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PROSPECTIVE OBSERVATIONAL

# Role of Perioperative Plasma D-dimer in Intracerebral Hemorrhage after Brain Tumor Surgery: A Prospective Study

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## Abstract

**Background:** Intracerebral hemorrhage (ICH) is one of the most feared complications after brain tumor surgery. Despite several factors are considered to influence bleeding, an increasing number of clinical studies emphasize that hemostatic disorders, developed during surgical aggression and tumoral status, could explain unexpected ICH. The objetive 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 tumor and post operatory stay in an intensive care unit. Three blood samples evaluated D-dimer levels (A-baseline, B-postsurgical and C-24 hours after surgery). 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 tumoral and hemostatic variables were analyzed. Chi-squared and Fisher's exact test were used in the inferential analysis for qualitative variables and Wilconxon and T-Test for quantitative ones. P-value < 0.05 was considered significant for 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 D- Dimer 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-Wilconxon test). Male group was also associated with ICH (p0.030 $X^2$ 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 $X^2$ 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 not statistical significance (p0.118, p0.195, p0.756 T-test). Platelets and prothrombin activity were associated with D-dimer levels in sample A (p 0.02 and p 0.20, W Wilconson).

**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 developed primary prevention strategies for stroke.

## Keywords

D-dimer, Intracerebral hemorrhage, Tumor, Neurosurgery, Coagulation, Biomarker, Bleeding

## Abbreviations

APTT: Activated partial thromboplastin time; CT: Computerized tomography; Fb: Fibrinogen; FP: Frozen plasma; Hb: Hemoglobin; Ht: Hematocrit; ICH: Intracranial hemorrhage; INR: International normalized ratio; P: Platelets; PA: Prothrombin activity; PCR: Prothrombin complex; PP: Pooled platelets; RBC: Red blood cells; TXA: Tranexamic acid

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## 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, 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 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 cross- linked fibrinogen when dissolution of fibrin clot, at the end of 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 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, measurement of D-dimer has become essential in clinical use to exclude deep vein thrombosis, pulmonary embolism, and disseminated intravascular coagulation. It is considered a predictive marker 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 risk markers of bleeding. The recent literature has 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 marker 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 markedly elevated D-dimer levels were observed in non survivors. It was considered, with a non-well established optimal cutoff, the earliest and most helpful marker to predict poorer outcomes and to 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 or non-tumoral tissue were exclusion criteria.

Two blood samples were drawn from a jugular central venous catheter placed prior to surgery (A-pre-surgery or baseline, B-post-surgery and C-24 hours after surgery). The cut-off value of D-dimer was < 500 mg/dl. D-Dimer was immediately measured with two auto analyzers 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 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 comitte of neuroradiologists and neurosurgeons. Other filiation data were collected (age, gender, previous coagulopathy, origin and tumour tissue and routine hemostasis and hemogram parameters). Perioperative management of antiplatelet and antiacoagulant agents was considered.

Categorical variables were presented as frequencies and percentages. The association between qualitative variables was determined by Pearson Chi- squared 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® Stadistic Software 21.0. Each participant was assigned a registration number 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 non-tumoral brain tissue. 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.

Surgery of primary brain tumor (68.80%) was more common than recurrent (21.10%) and metastases tumor (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 one (4.58%). Volume were < 30ml in most of them (64%) and subtotal removal ( ≥ 90% of volumen) was possible in more than 85%. Most of patients (71.5%) did not have postoperative neurological complications: focal neurologic deficit 24.77% was the most prevalent, followed by headache (5.5%). Only 11 patients (10%) suffered from critical care complication, 8 of them sepsis.

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). No one needed neither frozen plasma (FP) nor FVIIa. Just one patient has preoperative anemia 8.9 g/dl. It should be highlighted that antiplatelet and anticoagulant therapy were both adequately stopped.

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).

**Table 1**: Clinical and tumoral data and ICH.

| | | ICH | No ICH | p value |
|---|---|---|---|---|
| **AGE** | < 50y.o | 12 | 22 | |
| | > 50y.o | 27 | 48 | 0.73 |
| **GENDER** | Male | 30 | 39 | |
| | Female | 9 | 31 | **0.03** |
| | Primary | 25 | 50 | |
| **TUMOR ORIGIN** | Recurrent or Metastasis | 14 | 20 | 0.25 |
| | Meningioma | 9 | 21 | |
| **HISTOPATHOLOGY** | Glioma | 21 | 32 | |
| | Others | 1 | 14 | 0.22 |
| | 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 | |
| | Seizures | 0 | 1 | |
| **POSTOPERATIVE COMPLICATIONS** | Hydrocephalus | 0 | 1 | |
| | Headache | 2 | 4 | > 0.1 |
| | Ischemia | 2 | 2 | |
| | Neurologic | 13 | 14 | |
| | Deficit | | | |
| | Sepsis | 5 | 3 | |
| | Red Cells | 6 | 8 | |
| | Platelets | 1 | 0 | |
| **TRANSFUSION** | Frozen Plasma | 0 | 0 | |
| | FVII | 0 | 0 | > 0.1 |
| | Prothrombin | 1 | 0 | |
| | Complex | | | |
| | Tranexamic | 4 | 1 | |
| | Acid | | | |
| **ICU STAY** | 3,34 ± 2,77 | 1,88 ±1, 31 | | **< 0.01** |
| (mean days) | | | | |
| **DEATH** | Death | 2 | 0 | 0.06 |
| | No Death | 37 | 70 | |

According to hemoglobin (Hb), hematocrit (Ht), platelets (P), international normalized ratio (INR), activated partial thromboplastin time (APTT), prothrombin activity (PA) and fibrinogen (Fb), most of patients had normal ranges (Table 2, Table 3 and Table 4).

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-1.06 1.88 ng/dl and C-1.330, 91 ng/dl. HD-D-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 tumoral data analyzed were statistically associated with ICH, except male group (p0.030 $X^2$ test) and ICU stay (< 0.01 W Wilconxon) (Table 1). D-dimer levels in two dead patients were < 500 ng/ml in three blood samples.

Increased levels of plasma D-dimer A and C were associated with ICH (A p0.039, B p0.223 and C p0.042 W-Wilconxon), but there was absence of association in patients without ICH (Table 6). No differences also in D-dimer variation (A-B p0, 118, A-C p0, 195, B-C p0, 756 T-test) (Table 7).

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 $X^2$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. D-dimer was also statistically associated with P and PA in sample A (p0.02, p0.20,

**Table 2:** Routine hemogram and hemosthasis. Sample A.

| | 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 hemosthasis. Sample B.

| | 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 |

**Table 4:** Routine hemogram and hemosthasis. Sample C.

| | 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 |
|---|---|---|---|---|---|
| | ICH | 39 | 1526,70 | 3,149,980 | 671,578 |
| **Dd A** | no ICH | 70 | 543,97 | 762,344 | 130,741 |
| | ICH | 39 | 1061,88 | 1,217,571 | 238,785 |
| **Dd-B** | no ICH | 70 | 572,02 | 595,984 | 83,454 |
| | ICH | 39 | 1330,91 | 1,176,957 | 2,014,882 |
| **Dd-C** | no ICH | 70 | 965,23 | 1,199,463 | 164,759 |

**Table 6:** D-dimer and ICH.

| | W Wilcoxon | Z | Bil. A Sig |
|---|---|---|---|
| **D Dimer-A** | 846,000 | -2,064 | **0,039** |
| **D Dimer-B** | 2,365,000 | -1,218 | 0,223 |
| **D Dimer-C** | 2,076,000 | -2,038 | **0,042** |

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

| | | N | Mean | DS | SEM | T-test Bil. Sig |
|---|---|---|---|---|---|---|
| | ICH | 39 | 9,694,667 | 3023,51834 | 78,066,908 | |
| **A-B Dd** | no ICH | 70 | -650,000 | 1135,88224 | 21,860,064 | 0,118 |
| | ICH | 39 | 4,404,750 | 2904,29784 | 64,942,074 | |
| **A-C Dd** | no ICH | 70 | -3,443,929 | 1065,71709 | 20,140,160 | 0,195 |
| | ICH | 39 | -3,526,000 | 98,120,275 | 14,491,832 | |
| **B-C Dd** | no ICH | 70 | -4,291,875 | 1004,02356 | 19,624,055 | 0,756 |

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

| | | D-dimer | Hb | Ht | P | INR | APTT | PA | Fb |
|---|---|---|---|---|---|---|---|---|---|
| | D-dimer | 1,000 | 0,121 | -0,096 | -0,071 | -0,076 | -0,092 | 0,027 | -0,066 |
| | Hb | -0,121 | 1,00 | 0,489 | 0,019 | 0,164 | -0,014 | -0,116 | 0,091 |
| | Ht | -0,096 | 0,489 | 1,000 | 0,025 | 0,214 | -0,032 | 0,174 | 0,116 |
| | P | -0,071 | 0,019 | 0,025 | 1,000 | -0,010 | 0,015 | 0,058 | 0,004 |
| Corre lación de Pearson | INR | -0,076 | 0,164 | 0,214 | -0,010 | 1,000 | -0,098 | 0,070 | -0,021 |
| | APTT | -0,092 | 0,014 | -0,032 | 0,015 | -0,098 | 1,000 | -0,192 | 0,125 |
| | PA | 0,027 | 0,116 | 0,174 | 0,058 | 0,070 | -0,192 | 1,000 | -0,370 |
| | Fb | -0,066 | 0,091 | 0,116 | 0,004 | -0,021 | 0,125 | -0,370 | 1,000 |
| | D-dimer | | 0,151 | 0,206 | 0,273 | 0,259 | 0,215 | 0,410 | 0,288 |
| | Hb | 0,151 | | 0,000 | 0,434 | 0,080 | 0,453 | 0,161 | 0,218 |
| | Ht | 0,206 | 0,000 | | 0,416 | 0,033 | 0,391 | 0,068 | 0,161 |
| | P | 0,273 | 0,434 | 0,416 | | 0,468 | 0,449 | 0,311 | 0,487 |
| Sig. | INR | 0,259 | 0,080 | 0,033 | 0,468 | | 0,202 | 0,274 | 0,431 |
| | APTT | 0,215 | 0,453 | 0,391 | 0,449 | 0,202 | | 0,050 | 0,142 |
| | PA | 0,410 | 0,161 | 0,068 | 0,311 | 0,274 | 0,050 | | 0,001 |
| | Fb | 0,288 | 0,218 | 0,161 | 0,487 | 0,431 | 0,142 | 0,001 | |

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

| | | D-dimer | Hb | Ht | P | INR | APTT | PA | Fb |
|---|---|---|---|---|---|---|---|---|---|
| | D-dimer | 1,000 | 0,121 | -0,096 | -0,071 | -0,076 | -0,092 | 0,027 | 0,066 |
| | Hb | -0,121 | 1,00 | 0,489 | 0,019 | 0,164 | -0,014 | -0,116 | 0,091 |
| | Ht | -0,096 | 0,489 | 1,000 | 0,025 | 0,214 | -0,032 | 0,174 | 0,116 |
| | P | -0,071 | 0,019 | 0,025 | 1,000 | -0,010 | 0,015 | 0,058 | 0,004 |
| Corre lación de Pearson | INR | -0,076 | 0,164 | 0,214 | -0,010 | 1,000 | -0,098 | 0,070 | 0,021 |
| | APTT | -0,092 | 0,014 | -0,032 | 0,015 | -0,098 | 1,000 | -0,192 | 0,125 |
| | PA | 0,027 | 0,116 | 0,174 | 0,058 | 0,070 | -0,192 | 1,000 | 0,370 |
| | Fb | -0,066 | 0,091 | 0,116 | 0,004 | -0,021 | 0,125 | -0,370 | 1,000 |
| | D-dimer | | 0,151 | 0,206 | 0,273 | 0,259 | 0,215 | 0,410 | 0,288 |
| | Hb | 0,151 | | 0,000 | 0,434 | 0,080 | 0,453 | 0,161 | 0,218 |
| | Ht | 0,206 | 0,000 | | 0,416 | 0,033 | 0,391 | 0,068 | 0,161 |
| | P | 0,273 | 0,434 | 0,416 | | 0,468 | 0,449 | 0,311 | 0,487 |
| Sig. | INR | 0,259 | 0,080 | 0,033 | 0,468 | | 0,202 | 0,274 | 0,431 |
| | APTT | 0,215 | 0,453 | 0,391 | 0,449 | 0,202 | | 0,050 | 0,142 |
| | PA | 0,410 | 0,161 | 0,068 | 0,311 | 0,274 | 0,050 | | 0,001 |
| | Fb | 0,288 | 0,218 | 0,161 | 0,487 | 0,431 | 0,142 | 0,001 | |

Pearson correlation) (Table 8, Table 9 and Table 10).

## Discussion

Poor neurological outcomes after ICH increased the interest to determine new biomarkers with the aim of identifying the risk factor for life-threatening complications and reliable prognostic criteria. Sequencial D-dimer levels have been traditionally determined to detect thromboembolism, structural disorder in traumatic brain injury, as a worse-outcome marker in cardiovascular disease or, despite being uncommon in neurosurgery field, 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 D- dimer levels in 98 consecutive acute ICH. Chiu, et al. [34] confirmed higher D-dimer level after spontaneuous ICH was associated with 30- day mortality and Castelnouvo [35] provided clear evidence in 832

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

| | | D-dimer | Hb | Ht | P | INR | APTT | PA | Fb |
|---|---|---|---|---|---|---|---|---|---|
| | **D-dimer** | 1,000 | -0,162 | -0,072 | -0,094 | 0,098 | -0,073 | -0,107 | 0,105 |
| | **Hb** | -0,162 | 1,000 | 0,191 | -0,172 | -0,037 | -0,150 | -0,001 | -0,144 |
| | **Ht** | -0,072 | 0,191 | 1,000 | -0,159 | -0,143 | -0,052 | 0,138 | 0,000 |
| **Pearson Correlation** | **P** | -0,094 | -0,172 | -0,159 | 1,000 | 0,001 | 0,088 | -0,040 | 0,137 |
| | **INR** | 0,098 | -0,037 | -0,143 | 0,001 | 1,000 | 0,093 | -0,921 | 0,170 |
| | **TTPA** | -0,073 | -0,150 | -0,052 | 0,088 | 0,093 | 1,000 | -0,169 | -0,024 |
| | **PA** | -0,107 | -0,001 | 0,138 | -0,040 | -0,921 | -0,169 | 1,000 | -0,121 |
| | **Fb** | 0,105 | -0,144 | 0,000 | 0,137 | 0,170 | -0,024 | -0,121 | 1,000 |
| | **D-dimer** | | 0,074 | 0,262 | 0,201 | 0,191 | 0,257 | 0,170 | 0,175 |
| | **Hb** | 0,074 | | 0,044 | 0,062 | 0,370 | 0,091 | 0,497 | 0,100 |
| | **Ht** | 0,262 | 0,044 | | 0,078 | 0,101 | 0,321 | 0,110 | 0,499 |
| | **P** | 0,201 | 0,062 | 0,078 | | 0,498 | 0,217 | 0,362 | 0,111 |
| **Sig.** | **INR** | 0,191 | 0,370 | 0,101 | 0,498 | | 0,206 | 0,000 | 0,064 |
| | **APTT** | 0,257 | 0,091 | 0,321 | 0,217 | 0,206 | | 0,066 | 0,414 |
| | **PA** | 0,170 | 0,497 | 0,110 | 0,362 | 0,000 | 0,066 | | 0,141 |
| | **Fb** | 0,175 | 0,100 | 0,499 | 0,111 | 0,064 | 0,414 | 0,141 | |

patients that elevated levels of D-dimer were potential risk factor for both ischaemic and haemorrhagic stroke, similar findings to Zakai N.A, 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.

Recently, 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.

However, this is the first prospective study in the literature to evaluate plasma D-dimer levels after brain tumor surgery and also the first that demonstrates high levels of perioperative D-dimer could increase the risk of ICH.

Unfortunately, it suffers from some limitations. Although D-dimer's role in coagulation and fibrinolytic systems is attractive, the pathophysiologic mechanism of D-dimer in ICH has not been fully elucidated [21].

It is based on a small sample size of a single-center and there is no data to compare in brain tumor patients, so findings should be interpreted with caution. It is also known that several comorbidities, biological conditions and surgical factors could also influence bleeding. However, heterogeneity was minimal and epidemiological and tumoral features were similar to general population [1-6,37]. Neurosurgeons were experts on aplying the latest knowledge and minimally invasive neurosurgical techniques in brain tumor. The lack of established criteria in the literature lead to measure the main variable ICH objectively: radiological signs of intracranial hypertension on the routine CT scan 24 hours after surgery evaluated by a committe of neuroradiologists and neurosurgeons, avoiding evacuation criteria very controversial between studies.

Literature review didn't find studies to evaluate association between gender and ICH after brain tumor surgery. Prevalence of cardiovascular disease and spontaneous ICH increases 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.

Despite these review, without evidence in brain tumor population, more studies focusing on hemorrhagic stroke are needed to clear out the mechanism for the association with D-dimer, multifactorial probably: unclear haemostatic disorder, biological and surgical conditions, heritability of a prethrombotic state or even not be the causation, but a marker linked to the risk of hemorrhage, with a high impact on future research to screen patients at risk of stroke.

Obviously, we can not discard that our results were influenced by those factors, but high levels of D-dimer determined in three consecutive samples, especially in baseline and 24-hour ones, were statistically associated to ICH after brain tumor surgery, with a relative risk of developing ICH increased 0.36-fold and 0.40-fold, respectively.

Several of our patients also suffered from a low disorder of hemostasis and standard coagulation in three sequencial samples, however inferential analysis only found association between D-dimer with baseline ATTP and postsurgery platelets. It is likely to be coherent (explained by consumption coagulopathy during

surgical agression in a tumoral state), but a very specific association without data to compare in the literature, so they can not be considered neither influencers of D-dimer levels nor markers of bleeding.

These findings would confirm that perioperative D-dimer levels could be a risk marker of ICH. More studies may be worthwhile to confirm this association and developed primary prevention strategies for hemorrhagic stroke. It may also help to identify patients that could benefit more from agents targeted at hemostasis rather than platelet or inflamatory function.

## 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 developed primary prevention strategies for stroke.

## Declarations

§ Ethics approval and consent to participate ✔

§ Consent for publication ✔

§ Availability of data and material ✔

§ Competing interests: 'The authors declare that they have no competing interests'

§ Funding: 'Not funding to declare'

§ Authors contributions ✔

## Author's Contributions this Study are

EVJ: Main author, design, methodology and writing

ANP: Coordination and design

JCP: Collection and analysis of neurosurgery data

CRL: Statistical analysis

NFM: Blood sample analysis

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

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

JCL: Visualization, writing-review and editing

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