

Universitat de Girona  
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# Surgical Evacuation of Cerebral Intraparenchymal Hemorrhage: Prognostic Factors and Outcome

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A retrospective study



**END OF TERM PROJECT**

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*Challenges make us grow, learn and know more about ourselves.  
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*Als meus pares, falten paraules; gràcies per tant.  
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*"Medicine is a science of uncertainty and an art of probability".*

*William Osler.*

## **ABSTRACT**

**BACKGROUND:** Cerebral intraparenchymal hemorrhage (CIPH) is a major cause of morbidity and mortality worldwide. Despite its detrimental prognosis, treatment options are few and have remained invariable over the last years. Many studies have been conducted worldwide in order to establish the role of evacuating surgery as a potential treatment, but they all failed to provide significant evidence of its benefits. Nevertheless, subgroup analysis of these studies suggest certain patients would benefit from it. More studies are necessary in order to clarify this controversy.

**PURPOSE:** the aim of this study is to describe the outcome of evacuating surgeries for CIPH at our center, and to find some variables that might be associated to a better prognosis of these patients.

**METHODS:** In a descriptive, retrospective cohort study we analysed the medical history of all patients with CIPH who underwent evacuating surgery in Doctor Josep Trueta Hospital (JTH) in 10 years (from January 2009 to December 2018). Descriptive, bivariate and multivariate analysis were performed in order to assess the association between certain variables and the functional outcome and mortality of these patients.

**RESULTS:** a total of 43 patients were studied, with a mean age of  $59,91 \pm 12,8$ . 58,1% were women. 67,4% had AHT and 18,6% were OAC or antiplatelet consumers. The median NIHSS was 18 [13,21] and the median volume was 50 [36,77]. The most frequent cause of CIPH in our series was arterial hypertension (AHT), followed by arteriovenous malformations (AVM). 3 months after the surgical intervention, 16 (37,2%) patients had died and 40 (93%) patients presented a poor outcome. 35 (81,4%) patients were functionally dependent 1 year after surgery. Neither the volume of the hematoma nor the time to surgery were significant independent predictors of the outcome of those patients.

**CONCLUSION:** Mortality stood at 37,2%, and 81,4% of patients were dependent at 1 year of the surgery. Our study did not find any factor associated to a worse outcome on patients operated from evacuation of a CIPH in JTH. Mortality rates in our sample were not different from those reported in previous studies.

**KEY WORDS:** intracerebral hemorrhage ♦ evacuating surgery ♦ hematoma volume.

## **ABBREVIATIONS**

<b>AHT</b>	Arterial Hypertension	<b>PE</b>	Pulmonary Embolism
<b>AVM</b>	Arteriovenous malformation	<b>SAH</b>	Subarachnoidal Hemorrhage
<b>BBB</b>	Blood-Brain Barrier	<b>SBP</b>	Systolic Blood Pressure
<b>CAA</b>	Cerebral Amyloid Angiopathy	<b>TIA</b>	Transient Ischemic Attack
<b>CIPH</b>	Cerebral Intraparenchymal Hemorrhage	<b>VC</b>	Ventricular Catheter
<b>CNS</b>	Central Nervous System	<b>VKA</b>	Vitamin K Antagonists
<b>CPP</b>	Cerebral Perfusion Pressure		
<b>CSF</b>	Cerebrospinal Fluid		
<b>CT</b>	Computerised Tomography		
<b>DBP</b>	Diastolic Blood Pressure		
<b>DM</b>	Diabetes Mellitus		
<b>DVT</b>	Deep Vein Thrombosis		
<b>ED</b>	Emergency Department		
<b>FMD</b>	Fibromuscular Dysplasia		
<b>GCS</b>	Glasgow Coma Scale		
<b>ICH</b>	Intracerebral Hemorrhage		
<b>ICP</b>	Intracranial Pressure		
<b>INR</b>	International Normalized Ratio		
<b>IVH</b>	Intraventricular Hemorrhage		
<b>JTH</b>	Josep Trueta Hospital		
<b>MAP</b>	Mean Arterial blood Pressure		
<b>MMD</b>	Moya-Moya Disease		
<b>MRI</b>	Magnetic Resonance Imaging		
<b>mRS</b>	Modified Rankin Scale		
<b>NIHSS</b>	National Institutes of Health Stroke Score		
<b>OAC</b>	Oral Anticoagulant		
<b>PCC</b>	Prothrombin Complex Concentrates		

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## **1. INTRODUCTION**

### **1.1. EPIDEMIOLOGY**

Cerebrovascular disease is one of the main causes of mortality and disability in developed countries. It can be produced by two different mechanisms: ischemia and hemorrhage. Ischemia is defined as the interruption of the blood flow, thus impairing irrigation to the tissue dependent on the affected vessel. Ischemic strokes account for about 80% of all strokes. Hemorrhage consists of the extravasation of blood outside the vessel after its rupture, invading the surrounding parenchyma. Cerebral hemorrhages represent approximately 20% of all strokes. These can be divided in intracerebral hemorrhages (ICH) and subarachnoid hemorrhages (SAH). ICH accounts for 10 to 15% of all strokes, and it includes both intraparenchymal and intraventricular hemorrhage (IVH). Cerebral intraparenchymal hemorrhage (CIPH) is produced by a vessel rupture and extravasation of blood into the brain parenchyma (1).

Worldwide incidence of ICH is 10-20 cases per 100.000 inhabitants/year. In Spain the incidence is similar, reaching 15 cases per 100.000 inhabitants/year, more frequently in males over 55 years old (2).

### **1.2. ETIOLOGY**

Intracerebral hemorrhage can occur spontaneously or be a consequence of an underlying disease. Spontaneous CIPH is mostly due to hypertension or cerebral amyloid angiopathy, while secondary CIPH is often caused by coagulopathies, aneurysms, arteriovenous malformations (AVM), use of antithrombotic drugs, tumours or intake of abuse drugs (cocaine, amphetamines) (3).

#### ***1.2.1. Hypertension***

Hypertension has proved to be the most prevalent and most significant modifiable risk factor for spontaneous intracerebral hemorrhage and when hypertension is better controlled, the incidence of this condition appears to diminish. Arterial hypertension (AHT) is present in 91% of patients at the onset of the hemorrhage (4).

The mechanism through which chronic hypertension would lead to an increased risk of hemorrhage is the hyperplasia of smooth muscle cells together with the deposition of collagen fibers on the vessel's wall. These changes imply a reduction of the vessel's contractility and an impaired cerebral autoregulation. Cerebral autoregulation allows for cerebral blood flow to be almost constant, despite wide variations of systemic pressure.

Hypertensive hemorrhage is to be expected in areas of the brain packed with small arterioles and perforating arteries, which are more sensible to vessel changes induced by chronic hypertension. Those areas are deep structures like putamen, thalamus, cerebellum, caudate nucleus and brain stem (5).

Aggressive management of chronic hypertension has led to a significant reduction of both ischemic and hemorrhagic strokes worldwide (6). However, it remains unclear how aggressive the management of AHT should be in the acute phase of CIPH. Several studies have shown that an aggressive treatment of AHT during the first hours after CIPH would reduce the hematoma expansion, although that does not necessarily imply an improved clinical outcome (7).

### ***1.2.2. Cerebral amyloid angiopathy***

Another cause of primary intracerebral hemorrhage is cerebral amyloid angiopathy (CAA), affecting particularly elderly people. It consists of the deposition of  $\beta$ -amyloid protein in the blood vessels of both the cerebral cortex and leptomeninges. Alleles  $\epsilon 2$  and  $\epsilon 4$  of apolipoprotein E gene have been found to triple the risk of recurrent intracerebral hemorrhage among survivors of lobar intracerebral hemorrhage related to amyloid angiopathy. The presence of any of these two alleles increases the vasculopathic effects of amyloid deposition in cerebral vessels, therefore incrementing the risk of hemorrhage (3,8). CAA patients are at a higher risk of aneurysm formation, vessel wall weakening and potential rupture of vessels due to amyloid deposition at media and adventitia layers of characteristically small arteries or veins (3).

Hypertension and CAA combined represent together up to 88% of CIPH (9).

### **1.2.3. Coagulation**

Hemophilia type A (factor VIII deficiency) and type B (factor IX deficiency), together with other coagulation factor deficiencies (I, VII, VIII and Von Willebrand factor) are all associated to CIPH (10).

Platelet aggregation and its interaction with the endothelium can be impaired by hepatic dysfunction due to conditions such as chronic hepatitis, chronic alcoholism or cirrhosis, increasing the risk of both systemic bleeding and CIPH. Thrombocytopenia and antiplatelet antibodies may as well affect the coagulation process leading to CIPH (3,10).

Patients with coagulopathy-related CIPH generally present large hematomas and are at a greater risk of hematoma expansion over an extended time frame(11–13).

### **1.2.4. Aneurysms and AVM**

Infective endocarditis, meningitis and oral-orbital-facial infections may produce either mycotic aneurysms or infective arteritis, which commonly take place in medium or small size intracranial vessels, inducing CIPH when they burst (14).

AVM and fistulas are anastomoses of arterial and venous systems, lacking a normal capillary network in between. This means that blood drains from a high pressure fast arterial system directly to a low pressure and slow flowing venous duct. Neovascularization then takes place and forms the bed of AVMs (15). AVMs are an important cause of CIPH, especially among young people.

The effectivity of prophylactic interventional therapy for unruptured AVMs was tested by the ARUBA study (16), which had to be interrupted because of excessive superiority of the medical management group. With all its limitations, it also failed to stratify and allow validation for any of the interventions at an individual level.

### **1.2.5. Vasculopathies**

Blood vessel walls may also be weakened by intracerebral vasculopathies such as fibromuscular dysplasia (FMD), Moya-Moya disease (MMD) and central nervous system (CNS) vasculitis. Suspicion of underlying vascular abnormalities as a cause for the CIPH should rise

in front of patients with an age under 65 years old, females, nonsmokers, lobar CIPH, intraventricular extension and no history of hypertension or coagulopathy (17).

FMD is a vascular disease consisting on media hyperplasia, being a rare cause of CIPH but rather causing SAH, ischemic strokes or transient ischemic attacks (TIA)(3).

Moya-Moya disease consists of a spontaneous vase-occlusion of the circle of Willis, and it commonly produces ischemic symptoms in children and hemorrhagic episodes in adults.

The occlusion of the circle of Willis increases blood pressure, which prompts the formation of collateral vessels to distribute the load. The rupture of those vessels may result in the hemorrhages seen mostly in adults. It entails high mortality and morbidity rates, and most of the CIPH associated to MMD occur around the deep nuclei (3,18).

### **1.2.6. Tumours**

CNS tumours such as glioblastoma or oligodendrogliomas have been associated with some frequency to CIPH. However, due to the high prevalence of lung cancer, lung metastasis remain the most frequent tumour causing CIPH (3).

Tumours commonly imply vascular proliferation, and these newly formed vessels differ from rudimental ones: they lack mature blood-brain barriers and tight junctions, being susceptible to ruptures and hemorrhage (19).

### **1.2.7. Iatrogenic**

Antiplatelet therapy is very often used to treat and prevent ischemic cerebrovascular, cardiovascular and peripheric vascular diseases. The oldest antiplatelet agent is the aspirin, and studies have shown that its role triggering a CIPH or in the expansion of an hematoma is minimal (20,21). Nonetheless, the risk of CIPH increases substantially with the combination of aspirin with another antiplatelet agent (3).

Anticoagulants are widely used for prevention and treatment of many thromboembolic conditions. CIPHs associated to anticoagulant therapy are larger in size, have more frequent expansions and worse clinical outcomes compared to spontaneous CIPH (12,22).

Alcohol intake increases the risk of hematoma for being a hypertensor and causing liver pathology, which may then lead to impaired coagulation. Cocaine and amphetamines, as sympathomimetic agents, can lead to hypertensive crises and hemorrhages (3).

### 1.3. PATHOPHYSIOLOGY

CIPH starts with a rupture of chronically damaged vessels, followed by the formation of an hematoma. Hydrostatic pressure contributes to edema formation, a combination of the gradients of pressure between the hematoma and the brain parenchyma surrounding it. After the clot is formed, it suffers a process of retraction, in which the serum is expelled from the hematoma. This serum around the clot impairs normal blood flow circulation. The coagulation cascade is then activated and thrombin is formed, which plays an important role in clot retraction and the formation of edema. Heparinized patients have shown to have a much smaller edema after a CIPH (23). Hemoglobin breakdown products are released by the clot during the inflammatory process, producing a toxic effect. Brain parenchyma damage is mainly explained by two mechanisms: the mass effect produced by the hemorrhage, which compresses the surrounding parenchyma, and the toxicity of certain substances released from the blood cells. These mechanisms account for the early edema formation in the first hours after the onset of the hematoma (*figure 1*).

At this point, the hemorrhage can stop and be reabsorbed following the natural process.

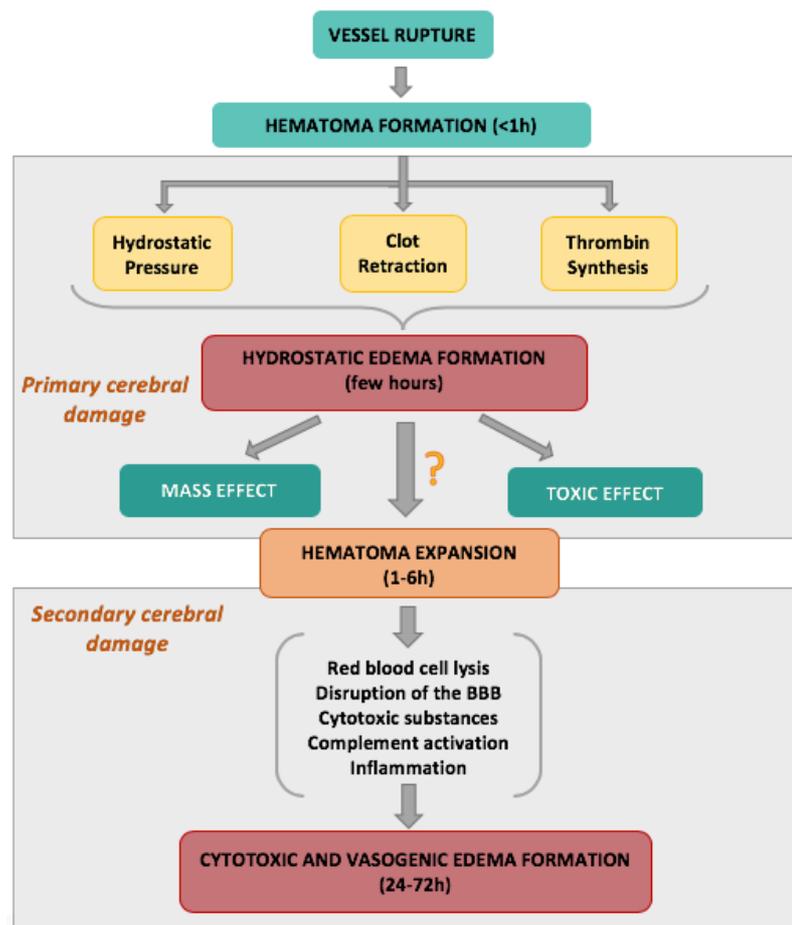


Figure 1 Pathophysiology of cerebral hemorrhage.

In approximately 38% of the patients, though, there is an expansion of the hematoma. The reasons for this enlargement are still unknown, but it is known to be the main cause of early neurologic deterioration and a clear prognostic factor. One quarter of patients suffer a deterioration of consciousness the first 24 hours, frequently associated with hematoma expansion (9,24).

Some hours later, perihematomal edema develops. This delayed edema formation might be explained by red blood cell lysis, when the oxyhemoglobin released causes toxicity and disruption of the blood-brain barrier (BBB). Heme group from hemoglobin can be degraded into iron, carbon monoxide and biliverdin, which will be later converted to bilirubin. These three substances are toxic for the brain, and contribute to edema formation by different mechanisms (2,23). The expansion of the edema keeps going from 3 to 7 days after the hemorrhagic event.

The complement reaches the brain parenchyma either through the extravasated blood of the hematoma or by the later disruption of the BBB. The complement cascade activation implies an inflammatory reaction and more cell lysis, increasing toxicity and edema expansion. The presence of plasma proteins from the extravasated blood in the parenchyma counteracts the oncotic pressure from blood vessels, and therefore after BBB disruption only hydrostatic pressure from the capillaries acts, promoting more fluid extravasation (2,23).

Although hematoma growth is observed in less than 40% of CIPH patients, its correlation with early neurological deterioration and poor functional outcome make it a very relevant feature. It is especially significant for its potential as a treatment target, since the process of expansion can be modified (25,26).

Multiple bleeding focus in the periphery of the clot have been associated to early hematoma growth. This active bleeding might be due to the rupture of vessels in the tissue surrounding the hematoma, a consequence of the mechanical shearing produced by the clot itself. The term "spot sign" is used to describe the visual appearance of this bleeding on different imaging techniques such as CT angiography, MRI and cerebral arteriography (27).

#### 1.4. SYMPTOMS

Symptoms of CIPH are generally indistinguishable from those of an ischemic stroke. There are, however, some features that might be more typically associated to one of the two. Low level of consciousness, for example, is more common in CIPH than in other types of stroke. It is a direct effect of intracranial pressure (ICP), often associated to compression of thalamus or brainstem, and it is more common in infratentorial hemorrhages (2,9).

Sudden, intense, pulsating and long-lasting cephalalgias are present in half of the patients with CIPH. Vomiting is more frequent in posterior hematomas, and is also related to ICP.

Supratentorial hemorrhages present with a sensory-motor impairment contralateral to the lesion. Infratentorial hemorrhages show brainstem dysfunction and cranial nerves damage. Cerebellar lesions commonly imply ataxia, nystagmus and dysmetria.

Focal convulsions are present in 5-15% of patients and are almost exclusive of supratentorial hemorrhages (28).

Fever is a consequence of either hypothalamus affection or neuroinflammatory mediators secreted in response to cellular necrosis.

If hemorrhage invades the intraventricular or subarachnoid spaces, nuchal stiffness may appear.

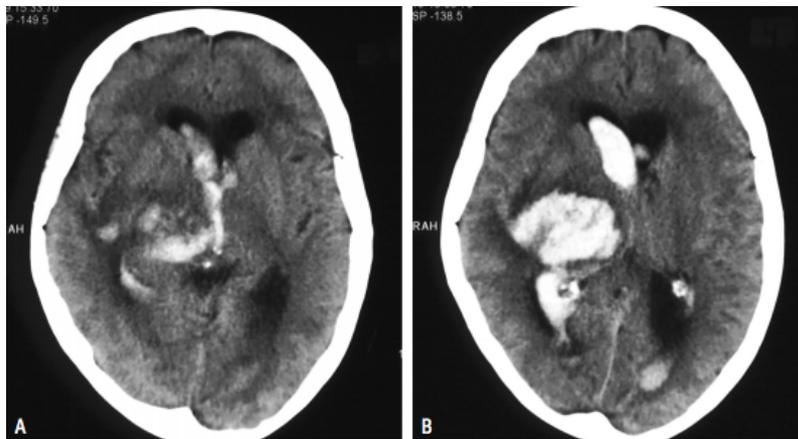
Neurological deterioration will take place over the first 24 hours in approximately 1 out of 4 patients with CIPH, mainly due to hematoma expansion, IVH or early edema (9,28).

#### 1.5. DIAGNOSIS

CIPH is a medical emergency. Sudden focal neurological symptoms are assumed to be vascular until proved the opposite. The first hours after the onset of the stroke are crucial, as early deterioration may appear. While there is no way of assuredly distinguish between an ischemic or hemorrhagic origin of the stroke, there are certain clinical signs that might guide our clinical suspicion to CIPH: vomiting, systolic blood pressure > 220 mmHg, coma, severe headache or progression of symptoms over minutes or hours are some of these signs (2).

Both computerized tomography (CT) and magnetic resonance imaging (MRI) can be used for the diagnosis of CIPH to determine size, location and hematoma growth (*figure 2*) (29), but CT is considered the Gold Standard in identifying acute hemorrhage, being very sensitive.

Gradient echo and T2 susceptibility-weighted MRI are, however, as sensitive as CT spotting acute hemorrhage and more sensitive detecting prior hemorrhage (29,30).



**Figure 2** CT on admission showing basal ganglia hemorrhage (A). CT on the same patient after 6h of admission, showing hematoma growth (B).

Early neurological deterioration associated to CIPH is related partly to the fact that active bleeding may be prolonged until hours after the onset. Identifying patients at high risk of hematoma expansion is, therefore, a main area of investigation (25).

As mentioned above, CT angiography and contrast-enhanced CT can help to determine the risk of hematoma enlargement, based on the presence of contrast within the hematoma, otherwise called spot sign (**figure 3**) (31). The extravasation of contrast is associated with hematoma expansion and is an independent predictor for mortality and functional outcome. Several studies affirm the appearance of spot sign is associated with subsequent hematoma growth. It has also been associated to larger hemorrhages, worse clinical presentation and IVH expansion(27,32).



**Figure 3** Patient with spot sign. Non-contrast CT shows left posterior basal ganglia hematoma (A). Small focus of enhancement constitutes the spot sign (black arrow) (B). Postcontrast CT shows enlargement of the spot sign (white arrow)(C). Non contrast CT after 1 day of the onset reveals hematoma growth and IVH (D) (30).

Angio-CT can be used for detection of AVMs and aneurysms as well, and CT is also better at revealing the presence of ventricular hemorrhage. MRI is superior at detecting chronic microbleeds, evaluating the evolution time of the hematoma and for edema delimitation.

CT is normally more used for its availability and quicker results (2).

Cerebral angiography is used in case of subarachnoid hemorrhage, abnormal calcifications or unusual hematoma location. Patients with lobar hemorrhage location, age <55 years and no history of hypertension are more likely to present a secondary cause of CIPH and MRI and conventional cerebral angiography would also be indicated (2,9).

### 1.6. PROGNOSIS

CIPH is responsible for the most devastating outcomes of all strokes. Mortality at one month is between 35% and 50%, and half of the deaths take place within the first 48h due to intracranial hypertension. It is also associated to severe morbidity, as only 10% of patients are independent after one month and 20% after 6 months. Up to half of the patients suffer from a certain degree of disability, which entails high healthcare costs (2,33).

Main prognostic factors include age, Glasgow Coma Scale (GCS, see *Annex D*), neuroimaging

Component	ICH Score Points
GCS score	
3-4	2
5-12	1
13-15	0
ICH volume, cm <sup>3</sup>	
≥30	1
<30	0
IVH	
Yes	1
No	0
Infratentorial origin of ICH	
Yes	1
No	0
Age, y	
≥80	1
<80	0
<b>Total ICH Score</b>	<b>0-6</b>

**Table 1 ICH Score (34).**

features (hematoma volume, hematoma growth, associated ventricular hemorrhage), temperature, hyperglycemia, antiplatelet and anticoagulant treatment. Hypertension has shown to be a main risk factor but has not yet proved to be associated with a worse prognosis (2,34,35).

Some scales like the ICH Score (**table 1**) are used to predict mortality, considering the most determinant variables affecting prognosis (36).

## **1.7. GENERAL MANAGEMENT**

Due to the risk of neurological deterioration and the poor long-term outcomes, aggressive early management is essential (34).

### ***1.7.1. Prehospital management***

The first approach to the patient who has suffered a stroke should be ensuring airway permeability, followed by cardiovascular support if required. While transporting the patient to the closest hospital prepared for stroke management, it is essential to alert the emergency department of the impending arrival of a stroke, so that they can start activating the necessary protocols. Advanced notification has proved to shorten the time from hospital arrival to the performance of a computed tomography (door-to CT time)(34). The timing of the onset of the symptoms (when unknown, the last time having seen the patient asymptomatic), concomitant treatments such as anticoagulants and the previous functional status of the patient are important data which must be collected from anyone accompanying the patient, as it will be determinant for deciding the treatment (37).

### ***1.7.2. Emergency department management***

At the arrival, diagnostic procedure is imperative: brain CT, blood-test, electrocardiogram and chest x-ray are required. Patients should be constantly monitored in a specialized stroke unit, as it has proved to reduce the risk of death or dependency in comparison with regular intensive care units or conventional wards (38). Emergency departments (ED) should be entirely prepared for the management of CIPH patients, having a transfer option available to a third level hospital if it is necessary. The use of telemedicine is an alternative for hospitals which have no consultants on-site (34,37).

A standardized severity score is necessary as a part of the evaluation in the ED. Several scales are used worldwide, with no consensus on the best one. The National Institutes of Health Stroke Scale (NIHSS, see *Annex C*) is usually used in ischemic stroke and is also useful in CIPH, although the latter patients present more often with depressed consciousness on the onset, which can lower the practicality of NIHSS. The most widely used is the ICH Score(34,37).

Once the diagnosis is made, a transfer to a stroke unit is primordial, while initiating early management in the time the patient waits for the bed to be arranged. Whereas pathways for the management of ischemic strokes are widely established, not many hospitals have specific protocols for the treatment of CIPH. A specific management for CIPH should stress the necessity of treating those conditions that are time dependent. Blood pressure lowering and coagulopathy reversal are good examples of that, and they shall be done immediately after the arrival to the ED. Blood pressure and oxygen saturation should be constantly monitored. An adequate ventilation and a strict control of the hemodynamic situation are primordial to avoid secondary cerebral damage. In severe cases ICP might need to be monitored and if hydrocephalus is present, implantation of a ventricular catheter (VC) should be considered (2,37,39,40).

## **1.8. THERAPEUTICAL MANAGEMENT**

### ***1.8.1. Hemostasis and coagulopathy***

Oral anticoagulants (OACs), antiplatelet agents, coagulation factor deficiencies and platelet abnormalities imply an additional risk of CIPH. One fifth of patients with CIPH are OAC consumers. Vitamin K antagonists (VKA) such as warfarin are the most frequently prescribed OACs, but new agents that do not require laboratory monitoring are being increasingly used, such as dabigatran, rivaroxaban and apixaban. These new agents are associated with a lower risk of CIPH (41).

When facing a patient with a CIPH episode, it is essential to consider the use of antithrombotic drugs and investigate the presence of an underlying coagulopathy in order to perform the appropriate management. In case we find a platelet deficiency or coagulopathy, platelets or coagulation factors must be replaced (34).

For CIPH patients taking VKAs, rapid correction of the International normalized ratio (INR) is recommended. Although fresh frozen plasma along with vitamin K has been the main treatment for years, prothrombin complex concentrates (PCCs) plus vitamin K have proved to rapidly normalize the INR in patients taking VKAs, and they have become the current recommendation. Recombinant activated factor VIIa has also emerged as a potential therapy, but it has shown not to be as effective as PCCs in restoring overall thrombin generation.

Moreover, it does not replenish all the vitamin-K dependent factors, it is expensive and it prompts to thrombotic events, so it is not currently recommended as warfarin reversal (42).

The effect of antiplatelet use on CIPH has not reached a consensus. Some studies suggest that platelet dysfunction has no association with hematoma growth, while others propose it might have. Platelet monitoring may be useful to guide hemostatic interventions, but there is still not enough evidence on this fact. A randomized multi-center trial showed no beneficial effect of platelet transfusion in CIPH related to antiplatelet-use, proving for it to be inferior to standard care alone (34,37).

After a CIPH, patients are at a high risk of thromboembolic disease. CLOTS 3 trial (Clots in Legs or Stockings After Stroke) found intermittent pneumatic compression begun the day of hospital admission reduced the incidence of deep vein thrombosis (DVT), particularly in patients suffering from hemorrhagic stroke (43).

The occurrence of DVT or pulmonary embolism (PE) in patients with CIPH implies considering full systemic anticoagulation or placement of an inferior vena cava filter. It is not clear whether one alternative is superior to the other, as well as the optimal anticoagulation regimen (37,44).

### **1.8.2. Blood Pressure**

High systolic blood pressure is a common finding in CIPH, and it is associated with hematoma expansion, neurological deterioration, death and dependency (34,37). It must be taken into account that whilst an elevated blood pressure can rise the bleeding risk, a very aggressive treatment of blood pressure could diminish cerebral perfusion pressure and lead to ischemic damage (2). Several studies have been conducted in order to establish the safety and efficacy of blood pressure reducing after a CIPH event. A consensus has been reached, and acute reduction of blood pressure to 140 mmHg has proved to be safe for those patients presenting with systolic blood pressure between 150 and 220 mmHg, as long as no contraindication exists to such treatment. This approach has been related to a better functional outcome for patients surviving the stroke. It is uncertain, though, whether patients with very high systolic blood pressures (>220mmHg) will benefit as much, but aggressive reduction of blood pressure by a continuous intravenous infusion and frequent monitorization is recommended in those cases(34,45). Intensive reduction of systolic blood pressure to a target of 110 to 139 mmHg

did not show a lower rate of death or disability compared to the less aggressive reduction of 140 to 179 mmHg (46).

### ***1.8.3. Glucose, fever and seizures***

There is an increased rate of mortality and poor outcome in CIPH patients presenting with high levels of glucose on admission, having or not diabetes mellitus. The optimal levels of glucose remain not yet clear, but both hyper and hypoglycemia should be avoided in order to prevent secondary neuronal damage (37,47).

Supratentorial CIPH is frequently associated with fever, especially if there is intraventricular hemorrhage. The duration of fever after the first 72h has been proportionally associated to a worse prognosis, and therefore it should be treated (37).

Antiseizure drugs can be used to treat clinical seizures in patients with CIPH, although prophylactic treatment is not recommended. Seizures are more often present when cerebral cortex is affected (9).

### ***1.8.4. Complications***

Pneumonia is a frequent complication of patients with CIPH, being dysphagia and aspiration its two major risk factors. A screening for dysphagia should be performed before starting oral feeding (34). Urinary infections should also be considered in these patients.

Deep venous thrombosis and pulmonary embolism are two other frequent complications. During the first 24h or until stabilization of the hemorrhage volume, pneumatic compression mechanisms are used for prevention of these two events. Once the volume is stabilized, LMWH is recommended (2).

### ***1.8.5. Intracranial pressure monitoring/treatment.***

Increased ICP is mainly due to either the mass effect produced by the hematoma and the edema surrounding it, or to hydrocephalus from intraventricular hemorrhage. It is also more frequent in young people and supratentorial CIPH. ICP is measured by inserting devices into the brain parenchyma or the ventricles. A VC can be placed in order to drain cerebrospinal fluid. There are no available studies proving management of ICP has an effect on the outcome,

so the decision of treating it is again difficult and based on the clinicians' judgement. Placing an intraparenchymal or a VC is not exempt of complications, such as sepsis or hemorrhage. Monitoring of ICP is recommended in patients with a GCS of 3-8 presumably related to the mass effect of the hematoma, those with severe IVH or hydrocephalus, or those with transtentorial herniation in order to keep ICP > 20mmHg; cerebral perfusion pressure (CPP) should be maintained between 50 and 70 mmHg (34,37,48).

Non-surgical treatment options for ICP include elevation of the head of the bed to 30°, mild sedation, hypertonic saline fluid or intravenous mannitol (34).

### ***1.8.6. Intraventricular hemorrhage***

IVH is present in almost half of the CIPH and is independently associated with poor outcome (49). It is more commonly secondary to hypertensive hemorrhages involving the basal ganglia and thalamus, rather than being primary (50).

It has been suggested that the administration of thrombolytic agents through a VC might lead to a better outcome than using a catheter alone. CLEAR III trial showed no significant difference when comparing alteplase versus saline irrigation, but it suggested that alteplase seems safe and further studies are required to try more frequent doses of it (34,51).

### ***1.8.7. Surgical treatment***

The role of surgery in CIPH is aimed at mass effect and ICP reduction, avoiding toxicity from blood to healthy tissue and preventing mechanical effect due to brain herniation (34).

We will review the available bibliography to picture the current situation in reference to the surgical CIPH treatment, as well as the ongoing debate resulting from the lack of significant evidence in favor of any of the possible approaches.

#### ***1.8.7.1. Supratentorial hematomas***

The largest studies conducted so far have failed to prove a significant advantage for surgery in the management of supratentorial CIPH, although subgroup analysis conclusions point to a potential benefit of this approach in certain patients, such as those with hemorrhage less than 1cm from the cortex surface (52–54).

In 1989 Auer et al. (55) conducted a randomized controlled trial which tested endoscopic surgical removal of spontaneous intracerebral hematoma against conservative treatment. A significant lower mortality was associated to surgical evacuation in patients with subcortical hematomas. It also found that patients with hematomas smaller than 50cc surgically treated had a better functional recovery than those with the same hematoma volume treated medically, with no differences in mortality. When the hematoma was bigger than 50cc, patients who were alert or somnolent before surgery had a lower mortality than those treated medically, but that was not the case in stuporous or comatose patients.

In that same year, Juvela et al. (56) also compared in a randomized controlled trial surgical and medical management of spontaneous supratentorial CIPH. Their study showed a significant lower mortality rate on the surgical group of patients with a GCS from 7 to 10. It has to be noted that in this subgroup of patients, surgery took place within the first 6 to 13 hours. No significant differences were found in the overall mortality rates between the two groups. The study concluded that CIPH should be treated conservatively, needing further studies to assess whether stuporous or semicomatose patients (GCS 7-10) would benefit from very early surgeries.

Zuccarello et al. (57) concluded in their feasibility study in 1999 that no significant differences in mortality were observed when comparing surgical and medical therapy for patients with CIPH. However, they found a significant difference in the NIHSS score at 3 months, in favor of the surgical group. There was no difference in other outcome measures.

The International Surgical Trial in Intracerebral Hemorrhage (STICH)(52), published in 2005, has been the largest randomized treatment trial of CIPH. It is a randomized multicenter study which aimed to determine if early surgical evacuation of the hematoma in patients with spontaneous supratentorial CIPH would improve the outcome, measured by death and disability. It included 1033 patients from 27 countries. In all cases there was clinical uncertainty on the best treatment. Patients were randomized into two groups. The first group of patients were treated with hematoma evacuation during the first 24h combined with the best medical treatment, and the second group of patients received the best medical treatment alone. The type of surgical evacuation was left to the neurosurgeon's choice, and a vast majority performed craniotomies. The study did not observe a benefit of surgery, and detected no significant difference in the outcome of both groups. When performing subgroup

analysis, a nonsignificant trend to favorable outcome for patients with hematomas less than 1cm from the cortical surface was observed in the surgical group. It was suggested that the trauma produced by open craniotomy for deep hematomas might have been more detrimental than the possible benefits obtained. Most of the patients with an initial state of coma showed unfavorable outcomes in both groups, being surgery probably harmful for those patients. What STICH left unanswered is the role of less invasive surgery to remove CIPH, specially at earlier time windows and in deeper hematomas.

With the objective of correcting the limitations of their prior study, STICH II trial (54) was conducted. It was an international multicenter study designed to assess whether early surgery would improve outcome in patients with superficial lobar supratentorial CIPH compared with initial conservative treatment. The patients included had an hematoma  $\leq$  1cm from the cortical surface of the brain, a volume between 10 and 100 mL and no evidence of IVH. Evacuating surgery was expected to be performed within the first 12h, and this was true for 93% of patients.

The study failed to find significant evidence to support its hypothesis. It has to be taken into account that the population was heterogenous, being some patients fully conscious or only a little confused, for whom a close observation and conservative treatment followed by surgery in case of deterioration might have been the best approach. Additionally, 21% of patients of the conservative treatment group had delayed surgery due to severe deterioration, but were still considered in the initial conservative group because of an intention-to-treat analysis. There was a statistically nonsignificant but clinically relevant survival advantage in favor of the surgical group. Subgroup analyses showed that early surgery benefited patients with a poor prognosis (GCS=8-12). STICH II confirmed the rates of death or disability at 6 months are not increased by early surgery.

#### **1.8.7.2. Cerebellar and Brainstem hematomas**

Cerebellar hemorrhages rapidly produce compression of the brainstem or mass effect, given that posterior fossa is a narrow space. Several non-randomized studies have suggested craniotomy to be beneficial for cerebellar hemorrhages larger than 3cm and those associated with hydrocephalus or severe brainstem compression (58,59).

Da Pian et al (58) conducted a cooperative study in 1984 to define the best management of posterior fossa hematomas. They concluded that 4<sup>th</sup> ventricle obliteration as well as IVH, both in the presence of hydrocephalus, were the most determining factors for the prognosis of cerebellar hematomas. Previous studies had agreed that the critical size for a cerebellar hematoma was 3cm, recommending surgery in cases of larger volume. Da Pian et al, however, stated that hematoma size was secondary to the above mentioned prognosis factors. Therefore, an hemorrhage smaller than 3cm but involving hydrocephalus should also be operated as soon as any clinical deterioration appears.

Regarding brainstem hematomas, Da Pian et al proposed medical treatment as the best treatment option for hematomas of limited size, while establishing that in the case of larger lesions the outcome would be fatal despite the treatment applied .

Matthew et al (60) stated in their study in 1995 that in order to decide between conservative treatment and early surgery to avoid deterioration in patients with cerebellar hemorrhage, the main criteria to take into account were the consciousness level and the presence of hydrocephalus. Conscious patients with no evidence of hydrocephalus should receive conservative treatment and be observed for the first 48h in order to detect clinical deterioration immediately. On the other hand, conscious patients who present hydrocephalus should undergo an evacuating surgery.

A single-center retrospective study conducted in 2017 (61) showed no significant difference in the outcome of surgical and conservative treated cerebellar hematomas. It must be taken into account, though, that those of the surgical group also had worse clinical and radiological findings, which might have contributed to the high morbidity and mortality in this group. They found the GCS on admission to be a significant short-term outcome predictor for patients with cerebellar hemorrhage.

### **1.8.7.3. Basal Ganglia hematomas**

Hypertensive putaminal hematomas have been a subject of study for years. The insular cortex extends laterally to the Sylvian fissure, occupying a fairly superficial place. Therefore, several studies have been conducted with the aim of surgically decompressing the area and improving morbidity and mortality, and none of them has proved a benefit of conventional craniotomy over conservative treatment (56,62,63).

A study of Kaya et al. (64) conducted in 2001 proved a superiority of surgery in hypertensive putaminal hematomas larger than 30cc through a transsylvian transinsular approach. Patients benefiting the most from surgery in this study were those with stuporous or semicomatose state on admission and no signs of herniation.

Neuroendoscopic surgery has some advantages versus craniotomy in the surgical treatment of basal ganglia hematomas. It is less invasive, has lower rates of complications and produces less damage on the healthy tissue surrounding the hemorrhage (65).

#### **1.8.7.4. Minimally invasive surgery**

Minimally invasive surgery is a less invasive approach for the hematoma removal that might lead to a better outcome compared to standard craniotomies (66,67). Its advantages include a shorter surgical time, possibility of local anesthesia, earlier interventions and reduction of tissular trauma in deep hemorrhages.

The most updated study up to date assessing the role of minimally invasive surgery for CIPH was published in august 2018 (68). It concluded that minimally invasive surgery was correlated with a lower mortality and a better functional outcome compared to conventional craniotomy or medical treatment separately. Subgroup analyses showed that amongst the minimal invasive surgeries performed (endoscopic surgery and stereotactic thrombolysis), endoscopic surgery was found to be beneficial, whilst stereotactic thrombolysis was not associated with a significant survival benefit. Patients treated within the first 24 hours were identified as having better functionality in the long term.

Another surgical option is decompressive craniectomy, which could benefit patients with ICP or mass effect related to the CIPH, who are normally patients with a worse GCS (69,70). However, there are no controlled randomized studies on the subject.

One of the aspects related to surgery is the time from the onset of the symptoms to the surgical evacuation. Best timing of surgery has not yet been established, with subgroup analyses from STICH II trial suggesting a better outcome in patients who underwent surgery within the first 21h after onset (54), while very early surgery has been associated with a higher risk of rebleeding (71).

To conclude, a multitude of studies have been conducted over the last years with the aim of providing some evidence supporting the role of surgery in the treatment of CIPH. As summarized above, this subject is still in controversy: some studies suggest evacuating surgery might be beneficial, while others point to conservative treatment as the best option. The results depend on several factors, among which is the location of the hematoma. We have seen that deeper hematomas are more difficult to access surgically, and those of the posterior fossa produce compression much faster due to its confined space. Another factor influencing the results of surgery is the technique: minimally invasive surgery has become more feasible and is being tested as an alternative both to conventional craniotomy and conservative treatment, having shown positive effects on both the outcome and mortality in several studies (68). This technique, however, is not available in all centers.

More prospective randomized trials are necessary, on the basis of previous studies' limitations, in order to provide clear evidence of the best treatment for CIPH.

## **2. JUSTIFICATION**

Cerebral intraparenchymal hemorrhage is responsible for the highest mortality and morbidity rates of all strokes. Only 10% of patients are independent 1 month after the onset, and mortality reaches the 50% of cases at that time. Thus, CIPH is an important cause of morbidity and mortality worldwide. It is a medical emergency and we know that the therapeutic window is very short, since a majority of the patients deteriorate in the first few hours. Consequently, CIPH needs to be diagnosed and treated in the shortest time possible. Despite its high mortality, there are little therapeutic options and these have rested invariable through many years. Among the treatment options the role of surgery remains unclear; whether or not to operate patients is nowadays mostly a choice of the neurologists and neurosurgical team. This problem is partly because of CIPH's complex pathophysiology and partly due to the lack of treatments' evidence. Several trials have been conducted over the last 50 years in order to establish the beneficial effects of early surgery in selected cases, but none of them has succeeded in proving a significant benefit when compared to conservative treatment. Subgroup analysis of these trials and nonsignificant tendencies suggest, though, that early surgery might reduce mortality, especially in patients with particular features such as high intracranial pressure or low GCS score.

Given the controversy of those studies, and due to the lack of evidence supporting either the conservative or the surgical approach, we conducted an observational, retrospective study in order to describe the outcome of patients who have been treated with evacuating surgery for CIPH in our center. We also aim to identify some factors that might be linked to a worsening of the patient after the surgical removal.

### **3. HYPOTHESIS**

- 1) The evolution of patients with a surgically evacuated CIPH does not differ from what is registered in bibliography.
- 2) An hematoma volume >30 mL is associated with a worse outcome in patients with spontaneous non traumatic CIPH evacuated surgically.
- 3) Early surgery is associated with a better outcome in patients with spontaneous non traumatic CIPH.

#### **4. OBJECTIVES**

- 1) To describe the functional outcome and mortality of patients who underwent evacuating surgery for spontaneous non traumatic CIPH at our center.
- 2) To determine the association between the outcome and the hematoma volume.
  - To assess the hematoma volume of patients at the moment of the surgery.
  - To evaluate the impact of the hematoma volume with the outcome of our patients.
- 3) To determine the association between the outcome and the time frame from the onset of the symptoms to the surgery.
  - To calculate the time from the onset of the symptoms to the surgical evacuation.
  - To evaluate the time to surgery with the outcome of patients.

## 5. METHODS

### 5.1. STUDY DESIGN

This is a descriptive, retrospective cohort study reviewing patients diagnosed and operated from non-traumatic spontaneous CIPH admitted in Josep Trueta Hospital (JTH) from 2009 to 2018.

### 5.2. POPULATION IN STUDY

Studied population includes all patients over 18 years old with a diagnosis of an acute spontaneous CIPH who have been treated with evacuating surgery of the hematoma, from January 1<sup>st</sup>, 2009 to December 31<sup>st</sup>, 2018 in JTH.

### 5.3. SAMPLE

#### *5.3.1. Sample selection and size*

Sample selection has been conducted through a consecutive non-probabilistic method. The sample size corresponds to all patients (N) who have been derived and operated in JTH within the established period. All patients over 18 years old having undergone a surgical evacuation of CIPH in JTH during this period have been collected. Patients who were only treated with a ventricular drainage were excluded. Patients who did not have a signed consent for data cession were excluded. The final size of the sample is made of 43 patients.

#### *5.3.2. Statistical power*

In a bilateral contrast for a cohort design with a level of significance  $\alpha$  of 5% and assuming the effect of the independent variables over the dependents is high, the statistical power of this study is 90,63%.

The computations have been carried out with Prof. Marc Saez' software based on the library pwr of the free environment statistical software R (version 3.5.1).

#### 5.4. Inclusion criteria

- ⇒ Patients older than 18 years old diagnosed with CIPH between 2009 and 2018.
- ⇒ Patients who underwent hematoma evacuating surgery.
- ⇒ Patients who had signed the informed consent for the cession of data.

#### 5.5. Exclusion criteria

- ⇒ Patients with a traumatic CIPH or a tumour responsible for the hemorrhage.
- ⇒ Patients to whom only a VC was placed and the hematoma was not evacuated.

#### 5.6. Data

All data has been collected through medical histories of patients, which are electronically stored in the informatic system of SAP. The necessary variables were compiled in an organized and systematic way to guarantee the quality of the information.

The data was gathered in an excel sheet, and the privacy and the safety of this form has been ensured.

Once the data collection was concluded, all the data was moved to the SPSS program.

#### 5.7. Variables

##### 5.7.1. Variable description

###### DEMOGRAPHIC VARIABLES

**Age:** expressed as a number of years.

**Gender:** expressed in categories, woman or man.

###### CLINICAL VARIABLES

###### **Medical history:**

- **AHT:** expressed as “yes” or “no”.
- **DM:** expressed as “yes” or “no”.

**Hemodynamic parameters:** Blood pressure measured on admission and expressed with its systolic (SBP) and diastolic (DBP) values.

**Laboratory parameters:** Glucose levels present on admission and expressed by mg/dL.

**Toxic habits:** expressed as “yes” or “no” for smoking and alcohol intake. Due to its impact as a risk factor for CIPH, former smokers and recent quitters will be considered smokers and included in the “yes” category. Similarly, former alcohol consumers will be considered in the group of current consumers.

**Antiplatelet and anticoagulant treatment:** treated as dichotomic variables and expressed as “yes” or “no” for

**Neurological status:** measured with the National Institute of Health of Stroke Scale (see *annex C*), it quantifies the severity of stroke symptoms.

#### RADIOLOGICAL VARIABLES

**Hemorrhage location:** the location of the hematoma has been divided within supratentorial and infratentorial, and supratentorial hematomas have been divided into lobar or profound. In this way 3 categories have been obtained: lobar, profound and infratentorial hematomas.

**IVH:** expressed as a dichotomic variable, being either “present” or “absent”.

**Volume of the hematoma:** measured in cubic centimeters (cc). For the bivariate analysis it will be dichotomized in order to perform a better study according to the second hypothesis of this work. The two categories will be a volume  $\leq 30$ cc and a volume  $> 30$ cc.

**Cause of the hematoma.**

#### SURGICAL VARIABLES

**Time from the onset of symptoms to surgery:** measured in hours. For the bivariate analysis it will be dichotomized in order to test the third hypothesis of this project. Early surgery has been considered as the one performed  $\leq 6$ h from the onset of the symptoms, and the rest of surgeries will be included in the  $> 6$ h group.

#### CLINICAL OUTCOME AT 90 DAYS

**Functional capacity:** also considered dependency degree, it will be measured with the modified Rankin Scale (mRS, see *annex B*) 90 days and 1 year after surgery. In order to

ease the evaluation of functionality, mRS score has been dichotomized in those patients who had a good functional outcome (mRS <3) and those who had a poor functional outcome (mRS ≥3).

**Mortality:** 30 days after the surgical intervention, expressed as “yes” or “no”.

<b>VARIABLE</b>	<b>TYPE</b>	<b>VALUES</b>
<b>Age</b>	Continuous quantitative	Number of years
<b>Gender</b>	Nominal dichotomous qualitative	Male / female
<b>AHT</b>	Nominal dichotomous qualitative	Yes/No
<b>DM</b>	Nominal dichotomous qualitative	Yes/No
<b>Smoking habit</b>	Nominal dichotomous qualitative	Yes/No
<b>Alcohol consumption</b>	Nominal dichotomous qualitative	Yes/No
<b>TA on admission</b>	Continuous quantitative	Systolic and diastolic values in mm of Hg
<b>Glucose on admission</b>	Continuous quantitative	mg/dL
<b>Anticoagulant therapy</b>	Nominal dichotomous qualitative	Yes/No
<b>Antiplatelet therapy</b>	Nominal dichotomous qualitative	Yes/No
<b>Hemorrhage location</b>	Nominal qualitative	Lobar/Profound/Infratentorial
<b>IVH presence</b>	Nominal dichotomous qualitative	Yes/No
<b>Hemorrhage volume</b>	Continuous quantitative	Cubic centimeters
<b>Hemorrhage cause</b>	Nominal qualitative	Different causes
<b>Time to surgery</b>	Continuous quantitative	Hours
<b>NIHSS score</b>	Discreet quantitative	Scored number
<b>mRS score</b>	Discreet quantitative	Scored number
<b>Mortality</b>	Nominal dichotomous qualitative	Yes/No

### **5.7.2. Dependent variable**

Clinical outcome at 90 days and 1 year after the surgical intervention.

### **5.7.3. Independent variables**

Baseline hematoma volume and time from onset of the symptoms to surgery.

#### **5.7.4. Covariates**

The following covariates have also been collected as they might act as confounders:

Age

Gender

Medical history: AHT and DM

Toxic habits: alcohol intake and smoking

Hemodynamic parameters on admission: blood pressure (systolic and diastolic)

Laboratory parameters on admission: glucose level

Antiplatelet and anticoagulant treatment

NIHSS scoring on admission

Hemorrhage location

Presence of IVH

Cause of the hemorrhage.

### **5.8. STATISTICAL ANALYSIS**

#### **5.8.1. Descriptive analysis**

For the descriptive analysis, variables have been classified as qualitative or quantitative

⇒ **Quantitative variables:**

→ Discrete: NIHSS score, mRS score.

→ Continuous: Age, TA on admission, glucose on admission, hematoma volume, time from the onset of the symptoms to surgery.

⇒ **Qualitative variables:** Gender, AHT, Diabetes Mellitus (DM), smoking habit, alcohol consumption, anticoagulant therapy, antiplatelet therapy, hemorrhage localization, IVH presence, hemorrhage cause, mortality.

Quantitative variables have been described by measures of central tendency (mean, median) and dispersion (standard deviation, interquartile range).

Frequencies and percentages have been used to express qualitative (categorical) variables.

### **5.8.2. Bivariate analysis**

In our study, the volume of the hematoma and the time to surgery were dichotomized in two categories each. Therefore, both the dependent and the independent variables were categorical, and  $\chi^2$ -tests were performed in order to test our hypothesis. The same test was used for all other categorical data.

To compare normally distributed continuous variables, Student t-test was used. For those variables that were not normal distributed, the non-parametric Mann-Whitney-U test was used.

For all tests, a  $p < 0.05$  has been considered statistically significant.

### **5.8.3. Multivariate analysis**

Logistic regressions have been used to study the influence of some variables together in the outcome.

As explanatory variables, some of the variables above mentioned have been introduced. Because of the small sample of our study, not all the variables could be evaluated and therefore further and deeper analysis would be required. The purpose of these analysis is to build a risk equation to determine the probability of any of the variables to be an independent predictor of the outcome, once the rest of variables have been adjusted.

## 6. RESULTS

### 6.1. DESCRIPTIVE ANALYSIS

From January 1<sup>st</sup> 2009 to December 31<sup>st</sup> 2018, 43 patients underwent evacuating surgery due to a CIPH. Among them, the mean age was  $59,9 \pm 12,8$  years, with ages between 26 and 79 years, and 58,1% were women.

AHT was present in 69% of the patients, and 16,23% of the patients had DM.

A 32,6% of the patients were smokers, and 25,6% were regular alcohol consumers.

8 patients were taking antiplatelet agents and 8 patients were taking anticoagulant agents at the moment of the hemorrhage, constituting the 18,6% of the patients in each group.

Patients on admission presented mean systolic and diastolic blood pressures of  $168,81 \pm 34,32$  mmHg and  $88,98 \pm 19,33$  mmHg respectively. Mean initial glucose levels were  $163,19 \pm 46,90$  mg/dL.

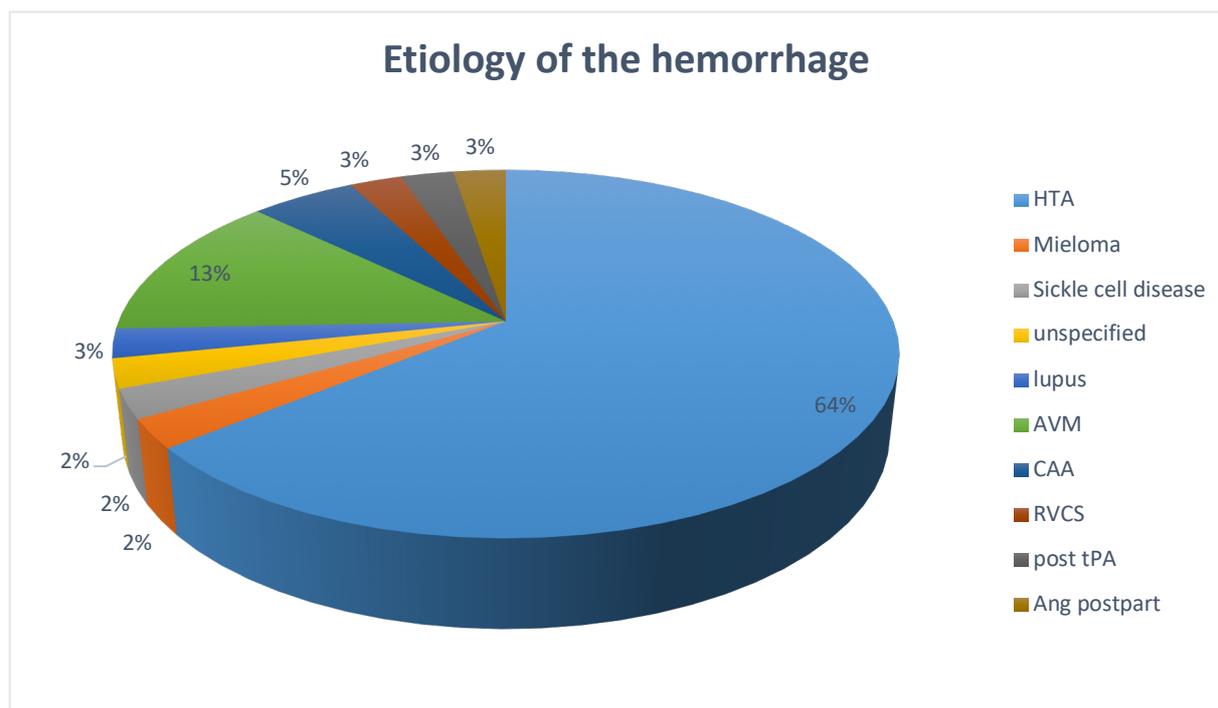
The volume of the hematoma has been considered a continuous variable in this section, being the median 50cc [36,5 , 77,5].

The presence of IVH was found in 25 patients (58,1%).

Regarding the location of the hematoma, 23 (53,5%) patients had a lobar hemorrhage, 8 (18,6%) had a profound hemorrhage and 12 (27,9%) presented an infratentorial hematoma.

The median NIHSS score on admission was 18 [13,21]. The mean time from the onset of the symptoms to surgery was  $26,48 \pm 41,66$  hours.

In the majority of the cases the cause of the hemorrhage was AHT (64%), followed by AVM (13%). **Figure 4** represents the proportion of the different etiologies of CIPH found in our patients.



**Figure 4** Percentages of the different etiologies of the cerebral intraparenchymal hemorrhages. AVM: Arteriovenous malformation. CAA: Cerebral amyloid angiopathy. RVCS: Reversible vasoconstriction syndrome. Post tPA: Posterior to the administration of Tissue Plasminogen Activator.

The mortality rate in our series was 37,2%. 3 (7%) of the patients had a good outcome (mRS<3) at 90 days after surgery and 40 (93%) had a poor functional outcome (mRS ≥ 3). One year after surgery, 7 (16,3%) patients had a good functional outcome after 1 year, and 35 (81,4%) patients had a poor outcome at this time. One of the patients had surgery in 2018, and therefore the outcome at 1 year from the onset of the hemorrhage has not been evaluated yet.

The description of all the variables mentioned above in terms of frequencies and central tendency measures is shown in **table 2**.

All patients		n=43
<b>DEMOGRAPHICAL VARIABLES</b>		
<b>Age</b>	Years ± SD	59,91 ± 12,8
<b>Sex</b>	Female (%) / Male (%)	25 (58,1) / 18 (41,9)

SURGICAL EVACUATION OF CIPH: PROGNOSTIC FACTORS AND OUTCOME

CLINICAL VARIABLES		
AHT	Yes (%)	29 (67,4)
DM	Yes (%)	7 (16,3)
SBP on admission	mmHg $\pm$ SD	168,81 $\pm$ 34,32
DBP on admission	mmHG $\pm$ SD	88,98 $\pm$ 19,33
Glucose on admission	mg/dL $\pm$ SD	168,7 $\pm$ 58,75
Smoking	Yes (%)	14 (32,6)
Alcohol consumption	Yes (%)	11 (25,6)
Antiplatelet use	Yes (%)	8 (18,6)
OAC use	Yes (%)	8 (18,6)
NIHSS on admission	Median score [25,75]	18 [13,21]
RADIOLOGICAL VARIABLES		
Location of the hematoma	Lobar (%) / Profound (%) / Infratentorial (%)	23 (53,5) / 8 (18,6) / 12 (27,9)
Presence of IVH	Yes (%)	25 (58,1)
Volume of the hematoma	Median cc [Q25,Q75]	50 [36,5 , 77,5]
SURGICAL VARIABLES		
Time to surgery	Hours $\pm$ SD	26,48 $\pm$ 41,66
OUTCOME		
mRS 90 days	$\geq 3$ (%)	40 (93,02)
mRS 1 year	$\geq 3$ (%)	35 (81,4)
Mortality 90 days	Yes (%)	16 (37,2)

**Table 2** Description of the sample according to the variables collected. AHT: Arterial Hypertension. DM: Diabetes Mellitus. SBP: Systolic Blood Pressure. DBP: Diastolic Blood Pressure. OAC: Oral Anticoagulants. IVH: Intraventricular hemorrhage. mRS: modified Rankin Scale.

## 6.2. BIVARIATE ANALYSIS

In order to assess the impact of the different collected variables on the functional and vital outcome of the patients, we performed a bivariate analysis.

### 6.2.1. Functional outcome at 3 months after surgery

When studying the impact on the functional outcome at 90 days after surgery, we observed a significantly higher proportion of women (62,5%) among patients who were in a functional dependent situation ( $mRS \geq 3$ ). Patients in this group also presented higher scores in the NIHSS on admission (19 [15,21]), being this association statistically significant ( $p=0,009$ ).

Patients who presented a poor functional outcome ( $mRS \geq 3$ ) were more often consumers of antiplatelet or anticoagulants. We observed higher levels of systolic and diastolic blood pressure among patients who were functionally dependent, and patients of this group also presented higher glucose levels on admission, although these associations are not statistically significant.

A tendency was observed of infratentorial and profound hemorrhages towards a worse functional outcome, since no patient of these two groups presented good functional outcome at 90 days of the surgery.

Regarding the time from the onset of the symptoms to surgery, no statistically significant differences among groups were observed. The same happened with the volume of the hemorrhage.

The distribution of variables according to the mRS score at 90 days after surgery are represented in **table 3**.

		mRS at 90 days after surgery		
		<3	$\geq 3$	p
	<i>n (%)</i>	3 (6,98)	40 (93,02)	
<b>Age</b>	<i>Years <math>\pm</math> SD</i>	63,67 $\pm$ 6,81	59,63 $\pm$ 13,15	0,21
<b>Gender</b>	<i>W (%) / M (%)</i>	0 (0) / 3 (100)	25 (62,5) / 15 (37,5)	0,03
<b>AHT</b>	<i>Yes (%)</i>	2 (66,67)	27 (67,5)	0,92
<b>DM</b>	<i>Yes (%)</i>	0 (0)	7 (17,5)	0,29
<b>Smoking</b>	<i>Smokers (%)</i>	1 (33,33)	13 (32,5)	0,97

<b>Alcohol consumption</b>	Yes (%)	2 (66,67)	9 (22,5)	0,09
<b>Antiplatelet use</b>	Yes (%)	0 (0)	8 (20)	0,39
<b>OAC use</b>	Yes (%)	0 (0)	8 (20)	0,39
<b>SBP on admission</b>	mmHg $\pm$ SD	163 $\pm$ 14,93	169,25 $\pm$ 35,41	0,18
<b>DBP on admission</b>	mmHg $\pm$ SD	84,33 $\pm$ 15,04	89,33 $\pm$ 19,74	0,64
<b>Glucose on admission</b>	mg/dL $\pm$ SD	140,33 $\pm$ 24,69	170,83 $\pm$ 60,16	0,32
<b>NIHSS on admission</b>	Median NIHSS score [25,75]	3 [2,7]	19 [15,21]	0,009
<b>Hematoma's volume</b>	Median cc [25,75]	66 [50,78]	48 [36,82]	0,4
<b>IVH presence</b>	Yes (%)	2 (66,67%)	23 (57,5)	0,75
<b>Hematoma's location</b>	Lobar (%) / Profound (%) / Infratentorial (%)	3 (100) / 0 (0) / 0 (0)	20 (50) / 8 (20) / 12 (30)	0,13
<b>Time to surgery</b>	Hours $\pm$ SD	38 $\pm$ 33,05	19,8 $\pm$ 21,6	0,95

**Table 3** Distribution of collected variables according to the mRS score 90 days after surgery. AHT: Arterial Hypertension. DM: Diabetes Mellitus. OAC: Oral Anticoagulants SBP: Systolic Blood Pressure. DBP: Diastolic Blood Pressure.. IVH: Intraventricular hemorrhage. NIHSS: National Institute of Health Stroke Scale. mRS: modified Rankin Scale.

### 6.2.2. Functional outcome at 1 year after surgery

When we analyzed functional outcome at 1 year from surgery, a tendency to a higher NIHSS score on admission was observed in the group of patients with a poor outcome (19 [15,21],  $p=0,09$ ).

Patients with lobar hematomas presented a trend to a better outcome one year after surgery (26%) in comparison with profound hematomas and hematomas of an infratentorial location (12,5 % and 0%, respectively). The totality of patients who suffered an infratentorial hemorrhage were in the poor functional outcome at 1 year from surgery.

Interestingly, among the group who presented a good functional outcome (mRS <3), none of them was a consumer of OAC. However, almost 23% of patients in the poor functional outcome group were taking OAC. The differences were not significant.

**Table 4** summarizes these findings.

	n(%)	mRS at 1 year after surgery		p
		<3	≥3	
<b>Age</b>	Years ± SD	58,86 ± 12,67	59,86 ± 13,1	0,91
<b>Gender</b>	W (%) / M (%)	4 (57,14)/3 (42,86)	20 (57,1)	1
<b>AHT</b>	Yes (%)	4 (57,14)	24 (68,57)	0,48
<b>DM</b>	Yes (%)	1 (14,29)	6 (17,14)	0,85
<b>Smoking</b>	Smokers (%)	2 (28,57)	12 (34,29)	0,77
<b>Alcohol consumption</b>	Yes (%)	2 (28,57)	9 (25,71)	0,87
<b>Antiplatelet use</b>	Yes (%)	1 (14,29)	7 (20)	0,72
<b>OAC use</b>	Yes (%)	0 (0)	8 (22,86)	0,16
<b>SBP on admission</b>	mmHg ± SD	161,29 ± 21,09	169,89 ± 36,83	0,16
<b>DBP on admission</b>	mmHg ± SD	80,57 ± 13,69	90,76 ± 20,29	0,49
<b>Glucose on admission</b>	mg/dL ± SD	188,43 ± 95,92	166,17 ± 40,80	0,19
<b>NIHSS on admission</b>	Median NIHSS score [25,75]	8 [3,20]	19 [15,21]	0,09
<b>Hematoma's volume</b>	Median cc [25,75]	50 [50,68]	48 [36,85]	0,4
<b>IVH presence</b>	Yes (%)	5 (71,43)	19 (54,29)	0,4
<b>Hematoma's location</b>	Lobar (%) / Profound (%) / Infratentorial (%)	6 (85,71) / 1 (14,29) / 0 (0)	17 (48,57) / 7 (20) / 11 (31,43)	0,06
<b>Time to surgery</b>	Hours ± SD	22,43 ± 24,95	20,75 ± 22,75	0,57

**Table 4** Distribution of collected variables according to the mRS score 1 year after surgery. AHT: Arterial Hypertension. DM: Diabetes Mellitus. OAC: Oral Anticoagulants SBP: Systolic Blood Pressure. DBP: Diastolic Blood Pressure. IVH: Intraventricular hemorrhage. NIHSS: National Institute of Health Stroke Scale. mRS: modified Rankin Scale.

### 6.2.3. Mortality at 3 months after surgery

When studying variables according to mortality 3 months after surgery, no significant differences were observed among them. However, it is interesting to point out that infratentorial hematomas had a tendency to present lower mortality, since they constituted only 12,5% of the patients who died. The volume of the hematoma and the time to surgery did not seem to have an impact on mortality.

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		Mortality at 90 days		
		No	Yes	p
	n(%)	27 (62,79)	16 (37,2)	
<b>Age</b>	<i>Years ± SD</i>	61,11 ± 12,05	57,88 ± 14,15	0,71
<b>Gender</b>	<i>W (%) / M (%)</i>	16 (59,26) / 11 (40,74)	9 (56,2)	0,84
<b>AHT</b>	<i>Yes (%)</i>	17 (62,96)	12 (75)	0,51
<b>DM</b>	<i>Yes (%)</i>	4 (14,81)	3 (18,75)	0,73
<b>Smoking</b>	<i>Smokers (%)</i>	9 (33,33)	5 (31,25)	0,88
<b>Alcohol consumption</b>	<i>Yes (%)</i>	9 (33,33)	2 (12,5)	0,13
<b>Antiplatelet use</b>	<i>Yes (%)</i>	5 (18,52)	3 (18,75)	0,98
<b>OAC use</b>	<i>Yes (%)</i>	5 (18,52)	3 (18,75)	0,98
<b>SBP on admission</b>	<i>mmHg ± SD</i>	172,52 ± 36,83	162,56 ± 29,65	0,42
<b>DBP on admission</b>	<i>mmHg ± SD</i>	91,81 ± 19,83	84,38 ± 18,15	0,23
<b>Glucose on admission</b>	<i>mg/dL ± SD</i>	171,41 ± 62,99	164,13 ± 52,45	0,95
<b>NIHSS on admission</b>	<i>Median NIHSS score [25,75]</i>	19 [15,21]	17 [7,21]	0,39
<b>Hematoma's volume</b>	<i>Median cc [25,75]</i>	55 [40,93]	48 [29,68]	0,23
<b>HIV presence</b>	<i>Yes (%)</i>	17 (62,96)	8 (50)	0,40
<b>Hematoma's location</b>	<i>Lobar (%) / Profound (%) / Infratentorial (%)</i>	11 (40,74) / 6 (22,22) / 10 (37,04)	12 (75) / 2 (12,5) / 2 (12,5)	0,07
<b>Time to surgery</b>	<i>Hours ± SD</i>	19,75 ± 20,94	23,31 ± 25,49	0,5

**Table 5** Distribution of collected variables according to mortality 90 days after surgery. AHT: Arterial Hypertension. DM: Diabetes Mellitus. OAC: Oral Anticoagulants SBP: Systolic Blood Pressure. DBP: Diastolic Blood Pressure. IVH: Intraventricular hemorrhage. NIHSS: National Institute of Health Stroke Scale. mRS: modified Rankin Scale.

In order to test our second hypothesis, we analyzed more deeply the role of the hematoma volume on the outcome. For this analysis, volume has been dichotomized as inferior or equal to 30cc and superior to 30cc. Tables 6 to 8 show the results.

Among patients with a poor functional outcome at 90 days after surgery, 80% had an hematoma volume superior to 30cc, compared to a 20% of patients who had a volume smaller or equal to 30cc. These differences, however, were not significant (**table 6**).

	mRS at 90 days of surgery		
	<3	≥3	p
n(%)	3 (6,98)	40 (93,02)	0,391
<b>Hematoma volume ≤ 30cc [n(%)]</b>	0 (0)	8 (20)	
<b>Hematoma volume &gt;30 cc [n(%)]</b>	3 (100)	32 (80)	

**Table 6** Distribution of hematoma volume ≤ 30cc or >30cc according to the mRS at 90 days of surgery. *mRS*: modified Rankin Scale. *Cc*: cubic centimeters.

The same pattern was maintained at one year after surgery: 80% of the patients with a poor functional outcome had an hematoma bigger than 30cc. Again these findings were non-significant (**table 7**).

	mRS at 1 year of surgery		
	<3	≥3	p
n(%)	7 (16,67)	35 (83,33)	0,09
<b>Hematoma volume ≤ 30cc [n(%)]</b>	0 (0)	7 (20)	
<b>Hematoma volume &gt;30 cc [n(%)]</b>	7 (100)	28 (80)	

**Table 7** Distribution of hematoma volume ≤ 30cc or >30cc according to the mRS at 1 year of surgery. *mRS*: modified Rankin Scale. *Cc*: cubic centimeters.

When studying mortality at 3 months after surgery, among patients who died there was a higher percentage of hematomas larger than 30cc than among those who survived. Most of the patients presenting with hematomas smaller or equal to 30cc (87,5%) survived. The difference was non-significative (**table 8**).

	Mortality at 90 of surgery		p
	No	Yes	
n(%)	27 (62,79)	16 (37,21)	0,08
<b>Hematoma volume ≤ 30cc [n(%)]</b>	7 (25,93)	1 (6,25)	
<b>Hematoma volume &gt;30 cc [n(%)]</b>	20 (74,07)	15 (93,75)	

**Table 8** Distribution of the hematoma volume ≤ 30cc or >30cc according to mortality at 90 days of surgery. *Cc*: cubic centimeters.

In order to analyze our third hypothesis, we divided the time from the onset of the symptoms to surgery in two categories:  $\leq 6h$  and  $>6h$ . We then evaluated the role of time to surgery on the outcome of patients. Results are shown in tables 9 to 11.

	mRS at 90 days of surgery		p
	<3	$\geq 3$	
n(%)	3 (6,98)	40 (93,02)	0,95
<b>Time to surgery <math>\leq 6h</math> [n(%)]</b>	1 (33,33)	14 (35)	
<b>Time to surgery <math>&gt;6h</math> [n(%)]</b>	2 (66,67)	26 (65)	

**Table 9** Distribution of time  $\leq 6h$  or  $>6h$  from the onset of the symptoms to surgery according to the mRS 90 days after surgery. mRS: modified Rankin Scale.

	mRS at 1 year of surgery		p
	<3	$\geq 3$	
n(%)	7 (16,67)	35 (83,33)	0,66
<b>Time to surgery <math>\leq 6h</math> [n(%)]</b>	2 (28,57)	13 (37,14)	
<b>Time to surgery <math>&gt;6h</math> [n(%)]</b>	5 (71,43)	22 (62,86)	

**Table 10** Distribution of time  $\leq 6h$  or  $>6h$  from the onset of the symptoms to surgery according to the mRS 1 year after surgery. mRS: modified Rankin Scale.

	Mortality at 90 days of surgery		p
	No	Yes	
n(%)	27 (62,79)	16 (37,21)	0,7
<b>Time to surgery <math>\leq 6h</math> [n(%)]</b>	10 (37,04)	5 (31,25)	
<b>Time to surgery <math>&gt;6h</math> [n(%)]</b>	17 (62,96)	11 (68,75)	

**Table 11** Distribution of time  $\leq 6h$  or  $>6h$  from the onset of the symptoms to surgery according to mortality 90 days after surgery. mRS: modified Rankin Scale.

As shown above, the time from the onset of the symptoms to surgery did not have a significant impact on the functionality at 90 days nor at 1 year after the surgical intervention. It also did not show to have an effect on mortality 90 days after surgery.

### 6.3. MULTIVARIATE ANALYSIS

Logistic regressions were performed in order to study the behavior of the independent variables (volume and time) once adjusted for other variables that might have been conditioning their impact on the outcome (tables 12 and 13).

MORTALITY AT 90 DAYS OF SURGERY				
Variable	OR	C.I. 95% for OR		p
		Inferior	Superior	
<i>Time to surgery</i>	1,034	0,944	1,134	0,471
<i>Hematoma volume</i>	1,001	0,952	1,053	0,96
<i>Gender</i>	0,299	0,014	6,215	0,435
<i>Age</i>	1,008	0,898	1,131	0,898
<i>Hematoma location (lobar)</i>				0,450
<i>Hematoma location (profound)</i>	6,624	0,216	203,223	0,279
<i>Hematoma location (infratentorial)</i>	0,000	0,000		0,492
<i>NIHSS on admission</i>	0,960	0,783	1,178	0,697
<i>Presence of IVH</i>	0,106	0,005	2,129	0,142

**Table 12** Logistic regression for mortality 90 days after surgery. NIHSS: National Institute of Health Stroke Scale. IVH: Intraventricular Hemorrhage.

mRS 1 YEAR AFTER SURGERY				
Variable	OR	C.I. 95% for OR		p
		Inferior	Superior	
<i>Time to surgery</i>	1,019	0,829	1,253	0,860
<i>Hematoma volume</i>	1,066	0,931	1,221	0,354
<i>Gender</i>	0,106	0,000	40,969	0,460
<i>Age</i>	1,028	0,904	1,169	0,674
<i>Hematoma location (lobar)</i>				0,285
<i>Hematoma location (profound)</i>	0,000	0,000	13,196	0,114
<i>Hematoma location (infratentorial)</i>	0,000	0,000	63,556	0,153
<i>NIHSS on admission</i>	1,353	0,869	2,105	0,181
<i>Presence of IVH</i>	0,024	0,000	321,491	0,441

**Table 13** Logistic regression for mRS 1 year after surgery. NIHSS: National Institute of Health Stroke Scale IVH: Intraventricular hemorrhage. mRS: modified Rankin Scale.

In this multivariate analysis, none of our variables was considered an independent predictive marker of poor functional outcome or mortality.

## **7. DISCUSSION**

Our study did not find the hematoma volume to have a significant association to the functional outcome or mortality. We did observe a tendency of smaller hematomas to have lower mortality, since 87,5% of patients with small hematomas ( $\leq 30$ cc) survived, while only 57% of those who had big hematomas ( $>30$ cc) did. Previous studies have found similar trends, Hemphill et al. stated in their study that volumes smaller than 30cc were significantly associated with a lower mortality. Other studies, like Auer et al.'s, found no differences in mortality according to the hematoma volume (36,55). Likewise, STICH I and STICH II did not find the hematoma volume to be significantly related with mortality either (52,54).

Similarly, time from the onset of the symptoms to the surgical intervention in our series has not proved to significantly affect the functional outcome or mortality of our patients. Most of the studies conducted up to date report the same findings, although Scaggiante J. et al. stated patients surgically treated within the first 24 hours had a better functionality in the long term, and subgroup analysis of the STICH II trial suggested a better outcome in patients who underwent surgery during the first 21 hours after the onset of symptoms (54,68).

In accordance with previous works, our study found that patients more severely affected on admission presented poor functional outcome after surgery. This finding was not maintained, however, when we performed a multivariate analysis.

The rate of OAC consumption among patients with CIPH in our study was 18,6%, not differing from the rates described in other series. Patients with a CIPH associated with anticoagulant treatment presented a trend to a worse functional outcome. However, no impact on mortality was observed in our study. This differs from previous series which found OAC consumption in patients with CIPH to be correlated with higher mortality. Purruicker J et al. described in their observational multicentric study a high mortality of patients with CIPH associated to OAC. In the same line, Flibotte J. et al found in their prospective study that warfarin was associated to increased mortality because of its higher risk of hematoma expansion (11,13). These differences could probably be attributed to the small size of our sample.

In our series, the location of the hemorrhage had a particular behavior. Patients with good outcome presented more frequently lobar hemorrhages, while deep and infratentorial hemorrhages were mostly seen in those patients with a functional dependency. These

findings recall what can be found in bibliography. The STICH trial also described a trend to a better outcome for patients with lobar hematomas less than 1cm from the cortical surface (52). Infratentorial hemorrhages are known to have a bad prognosis (59,61). Interestingly, though, when analyzing their impact on mortality in our series, a vast majority (83%) of patients presenting infratentorial hematomas survived. This fact exemplifies the importance of having to explain to the families that although surgery in these cases can be lifesaving (due to the rapid compression these hematomas produce) this survival is at the expense of remaining severely dependent. The same experience has been reported in literature before; Safatli et al already proposed in their study the necessity of weighting the benefit of survival against the high risk of significant functional disability and poor quality of life that may be achieved by extended therapy.

In our study mortality reached the 37,2% of patients. This mortality rate is similar to those of other series. Functional outcome, however, was a little poorer than that described in bibliography. Only 6,98% of our patients were independent 3 months after surgery. 16,67% were independent 1 year after the surgical intervention. This may have been due to the small size of our sample.

The technique by which neurosurgeons evacuated the hematoma has not been assessed, and according to some studies it could have an impact both in the functional outcome and mortality of patients (68).

This study, taking into account its several limitations, did not find any factor which is able to independently predict a worse outcome after a surgical evacuation of a CIPH. It is, therefore, in line with the lack of evidence available up to date. Further studies are required departing from the subgroup analysis of other studies as a starting point, in order to provide more evidence to solve the controversy.

## **8. CONCLUSIONS**

Our study is an attempt to describe the clinical outcome of patients with a CIPH treated by evacuating surgeries at our center. We also aimed to find if hematoma volume or time to surgery were associated to functional outcome and mortality. Mortality in our series reached the 37,2% of the patients, and 93% of the patients presented a poor outcome 90 days after the surgical intervention. 81,4% of the patients had a poor outcome 1 year after surgery.

The NIHSS score was the only variable significantly associated to a worse outcome at 3 months after surgery, but this association was not evident at 1 year from the surgery nor in the multivariate analysis.

The volume of the hematoma and time from the onset of the symptoms to surgery did not prove to have an impact on the functional outcome or mortality of patients after an evacuating surgery.

Infratentorial hematomas were associated to a worse clinical outcome both at 3 months and at 1 year after surgery.

All these conclusions have limitations, due to the small number of patients we studied and other factors that might have influenced the results, such as comorbidities that were not taken into account or the type of functional rehabilitation the patients went through.

We could not bring any light as to factors that would improve the outcome of surgically intervened patients for a CIPH at our center. Therefore, more studies are required in order to clarify what is the best management for CIPH.

## **9. LIMITATIONS**

The main limitation of this study responds to its retrospective design. The number of patients of our sample was small, and this might have been the reason for not finding many significant associations. Moreover, there are variables that have not been taken into account, such as the type of neurological rehabilitation the patient attended or some comorbidities they might have presented on admission. Additionally, we fully depended on the information registered on clinical histories, and the data required was not always available.

Furthermore, depending on the specialist who saw the patient different scales were used to evaluate their neurologic state (either GCS or NIHSS), making it difficult to compare them. Some patients were managed by the neurosurgical service, while others were treated by the neurologic service. There were patients who were admitted in the stroke unit and patients who went to the intensive care unit, which may have implied a different concomitant treatment between patients. Additionally, the process of neurorehabilitation after the episode might as well have been different, depending on the center the patients attended, and this could modify the prognosis. Finally, patients might have had other comorbidities which were not registered, and these could have had an impact on their evolution. To minimize information bias, the data collection was realized in a systematic and organized way, so the required information and its quality was assured.

Another weak point of our study is its very little external validity, since the patients studied have been those from JTH and the results are only descriptive of the population of the region (the province of Girona).

Since our study design does not involve randomization of the treatment options into a surgically intervened group and a conservatively treated group, any interpretations regarding the causal effect of any association must be taken with caution (i.e. other events may have influenced the outcomes of interest and thus alternative explanations for the outcomes cannot be omitted). Despite potential confounders have been added to the multivariate analysis for the adjustment of the results, there is the possibility of having left some unassessed.

Considering this study does not include a control group, it is merely descriptive and it does not attempt to compare surgery to any other treatment.

## 10. ETHICAL CONSIDERATIONS

The current study has been performed according to the ethical principles and human rights regarding medical research, expressed in the policy statement “Declaration of Helsinki (DoH) of Ethical Principles for Medical Research Involving Human Subjects”, signed by the World Medical Association (WMA), in June 1964. The last review of this policy statement, conducted in October 2013, is the official version at the present time (72).

The confidentiality of patients’ personal data has been strictly guaranteed, according to the “*Ley orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales*” (73) and the “*Ley orgánica 41/2002, de 14 de noviembre, básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica*” (74).

Since it is a retrospective study, we departed from the medical histories of the patients. Thus, this is an investigation without risk; there will be no changes on the biological, psychological, physiological or social individuals participating in the study variables performed.

Participants were duly informed and gave signed consent at the time of admission for the possible use of their medical records in a future, authorizing maintenance of a secure computerized data base with their personal data. Written Informed Consent (IC) (see *Annex A*) was obtained at that time from each patient or legal surrogates in situations where the patients were unable to do so.

The research protocol has been approved by the ethics committee “*Comissió d’Ètica per la Investigació Mèdica (CEIC)*” of JTH.

All data will be only used for the purpose of the research.

All data regarding to patients identity has been dissociated from personal data, and thus, respecting patient’s right to confidentiality. Only the main researcher and the FDP tutor had access to the database and they assured that personal data of the patients will not be distributed at any time.

The investigators of this study declare no conflict of interest.

## **11. STUDY PLAN AND CHRONOGRAM**

### **Phase 0: Preparation**

Meeting with the tutor, Yolanda Silva, to decide on the topic of the Final Degree Project.

Getting information about the subject and meeting again with the tutor to define the variables that will be collected and the inclusion and exclusion criteria for our study.

Requesting the hospital register of JTH for all clinical histories encoded as “cerebral hemorrhage” (code 431) from January 1<sup>st</sup>, 2009 to December 31<sup>st</sup>, 2018.

### **Phase 1: Data collection**

Identifying and selecting the subjects that will be included in our study according to the inclusion and exclusion criteria.

Collecting the variables of interest from each clinical history, and building the database for the study.

### **Phase 2: Analyses and conclusions**

Comparing the behavior of the collected variables and their associations. Interpreting the results and drawing conclusions.

### **Phase 3: Final writing**

Writing the protocol, together with the results and the conclusions.

<b>CHRONOGRAM</b>															
<b>PHASE 0. RESEARCHERS: Yolanda Silva, Naila Pagès</b>															
<b>Days (November 2018)</b>	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Meetings with FDP tutor															
Preparing the subject and collecting information															
Requesting the patients list															
<b>PHASE 1. RESEARCHERS: Yolanda Silva, Naila Pagès</b>															
<b>Days (December 2018)</b>	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Identifying the included patients															
<b>Days (December 2018)</b>	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Collecting variables of interest															
<b>PHASE 2. RESEARCHERS: Yolanda Silva, Marc Sáez, Naila Pagès</b>															
<b>Days (January 2019)</b>	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Data analyse															
Conclusions															
<b>PHASE 3. RESEARCHERS: Naila Pagès</b>															
<b>Days (December 2018)</b>	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Project writing															
<b>Days (January 2018)</b>	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Project writing															

## 12. BUDGET

For this study, the investigation team received no compensation. The database was created from clinical histories which had the necessary information, and computers and programs used to perform the collection and analysis of the data are used in the daily practice.

We considered a compensation for the statistician who guided the data analysis.

The following budget is proposed in case the study is published and dissemination costs have been estimated.

<b>Human Resources</b>	Investigators	<b>0€</b>
	Statistician (7 hours)      40€/hour	<b>280€</b>

<b>Dissemination of the results</b>	<b>National conference attendance for 3 people</b>	
	<i>Inscription (500€/person)</i>	<b>1.500€</b>
	<i>Transport and accommodation (1000€/person)</i>	<b>3.000€</b>
	<b>Publication and divulgation</b>	<b>1.000€</b>

<b>Total amount claimed.</b>	<b>5.780€</b>
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## **ANNEXES**

### **ANNEX A: CONSENTIMENT INFORMAT**

#### **INVITACIÓ**

Estimat pacient, està essent convidat a participar en futurs estudis sobre la malaltia vascular cerebral. L'objectiu d'aquests és conèixer millor la seva malaltia i poder-ne millorar el tractament, a partir de les dades de pacients com vostè. És important conèixer dades que presenta a l'ingrés, juntament amb la seva evolució i funcionalitat després de l'episodi, incloent dades d'una possible intervenció quirúrgica. Se'l convida a participar per presentar una hemorràgia intracerebral. Al cedir les seves dades, vostè autoritza que les dades obtingudes mitjançant entrevista, avaluació clínica i exàmens siguin utilitzades amb finalitats acadèmiques i de recerca. És important que vostè llegeixi i entengui les següents instruccions abans de firmar aquest document, donant el seu consentiment a la utilització de les seves dades mèdiques. La participació en aquests estudis és voluntària i la seva possible negativa a participar no afectaria, en cap cas, a la seva atenció sanitària. Així mateix, en cas de participar, podrà retirar-se en qualsevol moment, sense haver de donar explicacions i sense que això repercuteixi en la seva atenció sanitària, i en cas que les seves dades ja haguessin estat utilitzades per algun estudi d'investigació no conclòs, aquestes seran retirades immediatament del mateix.

#### **CONFIDENCIALITAT DE LA INFORMACIÓ**

Si vostè es compromet a participar d'aquests estudis es recollirà informació personal del seu historial mèdic. Aquestes dades seran utilitzades i processades pels investigadors designats que treballen en aquests estudis. No obstant, el seu nom no serà registrat, de manera que a partir de les dades no se'n podrà esbrinar la seva identitat. Aquestes dades seran recollides amb finalitats exclusives d'investigació. Li garantirem que es mantindrà la seva identitat en secret durant aquests procediments. Si vostè decideix participar i més tard decideix retirar-se'n, tota la informació respecte la seva participació serà eliminada de la base de dades. El tractament, la comunicació i la cessió de les dades de caràcter personal de tots els subjectes participants s'ajustarà al que es disposa en la Llei Orgànica 03/2018, del 5 de Desembre, de protecció de dades personals i garantia dels drets digitals. D'acord al que estableix la legislació

esmentada, vostè pot exercir els drets d'accés, modificació, oposició i cancel·lació de dades, pel qual s'haurà de dirigir al seu metge.

### **POSSIBLES BENEFICIS I MOLÈSTIES**

Per la seva participació en aquests estudis no obtindrà beneficis concrets immediats, però les dades que es puguin adquirir amb la participació de pacients com vostè poden generar nous coneixements i possibles millores en els tractaments a futurs pacients. La participació en aquest estudis de caràcter retrospectiu no implica cap risc addicional per a vostè.

### **COMPENSACIÓ PER LA SEVA PARTICIPACIÓ EN ELS ESTUDIS**

No s'oferirà cap compensació econòmica per la seva participació en els estudis, però aquesta tampoc li suposarà a vostè cap cost afegit.

### **ASSEGURANÇA**

Al tractar-se d'estudis observacionals i no d'intervenció no es precisa cap tipus de pòlissa d'assegurances per a cobrir danys i perjudicis.

### **PROBLEMES O PREGUNTES**

En cas que vostè tingui més preguntes sobre la participació d'aquests estudis, pot contactar l'hospital Josep Trueta.

**Moltes gràcies per molestar-se en llegir aquest full d'informació. Si està d'acord en cedir les seves dades, se li entregarà una còpia d'aquest full i del formulari de consentiment informat.**

*Dades de la finalitat pel que s'otorga el consentiment:*

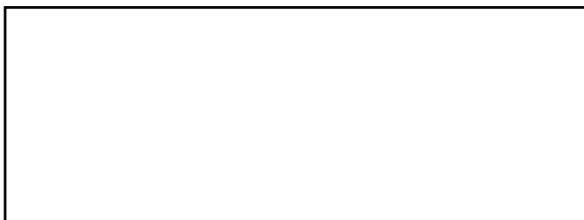
CESSIÓ DE DADES MÈDIQUES PER A LA SEVA UTILITZACIÓ EN RECERCA.

*Dades del participant/pacient*

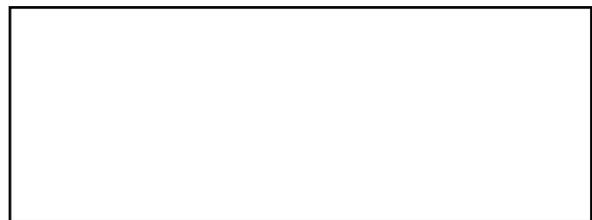
NOM I COGNOMS:

1. Declaro que he llegit la Full d'Informació al Participant sobre la cessió de dades.
2. Se m'ha entregat una còpia del Full d'Informació al Participant i una copia d'aquest Consentiment Informat, datat i signat. Se m'han explicat les característiques i l'objectiu de la cessió de dades, així com els possibles beneficis i riscos de la mateixa.
3. He disposat del temps i l'oportunitat de realitzar preguntes i plantejar dubtes que tenia. Totes les preguntes han estat contestades amb plena satisfacció meva.
4. Se m'ha assegurat que es mantindrà la confidencialitat de les meves dades.
5. El consentiment l'atorgo de manera voluntària i sé que sóc lliure d'aturar el consentiment en qualsevol moment, per qualsevol motiu i sense que tingui cap efecte sobre el meu tractament mèdic futur.

“ Faig constar que he explicat les característiques i l'objectiu de la cessió de dades i els seus riscos i beneficis potencials a la persona el nom de la qual apareix escrit més amunt. Aquesta persona concedeix el seu consentiment mitjançant la seva signatura datada en aquest document.”



*[Signatura de l'investigador o persona que proporciona la informació i el full de consentiment].*



*[Signatura del pacient que autoritza la cessió de les seves dades].*

## ANNEX B: MODIFIED RANKIN SCALE (mRS)

The modified Rankin Scale is one of the mostly used measures to grade the clinical outcome for strokes.

This scale was first introduced in 1957 by Dr. John Rankin, and it was last modified by C. Warlow in 1980. The current version differs from Rankin's original in the addition of grade 0. It consists on 6 grades (*table 2*), being 0 used for a lack of symptoms and 5 for severe disability.

In this study the mRS has been used to define the functional outcome of patients at 3 months and at 1 year after the surgical intervention.

Score	Description
0	No symptoms
1	No significant disability, despite symptoms; able to perform all usual duties and activities
2	Slight disability; unable to perform all previous activities but able to look after own's affairs without assistance
3	Moderate disability; requires some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend. To own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requires nursing care and attention
6	Death.

*Table 14* Described scores of the Modified Rankin Scale

## ANNEX C: NATIONAL INSTITUTE OF HEALTH STROKE SCALE (NIHSS)

The National Institutes of Health Stroke Scale is a tool that provides a quantitative measure of stroke-related neurologic deficit. It was originally designed for research, but it is nowadays widely used to evaluate the severity of stroke patients, predict short and long term outcomes and decide on treatments. It provides a common language for healthcare providers to know a patient's state at any time from clinical admission to discharge. Moreover, it allows for rapid detection of worsening or improvement compared to previous evaluations. An increase of 4 or more points compared to a previous score is indicative of significant neurologic deterioration.

The scale (*table 3*) is formed by 15 items. It allows any well-trained physician to neurologically explore patients evaluating their consciousness, language, negligence, extraocular movement, visual-field loss, sensory loss, motor strength, ataxia and dysarthria. The sum of the overall punctuation enables the gradation of the patient's neurologic severity.

In our study, NIHSS will be used to assess the neurologic state of patients on admission.

<p><b>1a. Level of Consciousness:</b> The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.</p>	<p><b>0</b> = Alert; keenly responsive.  <b>1</b> = Not alert; but arousable by minor stimulation to obey, answer, or respond.  <b>2</b> = Not alert; requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements  <b>3</b> = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic.</p>
<p><b>1b. LOC Questions:</b> The patient is asked the month and his/her age. Aphasic and stuporous patients who do not comprehend the questions will score 2.</p>	<p><b>0</b> = Answers both questions correctly.  <b>1</b> = Answers one question correctly.  <b>2</b> = Answers neither question correctly.</p>
<p><b>1c. LOC Commands:</b> The patient is asked to open and close the eyes and then to grip and release the non-paretic hand.</p>	<p><b>0</b> = Performs both tasks correctly.  <b>1</b> = Performs one task correctly.  <b>2</b> = Performs neither task correctly.</p>
<p><b>2. Best Gaze:</b> Only horizontal eye movements will be tested. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1.</p>	<p><b>0</b> = Normal.  <b>1</b> = Partial gaze palsy; gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present.  <b>2</b> = Forced deviation, or total gaze paresis not overcome by the oculoccephalic maneuver.</p>
<p><b>3. Visual:</b> Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate.</p>	<p><b>0</b> = No visual loss.  <b>1</b> = Partial hemianopia.  <b>2</b> = Complete hemianopia.</p>

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	<p><b>3</b> = Bilateral hemianopia (includes cortical blindness).</p>
<p><b>4. Facial Palsy:</b> Ask – or use pantomime to encourage – the patient to show teeth or raise eyebrows and close eyes.</p>	<p><b>0</b> = Normal symmetrical movements.  <b>1</b> = Minor paralysis (asymmetry on smiling).  <b>2</b> = Partial paralysis (paralysis of lower face).  <b>3</b> = Complete paralysis of upper and lower face).</p>
<p><b>5. Motor Arm:</b> The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds.</p>	<p><b>0</b> = No drift; limb holds for full 10 seconds.  <b>1</b> = Limb drifts down before full 10 seconds; does not hit bed or other support.  <b>2</b> = Drifts down to bed before 10 seconds.  <b>3</b> = No effort against gravity; limb falls.  <b>4</b> = No movement.</p>
<p><b>6. Motor Leg:</b> The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds</p>	<p><b>0</b> = No drift; leg holds for full 5 seconds.  <b>1</b> = Leg falls by the end of the 5-second period but does not hit bed.  <b>2</b> = Leg falls to bed by 5 seconds.  <b>3</b> = No effort against gravity; leg falls.  <b>4</b> = No movement.</p>
<p><b>7. Limb Ataxia:</b> This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness</p>	<p><b>0</b> = Absent.  <b>1</b> = Present in one limb.  <b>2</b> = Present in two limbs.</p>
<p><b>8. Sensory:</b> Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient.</p>	<p><b>0</b> = Normal; no sensory loss.  <b>1</b> = Mild-to-moderate sensory loss;  <b>2</b> = Severe or total sensory loss.</p>
<p><b>9. Best Language:</b> A great deal of information about comprehension will be obtained during the preceding sections of the examination.</p>	<p><b>0</b> = No aphasia; normal.  <b>1</b> = Mild-to-moderate aphasia; some obvious loss of fluency or facility of comprehension.  <b>2</b> = Severe aphasia; all communication is through fragmentary expression.  <b>3</b> = Mute, global aphasia.</p>
<p><b>10. Dysarthria:</b> If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list.</p>	<p><b>0</b> = Normal.  <b>1</b> = Mild-to-moderate dysarthria; patient can be understood with some difficulty.  <b>2</b> = Severe dysarthria; unintelligible .</p>
<p><b>11. Extinction and Inattention</b> (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing.</p>	<p><b>0</b> = No abnormality.  <b>1</b> = Extinction to bilateral simultaneous stimulation in one of the sensory modalities.  <b>2</b> = Profound hemi-inattention or extinction to more than one modality.</p>

*Table 15 National Institute of Health Stroke Scale.*

## ANNEX D: GLASGOW COMA SCALE (GCS)

The Glasgow Coma Scale was first described by Graham Teasdale and Bryan Jennett in 1974. It was designed as a tool to objectively assess the conscious state of patients who had suffered a head trauma. Its precision and feasibility let it extend to other fields, both traumatic and non-traumatic, and is nowadays applicable to all acute medical and trauma patients. It ranges

from 3 (deep coma or death) to 15 (fully conscious and oriented).

The score will be considered **mild** from 13-15, **moderate** from 9 to 13 and **severe** from 8 to 3.

<b>EYE(S) OPENING</b>	
Spontaneous	4
To speech	3
To pain	2
No response	1
<b>VERBAL RESPONSE</b>	
Oriented to time, place, person	5
Confused / Disorientated	4
Inappropriate words	3
Incomprehensible sounds	2
No response	1
<b>MOTOR RESPONSE</b>	
Obeys commands	6
Moves to localized pain	5
Flexion withdraws from pain	4
Abnormal flexion (decorticate posturing)	3
Abnormal extension (decerebrate posturing)	2
No response	1

*Table 16 Glasgow Coma Scale.*

