	36,90	4,31
P	70000	327000	165310,00	51574, 34
INR	0,77	1,24	1,00	0,08
APTT	21,10	37,70	27,35	2,93
PA	72	158,00	100,48	13,35
Fb	1,70	7,20	4,24	1,11

Table 5: D-dimer levels in ICH/no ICH group.

		N	Mean	SD	SEM
Dd-A	ICH	39	1526,70	3149,980	671,578
	no ICH	70	543,97	762,344	130,741
Dd-B	ICH	39	1061,88	1217,571	238,785
	no ICH	70	572,02	595,984	83,454
Dd-C	ICH	39	1330,91	1176,957	2014,882
	no ICH	70	965,23	1199,463	164,759

Table 6: D-dimer and ICH.

	W Wilcoxon	Z	Bil. A Sig
Dd-A	846,000	-2,064	0,039
Dd-B	2365,000	-1,218	0,223
Dd -C	2076,000	-2,038	0,042

Table 7: D-dimer variation in ICH/no ICH group.

		N	Mean	DS	SEM	T-test Bil. Sig
A-B Dd	ICH	39	969,4667	3023,51834	780,66908	0,118
	no ICH	70	-65,0000	1135,88224	218,60064	
A-C Dd	ICH	39	440,4750	2904,29784	649,42074	0,195
	no ICH	70	-344,3929	1065,71709	201,40160	
B-C Dd	ICH	39	-352,6000	981,20275	144,91832	0,756
	no ICH	70	-429,1875	1004,02356	196,24055	

Table 8: Standard coagulation and D-dimer -A.

		Dd	Hb	Ht	P	INR	APTT	PA	Fb
Pearson Correlation	Dd	1,000	-,077	-,059	,413	-,172	-,248	,307	-,222
	Hb	-,077	1,000	,863	-,172	-,156	-,348	-,022	-,025
	Ht	-,059	,863	1,000	-,077	-,116	-,365	,013	,006
	P	,413	-,172	-,077	1,000	-,029	-,188	,070	-,080
	INR	-,172	-,156	-,116	-,029	1,000	,261	-,693	,137
	APTT	-,248	-,348	-,365	-,188	,261	1,000	-,266	,173
	PA	,307	-,022	,013	,070	-,693	-,266	1,000	-,033
	Fb	-,222	-,025	,006	-,080	,137	,173	-,033	1,000
Sig.	Dd		,308	,349	,002	,129	,051	,020	,071
	Hb	,308		,000	,130	,154	,010	,442	,436
	Ht	,349	,000		,307	,223	,007	,467	,485
	P	,002	,130	,307		,426	,109	,324	,300
	INR	,129	,154	,223	,426		,042	,000	,184
	APTT	,051	,010	,007	,109	,042		,039	,128
	PA	,020	,442	,467	,324	,000	,039		,415
	Fb	,071	,436	,485	,300	,184	,128	,415	

Table 9: Standard coagulation and D-dimer -B.

		Dd	Hb	Ht	P	INR	APTT	PA	Fb
Pearson Correlation	Dd	1,000	,121	-,096	-,071	-,076	-,092	,027	-,066
	Hb	-,121	1,00	,489	,019	,164	-,014	-,116	,091
	Ht	-,096	,489	1,000	,025	,214	-,032	,174	,116
	P	-,071	,019	,025	1,000	-,010	,015	,058	,004
	INR	-,076	,164	,214	-,010	1,000	-,098	,070	-,021
	APTT	-,092	,014	-,032	,015	-,098	1,000	-,192	,125
	PA	,027	,116	,174	,058	,070	-,192	1,000	-,370
	Fb	-,066	,091	,116	,004	-,021	,125	-,370	1,000
Sig.	Dd		,151	,206	,273	,259	,215	,410	,288
	Hb	,151		,000	,434	,080	,453	,161	,218
	Ht	,206	,000		,416	,033	,391	,068	,161
	P	,273	,434	,416		,468	,449	,311	,487
	INR	,259	,080	,033	,468		,202	,274	,431
	APTT	,215	,453	,391	,449	,202		,050	,142
	PA	,410	,161	,068	,311	,274	,050		,001
	Fb	,288	,218	,161	,487	,431	,142	,001	

Discussion

Poor neurological outcomes after ICH increased the interest in new biomarkers which could identify the risk of life-threatening complications and reliable prognostic criteria. Sequential D-dimer levels have been traditionally determined to detect thromboembolism, structural disorder in traumatic brain injury, as a worse-outcome marker in cardiovascular disease and, despite being uncommon in neurosurgery field, also in prognosis after stroke, but mainly ischemic [28-31].

Juvela, et al. [32] analyzed D-dimer after aneurysmal ICH, with worse long-term results and more advanced stages if elevated, being probably useful as a risk marker of poor outcome. Delgado, et al. [33] predicted early neurologic deterioration and poor outcome after ICH with increased Ddimer levels in 98 consecutive acute ICH. Chiu, et al. [34] confirmed higher D-dimer level after spontaneous ICH was associated with 30 day mortality and Castelnouvo [35] provided clear evidence in 832 patients that elevated levels of D-dimer were potential risk factor for both ischaemic and haemorrhagic stroke, similar findings to Zakai, et al. [20]. The largest meta-analysis, 13 studies including 891 ICH patients, conducted by Zhike Zhou, et al. [36] revealed that high level of D-dimer was associated with risk of ICH, so it was suggested to be a potential biomarker of bleeding in ICH.

Qi Zhou, et al. [21] confirmed recently in a retrospective design with 1.332 patients the elevation of D-dimer is an independent risk factor for poor functional prognosis and mortality in spontaneous ICH.

It is clear D-dimer's role in coagulation and fibrinolytic systems is attractive, but the pathophysiologic mechanism on ICH has not been fully elucidated yet [21] and more studies focusing on hemorrhagic stroke would be needed to clear out the mechanism for this association, multifactorial probably: unclear hemostatic disorder, biological and surgical conditions, influence of transfusion- and finally heritability of a prethrombotic state.

Obviously, it is very difficult to discard the influence of all



Table 10: Standard coagulation and D-dimer –C.

		Dd	Hb	Ht	P	INR	APTT	PA	Fb
Pearson Correlation	Dd	1,000	-,162	-,072	-,094	,098	-,073	-,107	,105
	Hb	-,162	1,000	,191	-,172	-,037	-,150	-,001	-,144
	Ht	-,072	,191	1,000	-,159	-,143	-,052	,138	,000
	P	-,094	-,172	-,159	1,000	,001	,088	-,040	,137
	INR	,098	-,037	-,143	,001	1,000	,093	-,921	,170
	TTPA	-,073	-,150	-,052	,088	,093	1,000	-,169	-,024
	PA	-,107	-,001	,138	-,040	-,921	-,169	1,000	-,121
Sig.	Fb	,105	-,144	,000	,137	,170	-,024	-,121	1,000
	Dd		,074	,262	,201	,191	,257	,170	,175
	Hb	,074		,044	,062	,370	,091	,497	,100
	Ht	,262	,044		,078	,101	,321	,110	,499
	P	,201	,062	,078		,498	,217	,362	,111
	INR	,191	,370	,101	,498		,206	,000	,064
	APTT	,257	,091	,321	,217	,206		,066	,414
PA	,170	,497	,110	,362	,000	,066		,141	
Fb	,175	,100	,499	,111	,064	,414	,141		

Table 11: Standard coagulation –A and ICH.

	W de Wilcoxon	Z	Sig. asintót. (bilateral)
Hb	1760,500	-0,022	0,982
Hto	937,000	-0,564	0,573
Plaq	897,500	-1,292	0,197
INR	2132,000	-0,892	0,372
TTPA	1015,500	-2,318	0,020
AP	1160,000	-0,948	0,343
Fb	1168,500	-0,602	0,547

Table 12: Standard coagulation – B and ICH.

	W de Wilcoxon	Z	Sig. asintót. (bilateral)
Hb	1421,500	-1,040	0,298
Hto	1416,500	-0,961	0,337
Plaq	1285,500	-2,132	0,033
INR	2975,000	-1,849	0,064
TTPA	1798,500	-0,140	0,889
AP	1619,500	-1,426	0,154
Fb	1660,000	-,659	0,510

Table 13: Standard coagulation – C and ICH.

	W de Wilcoxon	Z	Sig. asintót. (bilateral)
Hb	1577,000	-1,731	0,083
Hto	1528,500	-1,868	0,062
Plaq	1608,000	-1,508	0,132
INR	3313,000	-0,603	0,547
TTPA	1813,000	-0,287	0,774
AP	1742,000	-0,667	0,505
Fb	1721,500	-0,929	0,353

those factors on the results but, despite several limitations, this is the first prospective study in the literature to evaluate how perioperative D-dimer behaves in the presence of ICH and with the rest of the hemostatic parameters in order to consider it as a risk marker of unexplained bleeding.

Baseline and 24-hour after aggression samples were statistically associated with ICH, so high D-dimer could be considered as risk marker of bleeding and poor prognosis in

the perioperative of brain tumor. Regression analysis only confirmed significant association with baseline P and PA, probably explained by hipercoaguability and inflammation. A larger sample would be necessary to be replaced.

In regard to standard parameters, several patients suffered from a minimal disorder during perioperative period, however statistical association with ICH only could be demonstrated with baseline APTT and postoperative P. This association seems to be coherent (by consumption coagulopathy during surgical aggression in that tumoral state) but too specific without data to compare in the literature, so these results can not consider the standard parameters as risk markers.

This study is based on a small sample size of a single-center and there is no data available to compare with other brain tumor patients, so findings should be interpreted with caution. There is also no literature for gender and ICH. An increased prevalence of cardiovascular disease and spontaneous ICH is described in males so, it could explain our association [38-40]. But a larger sample size would be necessary to compare this and the other features after ICH. Obviously, several comorbidities, biological conditions, bleedings disorders, drugs, skills and surgical factors could influence bleeding. Although it is very difficult to control all these interfering factors, heterogeneity was minimal and epidemiologic and tumor features were similar to general population [1-6,37], perioperative management of antiplatelet and antiacoagulant agents was adequately considered, preoperative samples were carefully analyzed and neurosurgeons were experts on applying the latest knowledge and minimally invasive neurosurgical techniques in brain tumors.

With regard to the main variable, the lack of established criteria in the literature lead to measure ICH objectively by a committee of neuroradiologists and neurosurgeons, avoiding evacuation criteria very controversial between studies. Other types of intracranial hemorrhage (epidural, subdural and subarachnoid) and ischemic stroke were also evaluated in the CT scan. Fortunately, no more types of hemorrhage were diagnosed. High levels of postoperative D-dimer found in two



patients with ischemic stroke and ICH were not considered for the analysis, however this result would support previous studies to consider high D-dimer as a potential risk marker for both ischaemic and haemorrhagic stroke with poor functional prognosis.

G6PD deficiency, considered latent and more severe in males, would manifest as hemolytic anemia. Despite normal preoperative hemostasis and coagulation, surgical aggression and/or some drugs could bring out this latent deficiency and lead to ICH. However, guidelines do not recommend prophylactic transfusion before major surgery. The association analysis was not considered with an only case [41,42].

All these findings would confirm that perioperative D-dimer levels could be a risk marker of ICH with a high impact on future research to screen patients at risk of stroke. More studies would be worthwhile to confirm this association and develop primary prevention strategies.

Conclusion

High levels of perioperative D-dimer could be considered a risk marker of ICH after brain tumor surgery. However, more studies would be worthwhile to confirm this association and develop primary prevention strategies for stroke.

Declarations

Ethics approval and consent to participate: Written informed consent was required for all participants. Comité de Ética de Investigación de la Comunidad de Aragón (CEICA) approved the study (N^oCP14/2013).

Availability of data and materials: All data generated or analyzed were included in this published article.

Authors contributions

Author's contributions this study are:

EVJ: main author, design, methodology and writing

ANP: coordination and design

BVS: coordination and design

JCP: collection and analysis of neurosurgery data

NFM: blood sample analysis

LSG: visualization, writing-review, expert in brain injury

SRR: visualization, writing-review

NRC: visualization, writing-review

GJJ: visualization, writing-review

MQD: visualization, writing-review and editing, expert in hemotherapy

MDVG: design, methodology, visualization, writing-review

DFE: visualization, writing-review

CRL: statistical analysis

JCL: visualization, writing-review and editing.

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