Universitat de Girona
Facultat de Medicina

Intracerebral Aneurysm's Risk of Rupture: ITARR SCORE. A new predictive tool

Final degree project

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Vull agrair:

A tot l'equip del Departament de Neurociències de l'Hospital Universitari Germans Trias i Pujol, per la vostra hospitalitat durant la meva estada.

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I sobretot, a la meva família i amics, pel vostre suport incondicional.

Sense vosaltres no hauria estat possible.

Moltes gràcies.

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1. LIST OF ABBREVIATIONS

ACA	Anterior cerebral artery
AChA	Anterior choroid artery
ACoA	Anterior communicating artery
ADPKD	Autosomal dominant polycystic kidney disease
ASA	Acetylsalicylic acid
aSAH	Aneurysmatic subarachnoid hemorrhage
AVM	Arteriovenous malformation
CI	Confidence interval
CREC	Clinical Research Ethics Committee
CSF	Cerebrospinal fluid
CT	Computed tomography
CTA	Computed tomography angiography
CVD	Cerebrovascular disease
HDL-chol	High-density lipoproteins cholesterol
HH	Hunt and Hess scale
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
HT	Hypertension
HUGTiP	Hospital Universitari Germans Trias i Pujol
ICA	Internal carotid artery
ICH	Intracerebral hemorrhage
ICU	Intensive care unit
ITARR SCORE	InTracerebral Aneurysm's Risk of Rupture SCORE
IQR	Interquartile range
LACI	Lacunar infarct
LDL-chol	Low-density lipoproteins cholesterol

MCA	Middle cerebral artery
mm	Millimeters
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
mRS	Modified Rankin Scale
OAHA	Oral antihyperglycemic agents
OR	Odds ratio
PACI	Partial anterior circulation infarct
PCA	Posterior cerebral artery
PCoA	Posterior communicating artery
PICA	Posterior inferior cerebellar artery
POCI	Posterior circulation infarct
SAH	Subarachnoid hemorrhage
SD	Standard deviation
SICU	Semi-intensive care unit
TACI	Total anterior circulation infarct
TBI	Traumatic brain injury
TG	Triglyceride
TIA	Transient ischemic attack
UIA	Unruptured intracerebral aneurysm
VA	Vertebral artery

2. ABSTRACT

Background. The worldwide prevalence of intracerebral aneurysms is 3.2%. Around 20 to 50% of cases, the aneurysm will rupture and cause a subarachnoid hemorrhage, which has a high morbimortality. Due to brain imaging accessibility and the developing of new diagnostic tools, the number of diagnosis of unruptured intracerebral aneurysms is increasing. However, we still have limited knowledge about risk factors and weak prediction models to decide which should be the best treatment to prevent its rupture.

Aims. The main porpoise of the study is to create a predictive risk SCORE for patients with unruptured intracerebral aneurysms. Secondary objectives are to perform a descriptive analysis of patients with intracerebral aneurysms as well as to determinate whether statins and antiplatelet drugs decrease the risk of rupture of intracerebral aneurysms.

Methods. Patients diagnosed, treated or follow-up of an intracerebral aneurysm (ruptured or unruptured) from *Hospital Universitari Germans Trias i Pujol* until December 2017 were recruited. We collected demographic, analytic, clinic, radiologic and angiographic variables and compared them in a bivariate and a multivariable analysis with a logistic regression.

Results. Up to 287 patients with a total of 345 intracerebral aneurysms (175 non-ruptured aneurysms and 170 ruptured aneurysms) were included in our sample. In the multivariate analysis, the variables inversely associated with rupture were: multiple aneurysms (OR 0.41, 95% CI 0.24-0.70), antiplatelet treatment (OR 0.23, 95% CI 0.09-0.59), statin treatment (OR 0.44, 95% CI 0.21-0.90) and paraophthalmic location (OR 0.15, 95% CI 0.03-0.72); and the variables independently associated with rupture were: age (OR 1.02, 95% CI 1.00-1.05), anterior and posterior communicating arteries location (OR 3.01, 95% CI 1.68-5.37), saccular type (OR 9.19, 95% CI 1.05-80.74) and lobulation (OR 1.48, 95% CI 1.11-1.99). Female gender (OR 0.80, 95% CI 0.44-1.47), small sac size (OR 1.02, 95% CI 0.94-1.11) and small neck size (OR 0.87, 95% CI 0.71-1.08) were also included in the model even though they were not statistically independent.

Conclusions. The Intracerebral Aneurysm's Risk of Rupture SCORE (ITARR SCORE) is a new easy-to-use predictive tool that, once validated, it can be useful in the daily clinical practice. Statins and antiplatelet drugs decrease the risk of rupture.

Key words: intracerebral aneurysm • subarachnoid hemorrhage • risk factors • protective factors • SCORE • statins treatment • antiplatelet treatment

3. INTRODUCTION

3.1 CEREBROVASCULAR DISEASES AND STROKE

Cerebrovascular diseases (CVD) are any sort of brain disorders produced by a quantitative or qualitative alteration of encephalic vascular irrigation, in one or more areas in the brain, that can be transient or permanent (1,2). Although most of them have an acute presentation, what we know as a stroke, they can also be asymptomatic (3).

3.1.1 Cerebrovascular disease's classification

Based on the lesion's physiopathology, we can divide acute CVDs in two main categories: ischemic (80-85%) and hemorrhagic strokes (15-20%) (4). Both of them can be divided in subtypes, with own etiologies, clinical characteristics, outcomes and treatments (5) (classification diagram on *Annex 1*).

Ischemic strokes, with a first month mortality rate of 16% (4), are caused by an insufficient supply of blood, which leads to cellular necrosis. It occurs when brain's vessels get obstructed and cannot arrive enough nutrients and oxygen to the tissue. Most common etiologies are: atherothrombotic, embolic and hemodynamic (1,3). Depending on the place of the obstruction, the ischemic stroke can be *global* (when the whole brain circulation is affected) or *focal* (if it only affects an area), and depending on the symptoms duration it can be a *transient ischemic attack* (TIA, it lasts less than 24 hours with a later full recovery) or an *ischemic stroke* (it lasts more than 24 hours) (1).

Hemorrhagic strokes however, have a poorer outcome (mortality rates along the first month: 42% in intracerebral hemorrhage and 32% in subarachnoid hemorrhage) (4). In these cases, the rupture of a brain vessel is the responsible for the stroke, which results in an extravasation of blood. The location of the ruptured vessel will determinate which subtype of stroke it is (1,3). Depending on that, we can differentiate between:

- ***Intracranial hemorrhage*** (6)**.** It is an extra-parenchymatous hemorrhage. The bleed is located between the arachnoid layer and the bone. Depending on the specific location of the ruptured vessel, we can describe two subtypes of intracranial hemorrhages:
    - *Subdural hemorrhage*: the hemorrhage is confined in the subdural space, between the dura mater and the arachnoid layers of the brain. It is usually caused by a severe traumatic brain injury (TBI).

- *Epidural hemorrhage*: in this subtype, the vessel that ruptures is located between the dura mater and the skull or the vertebral conduct. Besides the TBI, another typical cause of epidural hemorrhage is a spinal traumatism.

- ***Intracerebral hemorrhage*** (ICH) (2,7). It is a collection of blood inside the brain parenchyma secondary to a non-traumatic vessel rupture. The beginning of the bleed is always into the brain tissue, but it can leak into the ventricular system and also to the subarachnoid space. We can classify it into:
  - *Parenchymal hemorrhage:*
    - *Lobar hemorrhage*: it is especially frequent in elderly patients who have amyloid angiopathy. The clinical features vary with the size and the exact location of the hematoma, but they usually have headache and altered level of consciousness.
    - *Deep hemorrhage*: the hemorrhage is located in the basal ganglia, putamen and thalamus and it is usually caused by hypertension (HT). Patients with hemorrhage in this location typically present aphasia and contralateral hemisensory deficit as well as hemiparesis.
    - *Brainstem hemorrhage*: the outcome of a patient with a brainstem hemorrhage depends on the level of the bleeding as well as its magnitude. Only when it is small, the effect is not devastating, and patients can have some functionality.
    - *Cerebellar hemorrhage*: this hemorrhage usually commences into the dentate nucleus, in one of the cerebellum hemispheres. The main symptoms that appear in these hemorrhages are: headache, dizziness, ataxia, nausea and vomiting among other.
  - *Intraventricular hemorrhage*: it is defined as a bleeding inside the ventricular system. It can be *primary*, if the responsible vessel of the hemorrhage ruptures inside the ventricles, or *secondary*, if a parenchymatous ICH leaks to the ventricles.

- ***Subarachnoid hemorrhage*** (SAH) (6,7). The hemorrhage is located inside the subarachnoid space (rupture of a blood vessel between the arachnoid and the pia mater). It can be:
  - *Traumatic: it occurs after a TBI*

- *Spontaneous*: the hemorrhage begins abruptly, without any obvious cause. We can differentiate two subtypes:
  - *Aneurysmatic SAH (aSAH)*, the rupture of a brain aneurysm is the cause of the bleeding
  - *Non-aneurysmatic SAH*, the bleeding is caused by a tumor, a vascular malformation, an intracerebral infection, a reversible cerebral vasoconstriction syndrome or cerebral amyloid angiopathy, among other causes.

3.1.2 Epidemiology of cerebrovascular diseases and stroke

All over the world, 25.7 million people have survived an stroke and 17 million people have had a new stroke (8). Of those, 6.5 million have died and 5 million have a permanently disability (9). In Spain, the incidence is around 132 to 174 cases per 100.000 inhabitants per year for all ages with a prevalence of 4.000 to 8.000 cases per 100.000 inhabitants. As incidence increases with age, aging population is responsible of its grow (3,4).

Last data available, from 2016, shows that CVDs were the second leading cause of death in Spain and also worldwide, after ischemic heart diseases (*Annex 2*) (10,11). If we analyze it for men and women separately, we can find that it was the third cause of death of Spanish men and the first one in Spanish women (11). However, as we can see in *Figure 1*, the mortality rates have been decreasing considerably since 1980 (12). This reduction can be explained with the advances of stroke's acute phase care and also with the improvement of actions in stroke's primary and secondary prevention (4).

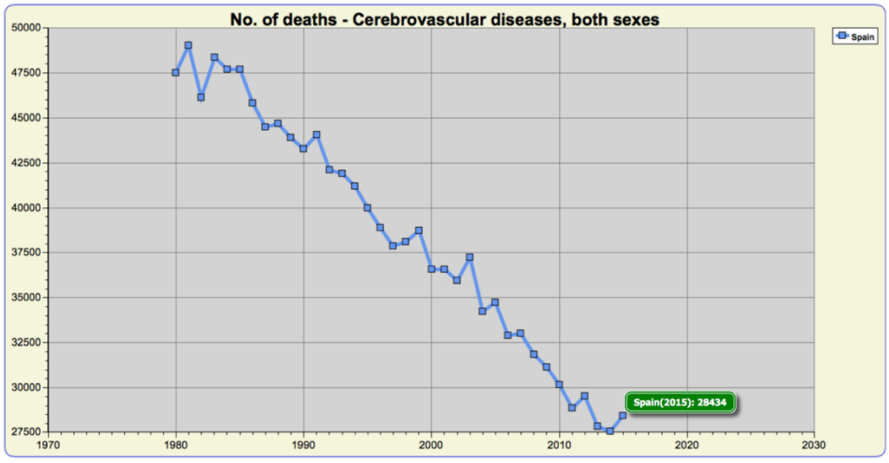


Figure 1 Number of deaths due to CVDs in Spain, between 1980 to 2015. Extracted from (12)

CVDs are a public health problem due to the high socioeconomic burden it causes and because it is a disease that can be present in all ranges of ages even though it is more frequent among aged population (75% have 65 years old or more). They also are the first cause of incapacity in the adulthood and the second cause of dementia in the world (3,4).

3.1.3 Clinical presentation: stroke alarm symptoms

Strokes, either ischemic or hemorrhagic, are **medical emergencies** where every minute counts: "**Time is brain**". Recovery options depend on that. If we can rapidly identify the symptoms we will be able to diagnose and treat them quickly, and our patient will have a better outcome (3,4).

As strokes do not have specific cause and neither specific alarm symptoms (3), we must suspect a stroke when one or more of the following symptoms appear **abruptly** (13):

- Debility of one side of the body
- Total visual loss in one eye or partial in both eyes
- Loss or difficulties to understand or produce speech
- Strength loss or palsy of one side of the body or face
- Sensibility loss of one side of the body or face
- Instability, imbalance and incapacity of walk
- Not habitual headache (very intense and abruptly, unexpectedly)

3.2 SUBARACHNOID HEMORRHAGE

3.2.1 Definition

As we saw before, SAH is defined as blood extravasation into the subarachnoid space, where the cerebrospinal fluid (CSF) is found. Depending on the place where the vessel rupture is produced, SAH can be:

- ***Primary***, when the bleed starts initially in a vessel inside the subarachnoid space.
- ***Secondary***, if the blood comes from another part of the brain (brain parenchyma or ventricular system).
- ***Spinal***, when it begins in the spinal or medullar subarachnoid space.

Depending on the cause of the bleed, it can be:

- ***Spontaneous***, usually by a rupture of a cranial aneurysm, aSAH, but it can also be produced by a brain arteriovenous malformation (AVM), tumor…

- **Traumatic**, hemorrhage after a TBI

The vessel responsible of the hemorrhage can be either an artery, a vein or a capillary bed (1–5,7,14,15).

3.2.2 Epidemiology

SAH, which has a high morbimortality, represents about 5% of all CVDs and has an overall annual incidence of 9.1 cases per 100.0000 persons-year. However, there are regions with much higher incidences, as Japan (22.7) and Finland (19.7), and some with much lower incidences, as South and Central America (4.2). The incidence also varies with gender and age, being more frequent in men during the young ages and in women after the age of 55 years old. Although SAH can happen in all ranges of age, the peak is found in 50-60 years old (SAH increases with age) (16).

About 12% of patients die before reaching the hospital and 30% of those who arrive alive, finally die during the first days (mortality rates during the first month 32%). The overall mortality rates vary from 22 to 26%, and only 42% of the survivors remain functionally dependent (mRS >2) (4,17,18).

3.2.3 Risk and protective factors

The table below shows a list with the main risk factors for presenting aSAH as well some important protective factors (19–24):

Table 1 Factors related with intracerebral aneurysms and their rupture

Non-modifiable risk factors	• Older age • Female gender • Japanese or Finnish descent • Black ethnicity • Aneurysms located on the posterior circulation • Contrast enhancement (25) • Lobulated aneurysms and daughter sac • Symptoms caused by the aneurysm • Multiple aneurysms • History of previous SAH • Family history of SAH • Autosomal dominant polycystic kidney disease (ADPKD)

	• Connective tissue disorders: Marfan syndrome, Ehler-Danlos syndrome type IV
Modifiable risk factors	• Smoking • Alcohol intake • HT
Protective factors against rupture	• Antihypertensive medication • Acetylsalicylic acid (ASA) treatment • Statins treatment • Aneurysms located on the internal carotid artery (segments C4-C5)

ADPKD: Autosomal dominant polycystic kidney disease; ASA: Acetylsalicylic acid; HT: hypertension; SAH: Subarachnoid hemorrhage

Another important factor is the size of the aneurysm which, depending on the location of the aneurysm, suppose a lower or higher risk of rupture:

Table 2 Rupture rates according to the aneurysm size and location. Adapted from (26).

Size / location	ACA, MCA, ICA	PCoA, Basilar
< 7 mm	0%	2.5%
7-12 mm	2.6%	14.5%
13-24 mm	14.5%	18.4%
> 24 mm	40%	50%

ACA: Anterior cerebral artery; MCA: Middle cerebral artery; ICA: Internal carotid artery; PCoA Posterior communicating artery

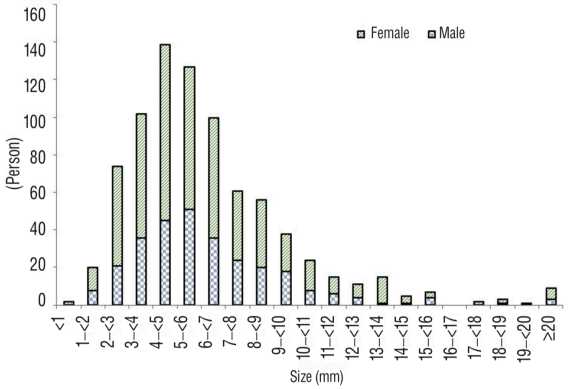
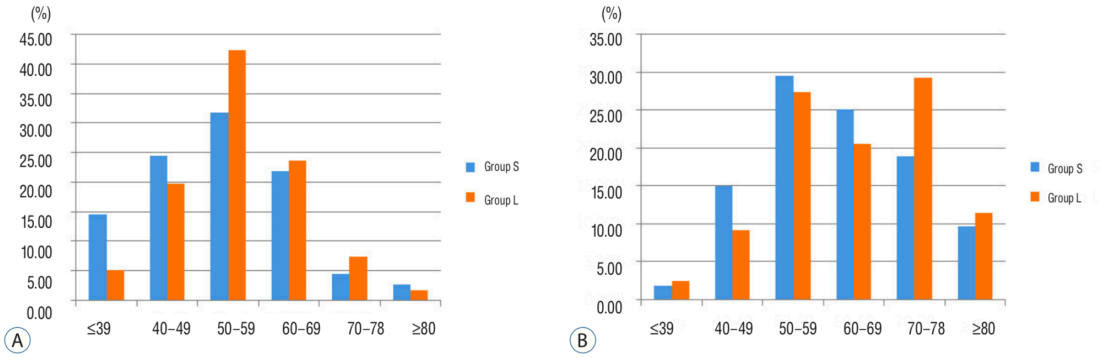


Figure 2 Ruptured aneurysms stratified by size. Obtained from (22).



Ⓐ Male; Ⓑ Female Group S: <5mm; Group L: ≥5mm

Figure 3 Distribution of patients with aSAH by age, gender and aneurysm size. Obtained from (22).

3.2.4 Etiology

Most SAH will happen because of a TBI. However, if we only talk of **spontaneous SAH**, the principal cause are **ruptured brain aneurysms** (70-80%), followed by perimesencephalic SAH (10%) (7). Even though all the efforts done to find the cause of the bleeding, still 10 to 20% of patients with spontaneous non-aSAH remain without an etiological diagnose (3). All the other possible etiologies, shown in *Annex 3*, are infrequent and rare.

3.2.5 Clinics

The most common clinical presentation of SAH, present in 85% of cases, is an abruptly (acme in seconds or minutes) and very intensive headache ("**thunderclap headache**"), described by the patients as "*the worst headache of my life*" (7,18). Its onset is related with a physical effort in 30% of patients (7).

Although it can be the only clinical feature, most of them (70%) suffer more **symptoms**: nauseas and vomits, photophobia, neurological deficits as consciousness loss (50%), palsy of 3rd cranial nerve (10-15%) and motor and sensitive alteration, agitation and seizures (6-15%) among others (7,14,18,27).

Between 30 and 45% of the patients will explain us the presence of **sentinel symptoms** during the previous days or weeks: headache similar to migraine or, less commonly, focal neurological deficits as aphasia, diplopia, paresis… (7,14).

These patients can also have signs of meningism (nuchal rigidity and positive Kernig and Brudzinski signs) and intraocular hemorrhages (subhyaloid, retinian and vitreous, 20-40%) (7,18).

In order to evaluate and grade the severity of the clinical condition of every patient with SAH, physicians should use the **Hunt and Hess scale** (HH), the **Glasgow Coma Scale** (GCS) and the **World Federation of Neurosurgeons Society classification** (WFNS) (14,18). See *Annex 4*, *Annex 5* and *Annex 6* respectively.

3.2.6 Diagnosis

Some studies show that 25 to 30% of patients with SAH have an erroneous initial diagnosis, which lead to late treatment with more complications and a worse outcome (17,18). In order to avoid it, it is very important to follow the next steps:

1. **Anamnesis and clinical exploration.** We have to correctly identify and suspect SAH if we found some of the symptoms and signs explained above. Although 85% of patients with SAH present a thunderclap headache (18), only 25% of patients with this type of headache will really have one (17). Because of SAH severity, unless noted otherwise, it should be handled it as if it was confirmed, until it is ruled out.
2. **Brain computed tomography** (CT) **without contrast**. Although with some false negatives cases (anemic patients, very light hemorrhages, subacute phase), it has a high sensibility and specificity (98-100% firsts 12h, it decreases with the time) (7). With this test, we are able to identify the bleeding inside the subarachnoid space (hyperdensity signal) as well as some of the complications and even the presence of aneurysms when they are big or calcified (7,27). Fisher CT scale is used to quantify the volume of blood (*Annex 7*) (14).
3. **CT angiography** (CTA). It draws intracerebral arteries, allowing us to find smaller aneurysms not seen in the CT (≤ 3 mm), define better the location and characteristics of the aneurysm (size, shape, thrombosis, calcification…) and also plan, together with the CT, the surgery in patients in clinical bad conditions who cannot undergo an angiography (7,27).
4. **Lumbar puncture and magnetic resonance imaging** (MRI). They are not necessary except if we have a high SAH suspicion and a negative CT (14). We expect to find hemorrhagic or xanthochromic CSF in the lumbar puncture, and presence of blood in FLAIR and T2 MRI sequences (positive during the subacute phase) (7).
5. **Angiography**. It is the Gold Standard, and it should be performed as soon as possible after the first 6h in every patient with SAH to confirm the diagnosis of intracerebral aneurysm and its features, describe the entire cerebral vasculature and also the presence of vasospasm (14). It can be negative in 20-25% of patients with a suggesting aSAH CT scan. In those cases, a second angiography should be performed after 1 to 3 weeks (7), because sometimes aneurysms cannot be seen due to vasospasm (18).

3.2.7 Treatment

We can separate the treatment in two sections:

» General measures

All the patients with an aSAH need to be admitted to the intensive care unit (ICU), semi-intensive care unit (SICU) or stroke unit, so they can be **checked regularly**, **ensuring their airway** (oxygen saturation ≥ 95% or pO_2 = 80-100 mmHg). **HT** should be treated with labetalol or nimodipine only in patients with a mean pressure over 110 mmHg after

correcting the possible causes (pain, hypoxia, etc). Prophylaxis treatment of **stress ulceration** and **deep vein thrombosis** should be performed with proton-pump inhibitors and intermittent pneumatic compression, enoxaparin or bemiparin respectively**. Analgesic** and **sedative treatment** should be administrated depending on patient status, as well as **antiemetic drugs**. **Serotherapy**, if indicated, should be with isotonic or hypertonic serums. Finally, patients who have had a **seizure**, should be treated with levetiracetam (14).

» Specific treatment

As the principal cause of spontaneous SAH is the presence of a ruptured aneurysm, we will only explain, on section *3.3.7 Treatment*, the **specific etiological treatment of aSAH**. We will also need to prevent and treat the appearance of possible complications (explained in the next section).

3.2.8 Complications

The most frequent complications seen in patients who have suffered a SAH are the ones below:

» Rebleeding

Rebleeding is defined as a recurrent bleed after the initial SAH. It is one of the main causes of bad outcome in patients who have survived an aSAH and do not undergo surgical or endovascular treatment. It is the complication with a highest mortality rate, between 42 to 74% (5,14). The risk of having a rebleed in untreated patients is higher on the first day (3-4%) and it has an accumulative risk of 1-2% every day during the first month (14,17). The best way to prevent it is with an early SAH diagnose and an early definitive reparation of the aneurysm (7,14,17,27).

» Vasospasm and ischemia

Vasospasm is a late complication that appears mostly between the 4th and the 14th day (peak of incidence in the 7th day) after the SAH (5,14,27). Although 60 to 70% of patients have an angiographic vasospasm, only a third (20-30%) will have symptoms and 10 to 45% will have an observable infarction (5,14,17). It is the principal cause of morbidity, with a mortality of 7-20% (5,27). In order to prevent it, patients should have normovolemia and be treated it with oral nimodipine. If it is already present, triple H therapy (hypertension, hemodilution and hypervolemia) or endovascular treatment (intraarterial nimodipine or balloon angioplasty) should be considered (14).

» Hydrocephaly

Hydrocephaly is a dilatation of the brain ventricles due to an increase of CSF present in 20-40% of patients in the acute phase and 18-26% chronically (5,14). It is diagnosed with the Evans Index, calculated with the brain CT. Depending on the clinical features of the patient, the treatment is different: **expectant** (HH from I to III), **external ventricular drain** (clinical deterioration and/or HH of IV or V) or **ventriculo-peritoneal shunt** (chronic hydrocephaly) (14,27).

» Seizures

Less than 5% of patients will have a seizure after the SAH. Nowadays, the anticonvulsant prophylactic treatment with levetiracetam is **only** recommended, in patients who have high risk of presenting a seizure during the immediate post-hemorrhagic phase (< 3 days), always before the definitive treatment of the aneurysm (14,27).

» Hyponatremia

Hyponatremia, more common that hypernatremia, is presented in 30% of patients. It increases the risk of cerebral infarct due to vasospasm and also of brain edema. To prevented it, it is indicated to analytically control and correct hydroelectrolytic disorders (5,27).

3.3 INTRACEREBRAL ANEURYSM

3.3.1 Definition and epidemiology

Intracerebral aneurysms can be defined as vascular defects that consist on the dilatation of a vessel wall on the cerebral vasculature. Although intracerebral aneurysms can be venous, most of them are found in arteries (6).

The overall prevalence of unruptured intracerebral aneurysms (UIA) in the general population is 3.2%, being more prevalent in women and also in elderly population (28). Although they cause the 80% of spontaneous SAH (7), most of them (50-80%) will never rupture throughout lifetime (29). The overall risk of rupture during the first 5 years is about 1.2%, but it varies between patients depending on which rupture and protective factors they have (see *3.2.3 Risk and protective factors*) (21).

3.3.2 Aneurysm types with their own etiologies and physiopathology

As intracerebral aneurysms can have different shapes and etiologies, we can distinguish the following types of brain aneurysms (*Figure 4*):

- **Saccular aneurysms,** also called "berry aneurysms", are the most frequent type, being around 80% of all of the intracerebral aneurysms (18). It is an acquired lesion consisting in an outpouching of the vessel wall, due to structural defects in the arteries (thinner fibrotic wall, without tunica media nor muscular cells and elastic fibers' disintegration and rupture) and also due to hemodynamic stress that benefits its formation. This type of aneurysms is described with the size of their sac and neck, and also with the ratio sac/neck. They are mostly caused by HT (3,30,31).

- **Fusiform aneurysms**, with a prevalence of 0.06 to 5.8% in the general population, are described as areas with arterial dilatations (larger external diameter). They are caused by atherosclerosis as well as connective tissue diseases and some heredity factors. Although most of them are asymptomatic, they can have different clinical presentations: ischemic stroke due to thrombus formation, symptoms caused by the compression of the cranial-nerves, the brainstem or the third ventricle, and also SAH due to aneurysm rupture (3,32).

- **Mycotic aneurysms**, around 0.7 to 6.5% of all the aneurysms, are developed in patients with an infection (bacterial, fungal, mycobacterial or virial) due to the formation of a septic emboli which infects and weakness the vessel wall allowing its outpouching in the brain vasculature. The mortality rates in this specific kind of aneurysm ranges from 12 to 32% (3,33).

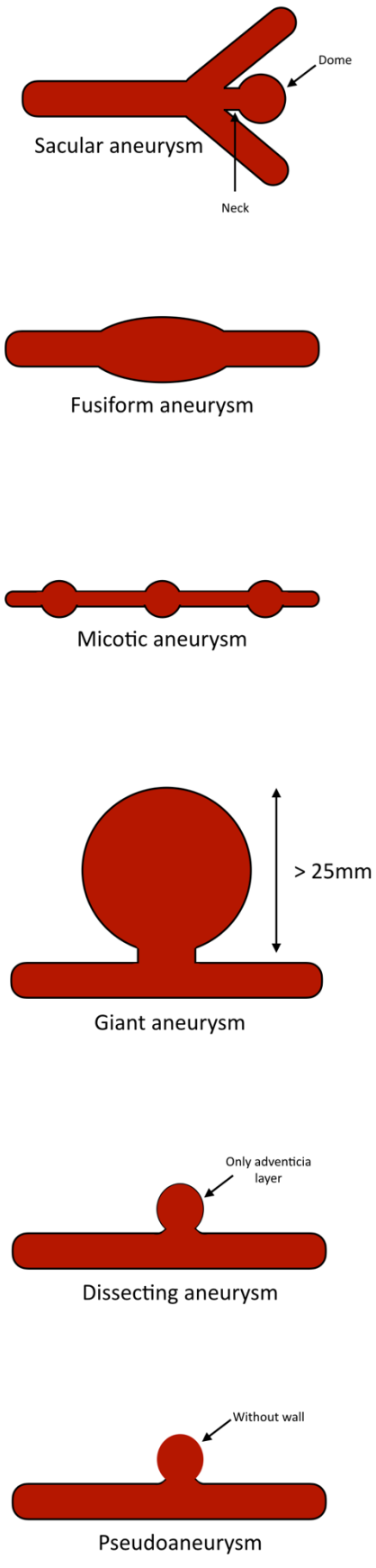


Figure 4 Types of intracerebral aneurysms

- **Giant aneurysms** are defined as aneurysms with a diameter size greater than 25 mm and suppose the 5% of all brain aneurysms. Around 33% are found in the posterior circulation, most on the basilar artery, while 66% are in the anterior circulation. As its size is considerable and most of them suffer a calcification and a complete thrombosis, they are usually presented with symptoms caused by its mass effect. However, they can also cause symptoms of SAH or ischemic stroke if the aneurysm ruptures or if a thrombus is released, respectively (3,34,35).

- **Dissecting aneurysms** are formed when the vessel wall is internally injured but not completely broken. Therefore, the bleeding is confined between the wall layers (intimal tunica and adventitia layer), forming an aneurysm with a thinner wall. It is usually related with HT and also as a complication of endovascular procedures (36).

- **Pseudoaneurysms**, or false aneurysms, are an infrequent type of brain aneurysms, defined as pulsatile and encapsulated hematomas that are communicated with the injured vessel. They are formed when a brain vessel wall completely ruptures, usually after a traumatism but also due to inflammation or due to a complication of a brain interventionist treatment. Unlike the other types of aneurysms, the blood leaks out to the extravascular space and the surrounding tissues, as well as blood clot and perivascular tissue and fibrosis, form the external sac wall, which encapsulates the hematoma (37,38).

3.3.3 Aneurysm location

In order of frequency, the locations with more incidence of aneurysms are (30,31):

1. Anterior communication artery (ACoA) (30%)
2. Posterior communication artery (PCoA) (25%)
3. Middle cerebral artery (MCA) (20%)
4. Internal carotid artery (ICA) bifurcation (7%)
5. Basilar tip (7%)
6. Pericallosal artery (4%)
7. Posterior inferior cerebellar artery (PICA) (3%)
8. Other less frequent locations (3,5%)

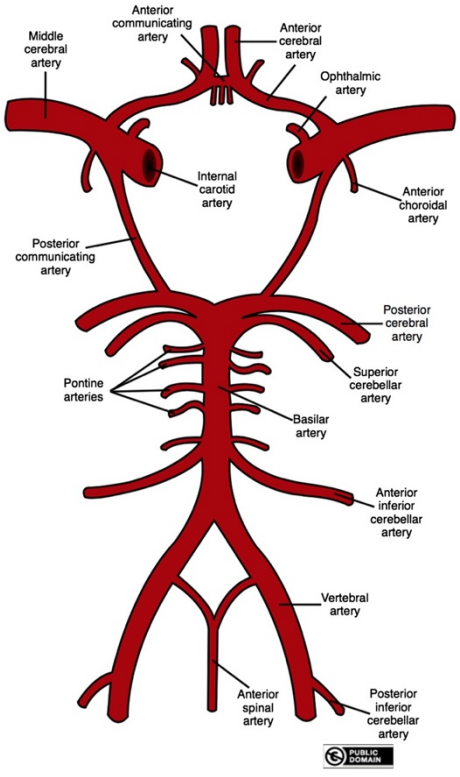


Figure 5 Circle of Willis

3.3.4 Clinics

Intracerebral aneurysms can be diagnosed before or after their rupture (aSAH in 50-60% cases, see *3.2.5 Clinics*) (31,39,40).

In contrast, UIA have a wide clinical presentation. Most of them are **neurologically silent** and are incidentally diagnosed (CT or MRI performed because another cause, as TBI, headache, dizziness…). However, they can also be **symptomatic**: headache, TIA or ischemic stroke (due to thrombus release), cranial-nerve compression deficits, symptoms of mass effect, convulsive disorders and other neurological symptoms (3,20,31,41).

3.3.5 Diagnosis

Intracerebral aneurysms, as we explained before, can be diagnose in two different phases:

- After their rupture: it is explained in the previous section (4.2.6 Diagnosis).
- Before their rupture: the test that will diagnose an UIA will be determinate by the symptoms presents in each patient. Usually, they are first seen in a brain CT or a brain MRI. If that occurs, the study needs to be completed with a CT angiography (CTA) and also confirmed by the gold standard test, a brain angiography.

The three most prevalent causes of diagnosis in UIA are headache ± dizziness (18 – 47,4%), ischemic cerebrovascular disease (17,6 – 22,6%) and cranial nerves deficits (2,2 – 15,4%) (42–45).

3.3.6 Treatment

It can be difficult to decide which is the best treatment for a **patient with an UIA**. Depending on the patient features, the aneurysm characteristics and the patient's preferences, the possible treatment options are the following ones:

» Conservative

When no interventional treatment is performed, it is recommended to undergo a close follow-up with non-invasive tests, as CTA or a magnetic resonance angiography (MRA), as well as visits with the specialist to review the results and evaluate the all the risk factors and patient's concerns (39). Although the interval of these follow-ups is not well defined, most studies have recommended they should be annual, or biannual, during the first 3 years and after that, if the aneurysm does not change (same size and shape) and do not appear new aneurysms, it can be less frequent (20,41).

It is mandatory to treat and control the possible rupture, and also cardiovascular, risk factors (41,46):

- Hypertension treatment
- Stop smoking
- Avoid illicit drugs and excessive alcohol intake
- Control diabetes and hypercholesterolemia
- Have good alimentary habits and practice exercise
- Weight control, avoiding overweight and obesity

» Surgical clipping

Surgical clipping requires general anesthesia and an open craniotomy. Once the aneurysm is dissected out, a metallic clip is fixed on its neck, achieving the isolation of the aneurysm of its parent blood artery. It is used to treat aneurysms that have a ratio sac-neck acceptable to place the clip (usually in saccular aneurysms) (41,47).

It obtains a complete and effective occlusion, without neck residua, in about 91% of cases (48). The morbidity rate varies from 4.1 to 10.9%, and the mortality rates from 1 to 2.6% (49,50).

Some risks and complications of this treatment are: infection, anesthesia allergic reaction, incomplete occlusion, hemorrhage due to intraoperative rupture, ischemic stroke due to thromboembolism, vasospasm, seizures and recurrence (31,41).

» Endovascular treatment

There are different endovascular treatment techniques, that can be performed under general anesthesia or only with sedation (31,41):

- Coils packing. It consists in delivery inside the aneurysm a soft platinum coil, which causes the exclusion of the aneurysm from its parent artery due to the induction of local thrombosis.
- Flow diverter stent. This technique is usually indicated on large saccular aneurysms with a wide neck, as well as fusiform aneurysms.
- Liquid embolic agents. The use of embolic agents (as *onyx*, *histoacryl* and *phil*), is only indicated in aneurysms that cannot undergo surgical clipping or the other endovascular technics (big saccular aneurysms with wide neck).

With the previous techniques, only 86.1% of aneurysms will be completely occluded while 24.4% will suffer a recurrence and 9.1% will need to be retreated (51,52). The 1-year morbidity rate is about 6.4% and the mortality of 3.4% (26).

In cases of aneurysm rupture the aneurysm reparation should be performed, if possible, during the first 72 hours after the initial hemorrhage, taking into account the clinical status of the patient (27).

3.3.7 Screening and prevention

Nowadays, screening should **only** be performed, with an **MRA** or a **CTA**, in patients that meet the following criteria:

Table 3 UIA screening recommendations. Adapted from (47)

Not recommended	Consider	Strongly recommended
• General population • People who have a contraindication to undergo a brain surgery / endovascular treatment • People who do not want to be treat	• ADPKD without family history of aneurysms • Patients with only one family member with UIA or SAH (per patient preference)	• ≥ 2 family members with history of UIA or SAH • ADPKD with family history of UIA o SAH • Patients with coarctation of the aorta

ADPKD: Autosomal dominant polycystic kidney disease; SAH: subarachnoid hemorrhage; UIA: unruptured intracerebral aneurysm

If the study results in a diagnosis of an UIA, patient should be treated with the aim to prevent its rupture, with one of the aneurysms occlusive treatments we have mentioned before: surgery clipping or endovascular treatment (depending on the patient and aneurysm's characteristics), as well as controlling risk factors explained in the conservative management (39,46).

3.4 ROLE OF STATINS AND ANTIPLATELET THERAPY IN ANEURYSM RUPTURE

3.4.1 Aneurysm's physiopathology

The formation, progression and rupture of UIA is mediated by inflammatory factors that are released when endothelial cells are damaged due to elevated hemodynamic stress, and also by the macrophages that these mediators recruit (53).

There is evidence that these substances end up provoking histological and pathophysiological differences between ruptured and unruptured aneurysms, showing that ruptured aneurysms present a damaged or destroyed endothelial cell layer, macrophages and leukocytes diffuse wall infiltration, thinner wall with compromised structural integrity (smooth muscle cells and collagen IV is replaced with fibrin and hyaline fibers) as well as arteriosclerotic changes (53,54).

3.4.2 Statins treatment

Statins are competitive inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase drugs indicated to treat patients with hypercholesterolemia and also in primary and secondary cardiovascular disease prevention (55).

By inhibiting this enzyme, statins cause a decrease of total cholesterol and low-density lipoprotein cholesterol (LDL-chol), an increase of high-density lipoprotein cholesterol (HDL-chol) and a decrease of triglycerides (TG). Apart from these effects, they also have **pleiotropic actions**, consisting in (55):

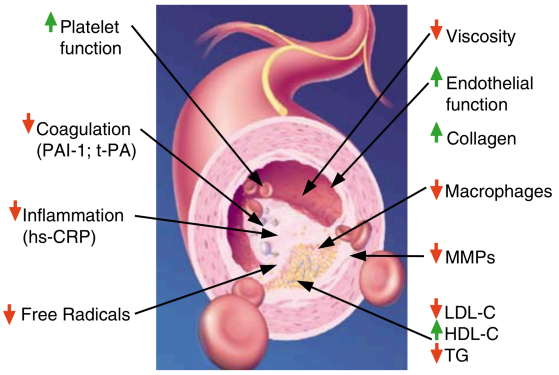


Figure 6 Statins pleiotropic actions. Obtained from (56)

- Improvement of endothelial cell integrity with preservation of endothelial function
- Reinforcement of atherosclerotic plaques stability
- Reduction of inflammation and oxidative stress
- Inhibition of thrombogenic response
- Immunomodulatory effect

Those actions could explain the beneficious effect of statins to reduce and prevent the aneurysm rupture that has been found in some studies. However, there is still controversy and remains unclear if this treatment should be recommended or not (57,58).

3.4.3 Antiplatelet therapy

Antiplatelet drugs are indicated as a primary and secondary prevention treatment of thrombotic cerebrovascular diseases and also cardiovascular diseases. Its main effect consists in reducing platelet aggregation as well as to inhibit thrombus formation. ASA, the most studied and recommended antiplatelet drug, in addition, also has an anti-inflammatory effect (59).

Some studies have demonstrated that patients who are undergoing ASA therapy have less risk of rupture (19,53). This effect, considering the aneurysm's physiopathology explained above, can be explained by ASA antiaggregant effect which reduces mural thrombi and this, in turn, decreases the consequent inflammatory cascade or by its own anti-inflammatory effect (53).

4. JUSTIFICATION

As stated above, cerebrovascular diseases (CVD) are a public health problem. Nowadays, all over the world, they are the second leading cause of death, the first cause of incapacity and the second cause of dementia, causing a high socioeconomic burden (3,4,10,11).

Although subarachnoid hemorrhage, characterized by a bleeding into the subarachnoid space between the arachnoid and the pia mater, only represents around 5% of all CVD and ischemic strokes are about 80 to 85% of them, SAH has a poorer outcome with higher rates of mortality and morbidity (overall mortality between 22 and 26% with a prevalence of functionally dependent patients of 42%) (4,6,16–18).

Spontaneous SAH is mostly caused by the rupture of intracerebral aneurysms (70 to 80%) (7). As some studies show, the overall prevalence of unruptured intracerebral aneurysms in the general population is around 3.2%, but only 20 to 50% of these aneurysms will rupture during patients lifetime (28,41).

Even though screening in general population is not recommended, due to the more accessibility of brain neuroimage (CT and MRI), lately, the number of UIA diagnosed as incidental findings in asymptomatic patients in increasing. As a result, there is an increase of UIA diagnosis and the need to decide which patients should be treated and which ones should not, by evaluating the risks and benefits of both options (39,46,47).

Currently, some studies have showed a higher incidence of aSAH in patients with some of the following characteristics, but their specific individually role is not proved enough: female gender, elderly, Japanese or Finish descendent, black ethnicity, history of previous SAH, family history of SAH and/or UIA, autosomal dominant polycystic kidney disease, some connective tissue disorders, hypertension, alcohol intake and smoking; and also aneurysms with any of these features: multiplicity, location on the posterior circulation, contrast enhancement, lobulation, daughter sac and/or symptoms caused by the aneurysm different from SAH symptoms. Even less evidence is available for those factors that seem to be protective, as antiplatelet and statins treatment (19–21,25).

Nowadays, to advise the decision of which treatment is better for every patient, there are only two scores available: **PHASES score** (60), that has not been externally validated and do not include the study of the recent findings in protective factors (antiplatelet and statins treatments) and mainly focus on location and size of the aneurysm with a sensibility and specificity rates to identify low-risk UIA of 85% and 52% respectively (61); and the **UIATS score** (62), which was developed through a Delphi consensus and cannot be used in non-saccular aneurysms and

neither in aneurysms associated in specific diseases and entities, and it does not consider antiplatelet nor statins treatment. Two studies have compared the treatment decision made in their hospitals with the score's recommendation and have found some discrepancy of opinions, as UIATS habitually overtreated patients with UIA (63,64).

Therefore, till now we just have approximate estimates of complication percentages, limited knowledge of factors of risk, and still weak prediction models (46).

Our study, the principal aim of which is to create a new predictive tool capable to precisely calculate the probability of having an aneurysmatic rupture in patients diagnosed with an UIA by elaborating a robust prediction model, is clinically relevant because of the existing lack of knowledge of the exactly factors involved in UIA rupture and its individually role, as well as the need of new instruments that, taking into account all the protective and risk factors known at the moment, will be able to help physicians to make a more accurately and individually treatment decision.

Moreover, if we are able to find statistically significative differences between unruptured and ruptured intracerebral aneurysms allowing the creation of the **InTracerebral Aneurysm's Risk of Rupture SCORE (ITARR SCORE),** further studies evaluating its validity as well as new prospective studies comparing endovascular and surgical treatment versus conservative management would be of interest.

Finally, if the protective role of antiplatelet and/or statins medication is reflected in our population sample, prospective studies should be performed to evaluate these drugs as new preventive treatments comparing them with the actual conservative management.

5. HYPOTHESIS

The main hypothesis of the study is that the use of a prognostic SCORE in patients with unruptured intracerebral aneurysms allows physicians to establish the risk of aneurysm rupture and gives a new tool that helps physicians to better select patients for treatment.

6. OBJECTIVES AND PURPOSE

6.1 MAIN OBJECTIVE

The main aim of the study is to create a SCORE for patients with unruptured intracerebral aneurysms that will predict –using demographic, analytic, clinic, radiologic and angiographic variables – which is the risk of rupture they have, in order to treat them and prevent their rupture and its complications/consequences.

6.2 SECONDARY OBJECTIVES

- To describe the demographic factors, treatments and clinical outcome in our study population.
- To prove whether the chronic intake of statins in patients with unruptured intracerebral aneurysms significantly decreases the risk of rupture in comparison with patients who do not intake these drugs.
- To determinate whether patients who intake antiaggregant drugs have less risk of rupture in comparison with patients who do not intake these drugs.

7. METHODS

7.1 STUDY DESIGN AND SETTING

The study consists in a case–control study of a prospective database that has been conducted in the Neuroscience Department of *Hospital Universitari Germans Trias i Pujol (HUGTiP)* of Badalona in 2018.

7.2 STUDY POPULATION

7.2.1 Participants

The study population includes patients diagnosed, treated or followed in the Interventional Neuroradiology Department of HUGTiP, until the end of 2017, with an angiography diagnosis of an intracerebral aneurysm, having excluded patients untreated.

7.2.2 Inclusion criteria

- Male and female patients aged 18 years old or older.
- Patients who have signed the informed consent form.
- Patients diagnosed of one or multiple ruptured or unruptured intracerebral aneurysms by a cerebral angiography.
- Patients who have been diagnosed, treat or followed in HUGTiP.

7.2.3 Exclusion criteria

- Patients who have been treat after December 31st of 2017.
- Patients with incomplete medical records where was impossible for us to collect all the variables information.
- Patients who, based on individual characteristics, have not been treated.

7.3 SAMPLE COLLECTION AND DATA SOURCE

Our database has been created throughout August 2018 in the Interventionist Neuroradiology Department of HUGTiP, taking as a basis a pre-existent aneurysm register from 2010. We have completed the missing data and added all the diagnosed, treated or followed patients with

intracerebral aneurysms in the HUGTiP until the end of 2017 that met the inclusion criteria explained above, using a consecutive non-probabilistic sampling technique.

All data has been extracted from "*SAP Assistencial*", the program used in the hospital by administrative and clinical-care personnel, which contains all the collected patient's information available: administrative data, medical history with demographic data, health problems, date of diagnosis, tests results, prescriptions… and also laboratory and radiology data and current medication.

The whole information we have introduced into our database is, in both groups (ruptured and unruptured intracerebral aneurysms), the one known at the moment of the angiography that diagnosed the aneurysm, avoiding possible actions by the patient to modify their life style or health care by knowing the diagnose of intracerebral aneurysm that could alter the variables that we have collected.

All personal identification data has been anonymized.

7.4 SAMPLE SIZE

Our simple size is constituted by **287 patients with a total of 345 aneurysms** diagnosed, treated and/or followed in HUGTiP's Neuroscience Department until the end of 2017 of a brain aneurysm (**175 non-ruptured aneurysms** and **170 ruptured aneurysms**) that met our inclusion criteria without any of the exclusion criteria.

In order to calculate our sample's statistical power, on account that data was ready to analyze because the sample size was previously established, we have used the Professor Marc Sáez's software based on the library "pwr" of the free statistical environment R (version 3.5.1).

With a bilateral test, accepting an alpha risk of 5%, with 147 patients with non-ruptured aneurysms and 158 patients with ruptured aneurysms, and assuming a medium effect size (i.e. odds, prob (ruptured aneurysms) / (1 - prob (ruptured aneurysms)) = 0.7) we have a **statistical power of 93.73%**.

7.5 VARIABLES AND MEASUREMENTS

7.5.1 Independent variable

» Sociodemographic variables

- **Age**. We have collected patient's age in years.
- **Gender**. Patients have been categorized into female and male gender.

» Health history data

- **Basal modified Rankin scale (mRS).** According to de mRS, we have classified the patients into 7 groups (*Annex 8*) depending on their basal status (mRS punctuation before the current episode) (65,66).
- **Tobacco smoking**. We have divided patients into two groups:
    - Patients who currently smoke and ex-smokers' patients who have not been smoking less than 5 years
    - Patients who currently do not smoke and ex-smokers' patients who have not been smoking more than 5 years
- **Alcohol intake**. Patients have been categorized into <40 grams/day alcohol consumers and ≥40 grams/day alcohol consumers, depending on their ongoing intake.
- **Hypertension (HT).** Patients have been divided into patients with HT (systolic blood pressure >140mmHg or diastolic blood pressure >90mmHg or ongoing hypotensive treatment) and non-HT patients.
- **Diabetes mellitus.** Patients have been categorized as diabetics (two determinations of basal capillary glycemia of ≥126gm/dl or ongoing hypoglycemic treatment) and non-diabetics patients.
- **Dyslipidemia**. Patients have been divided into dyslipidemic (total cholesterol >200 mg/dl, LDL-chol >130 mg/dl, HDL-chol <35 mg/dl, TG >170 mg/dl or ongoing hypo-lipidemic treatment) and non-dyslipidemic patients.
- **Previous ischemic stroke**. Patients have been categorized into two groups: patients with previous ischemic stroke history and patients without previous ischemic stroke history.
- **Ischemic heart disease**. Patients have been divided into patients with previous ischemic heart disease history and patients without previous ischemic heart disease history.
- **Atrial fibrillation**. Patients have been divided into patients diagnosed of atrial fibrillation before or during the hospital admission for the aneurysm study and patients without atrial fibrillation diagnosis.

- **Valvular hearth disease**. Patients have been categorized into patients with embolic valvular heart disease history and patients without embolic valvular heart disease history.
- **Epilepsy.** Patients have been categorized as epileptic patients and non-epileptic patients.
- **Allergies**. Patients have been divided into patients who suffer a known allergy and patients without known allergies.
- **Drug addiction**. Patients have been classified into patients with a diagnosis of drug addiction and patients with no history of drug addiction.
- **Previous TBI**. Patients have been divided into patients who have had a TBI and patients who have no history of TBI.
- **Surgery history**. Patients have been categorized into patients who underwent a surgery in the past and patients who have never been operated.
- **Hepatopathy**. Patients have been divided into patients diagnosed of hepatic pathology and patients with no hepatic disease.

» Ongoing medication

- **Birth control pills**. Female patients have been divided into patients who intake birth control pills and patients who do not intake those drugs.
- **Statins treatment**. Patients have been distributed into patients who intake statins and patients who do not intake these drugs. In addition, they have been categorized by type of statin (atorvastatin, fluvastatin, pravastatin and simvastatin) and the administrated dose (10mg, 20mg, 40mg or 80mg).
- **Antiplatelet treatment**. Patients have been divided into patients who intake antiplatelet drugs and patients who do not intake them. Moreover, they have been classified in groups according to the type of antiaggregant drug they are intaking (ASA, clopidogrel, ASA + clopidogrel or triflusal).
- **Oral anticoagulant intake**. Patients have been distributed into patients who intake any oral anticoagulant drug and patients who do not intake these drugs.
- **Oral antihyperglycemic agents (OAHA).** Patients have been classified into patients who intake OAHA and patients who do not intake these drugs.
- **Insulin**. Patients have been categorized into patients who are treat with insulin and patients who do not use insulin.

» Diagnosis

- **Cause of diagnosis**. Patients have been divided in groups according into the reason of the brain study that allowed the diagnosis of intracerebral aneurysms: headache, aSAH, cranial-nerves compression symptoms, rupture of another aneurysm, seizure, other neurological symptoms, thrombosis and stroke, incidental finding or other causes.
- **Initial Hunt and Hess scale (HH).** Patients have been categorized into five groups considering their HH punctuation (*Annex 4*) during their admittance on the medical center.
- **Initial Glasgow Coma Scale (GCS)**. Patients have been classified in groups considering their GCS punctuation (*Annex 5*) during the admittance on the medical center.
- **Initial World Federation of Neurosurgeons (WFNS) classification**. Patients have been distributed in five groups considering their WFNS punctuation (*Annex 6*) during their admittance on the medical center.
- **Admittance CT.** Patients have been categorized in groups considering the findings on their admittance brain CT: no brain CT, normal, cisternal bleed, intraventricular bleed, visible aneurysm, cerebral infarction, hematoma, hematoma that requires surgical evacuation and hydrocephaly.
- **Fisher CT grade**. Patients have been distributed in four groups considering their Fisher CT punctuation (*Annex 7*) during their admittance on the medical center.

» Aneurysm characteristics

- **Multiple aneurysms**. Patients have been categorized into one aneurysm and multiple aneurysms.
- **Aneurysms number**. We have collected the total number of intracerebral aneurysms, ruptured and unruptured, they have.
- **Aneurysm location**. Patients have been categorized into groups depending on the artery where the brain aneurysm is located: cervical ICA, cavernous ICA, choroidal ICA, supraclinoid ICA, ophthalmic ICA, ICA bifurcation, ACoA, PCoA, horizontal segment of the anterior cerebral artery (ACA) (A1), vertical segment of the ACA (A2), pericallosal artery, MCA, vertebral artery (VA), PICA, posterior cerebral artery (PCA), basilar artery, basilar tip, anterior choroid artery (AchA) and peripherical branches.
- **Paraophthalmic location**. Patients have been distributed into two groups: aneurysms with paraophtalmic location and aneurysms in another location.

- **ACoA or PCoA location**. Patients have been divided into two groups: aneurysms located in the anterior or posterior communicating arteries and aneurysms located in other locations.
- **Aneurysm type**. Depending on the aneurysm form, we have categorized patients into five groups: saccular aneurysm, fusiform aneurysm, dissecting aneurysm, giant aneurysm and pseudoaneurysm.
- **Thrombosis**. Patients have been distributed into three groups according to the angiography findings of non-thrombosis, partial thrombosis or complete thrombosis.
- **Lobulation**. Patients have been categorized into three groups according to the form of their aneurysm: non-lobulate aneurysm, bilobulate aneurysm and multilobulate aneurysm. They have also been classified into lobulated and non-lobulated aneurysms.
- **Alarm signs**. Patients have been separated into five groups according to the present of alarm signs: no history of alarm signs, presence of sentinel headache, presence of daughter aneurysm seen in an angiography, presence of contrast extravasation or presence of artery vasospasm.
- **Sac**. We have collected the sac's size in millimeters (mm).
- **Neck**. We have recorded the largest diameter size of the aneurysm neck in mm.
- **Sac-neck ratio**. We have calculated the sac-neck ratio dividing the sac size in mm between the neck size in mm.

» Treatment

- **Admittance to the intensive care unit (ICU) or in the semi-intensive care unit (SICU)**. Patients have been separated into patients who have been admitted in an ICU or SICU during their stay in the hospital and patients who have not been admitted it during their hospital stay.
- **Days in ICU or SICU**. We have collected the number of days that the patients have spent in the ICU and SICU units.
- **Type of treatment**. Patients have been categorized into eight groups according on their aneurysm treatment: coils, coils + stent, stent in stent, flowdiverter stent, flowdiverter stent + coils, liquid embolic agents, surgical clipping and others.
- **Closure**. Patients have been classified into seven groups according on the treatment result (measured throughout a brain angiography): complete exclusion of the aneurysm, exclusion of more than 95%, exclusion between 90 to 95%, exclusion between 50 to 89%, less than 50% exclusion, flowdiverter changes and no changes in the aneurysm.

- **Heparin dose**. We have collected the total heparin dose administered to the patient during the hole procedure in UI/Kg.
- **Vasospasm**. Patients have been divided in two groups: development of vasospasm and no vasospasm.
- **Day of vasospasm**. We have collected the day of vasospasm development.
- **Basal glycemia**. We have recorded the basal glycemia level in mg/dl.
- **Angiography complications.** We have separated the patients in two groups: patients with complications during the procedure and patients without complications during the procedure.
- **Complications**. Patients have been divided into groups according on the presence of angiography complications: no angiography complications, arterial rupture with contrast extravasation, arterial dissection, distal embolism, inguinal hematoma, vasospasm that needed treatment, hemodynamic complications (bradycardia, HT, or hypotension), cerebral hematoma, dispositive rupture, contrast allergy, embolization material complication, thrombosis and thrombosis + arterial occlusion.
- **Complications consequences**. Patients have been classified into four groups depending on the consequences of the angiography complication: non-consequence, transient neurological deficit, permanent neurological deficit and death.
- **General complications <72h.** We have collected general complications during the first 72 hours after the angiography: no complications, symptomatic intracerebral hemorrhage, progressive stroke, death, new stroke, auricular fibrillation, aspiration pneumonia, respiratory infection, peripheral embolism, acute urine retention, epileptic seizure, malignant stroke, coma, respiratory failure, medullar ischemia, intestinal ischemia, hepatic failure and other complications.
- **Death <72h**. We have collected whether the patient died during the first 72 hours or not.
- **Mortality < 7 days**. We have collected whether the patient died during the first 7 days or not.
- **mRS 7 days or discharge**. We have recorded the seven days or discharge mRS punctuation.

» Follow-up

- **Poor outcome**. Patients have been divided into two groups according on the 3 months outcome: poor outcome (mRS >2 at 3 months) or good outcome (mRS ≤2 at 3 months).

- **Mortality 3 months**. We have collected whether the patient died during the first 3 months.
- **6-months follow-up angiography**. We have recollected data of the 6-months follow-up angiography and divided the patients into groups according on the findings: no changes, complete occlusion, thrombosis, coils compaction, neck repermeabilization, aneurysm repermeabilization, rupture, greater size, partial occlusion, angiography does not proceed, and patient do not authorize the test.
- **1-year follow-up angiography**. We have recorded data of the 1-year follow-up angiography and categorized the patients into groups according on the findings: no changes, complete occlusion, thrombosis, coils compaction, neck repermeabilization, aneurysm repermeabilization, rupture, greater size, partial occlusion, angiography does not proceed, and patient do not authorize the test.

7.5.2 Dependent variable

- **Rupture**. Patients have been divided into ruptured aneurysm (patients presenting symptoms of aSAH in the moment of the hospital admission with a brain CT and/or a brain angiography suggesting or confirming the presence of a ruptured intracerebral aneurysm) and unruptured aneurysm (patients without aSAH symptoms and absence of blood on the neuroimages).

8. STATISTICAL ANALYSIS

In this study, IBM® SPSS® Statistics (version 22.0 for MacOS®) has been used to perform the statistical analysis of the variables. The results have been exhibit using Microsoft Excel® tool.

A two-sided test has been performed in inferential statistical analysis, and we defined a p-value of 0.05 to consider the results as statistically significant.

8.1 UNIVARIATE ANALYSIS

In the descriptive statistical analysis, **probability plots** and **Kolmogorov-Smirnov test** have been performed to assess the distribution of the variables. Continuous quantitative variables and discrete quantitative variables have been expressed as **means ± standard deviation (SD)** and **medians ± interquartile range (IQR)**, depending if they had a normal distribution or not, and they have been represented in box plots. However, nominal and ordinal qualitative variables have been expressed as **absolute (number of cases)** and **relative frequencies (percentages)**, and they have been represented in bar charts or pie charts.

8.2 BIVARIATE ANALYSIS

In the bivariate analysis, we have analyzed the differences in the independent variables between the group of patients with ruptured aneurysms with the group with unruptured aneurysms. In order to achieve it, we have performed the following tests:

- For continue's quantitative variables we have used the **Student-t test** and for the discrete's the **U-Mann Whitney test** to obtain the p value.
- For qualitative variables we have used **crosstabs** and the **chi-square test** ($\chi 2$ test) to obtain the p value.

The results have been displayed as bar charts or box plots.

8.3 MULTIVARIATE ANALYSIS

In the multivariate analysis, with the aim to identify and avoid the presence of confounders variables, a **logistic regression model** has been performed with the variables where, in the bivariate analysis, a significant statistical association (p value < 0,05) was found and those with

a medical significance based on previous literature. These results have been expressed with **crude and adjusted odds ratios (OR)**, their **confidence intervals (CI)** and the **p value**.

8.4 SCORE

Finally, with the aim to facilitate its clinical use, we created a **probabilistic equation** with the previous results, which we have used to build an **online probabilistic SCORE calculator**.

9. ETHICAL CONSIDERATIONS

The study has been evaluated and accepted by the **Clinical Research Ethics Committee** (CREC) of *Hospital Universitari Germans Trias i Pujol*.

It has been performed in harmony with the human rights and the ethical principles incorporated in the "*Ethical Principles for Medical Research Involving Human Subjects*" of the Declaration of Helsinki of the World Medical Association (67), last reviewed in Brazil (October, 2013), and also respecting the Good Clinical Practice guidelines.

All data, in order to guarantee and protect personal data and confidentiality, has been manipulated, during the collection and also the analysis process, according to the "Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation)" (68). It has been anonymized, removing any identificatory information, and it will not be revealed in any presentation of the results.

Patients have been comprehensively informed and invited to sign the **informed consent form** (*Annex 9*), allowing us using their personal and clinical data with research purposes.

As data was collected retrospectively and all the interventions, according with the actual medical practice, were already performed, participants have presented no risk.

The authors of the study declare no conflicts of interest.

10. STUDY STRENGTHS AND LIMITATIONS

As with every clinical study, our retrospective case-control study has some advantages, but it also has disadvantages. All these strengths and limitations are discussed below.

As a result of being a retrospective study, we had to face a **follow-up bias** due to the impossibility to retrieve data that was not included in the initial clinical history and medical reports. In order to decrease the number of participants excluded because of this reason, we searched the information in "*SAP Assistencial*".

A preexistent register started on 2010 was used as a basis to build our database. Because of that, we could not add more **variables** that, as some studies show nowadays, they are possible relevant factors for predicting aneurysms rupture, like contrast enhancement.

Another limitation present on this case-control study is the difficulty to correctly **match the case group with the control group participants** throughout a consecutive non-probabilistic sampling technique. With the aim to reduce this selection bias, we decided to exclude all untreated patients, as all the participants in the case group underwent surgery or endovascular treatment. Doing this, we assumed a smaller bias, but we also had to deal with its consequences: we excluded patients with unruptured intracerebral aneurysms that maybe had different features with the ones that had been treated. Therefore, we got a more homogenous sample.

Furthermore, in order to control all the possible confounding variables between both groups, we also performed a **multivariate analysis** with the aim to minimize the confusion bias.

Moreover, as we include only patients with an angiographic diagnosis of intracerebral aneurysm, we could not recruit all the patients that, due to its clinical condition, was not possible to perform the angiography and all the patients that died before arriving to the hospital.

Although the limitations explained above, the study also has **strengths**. We have been able to study, at the same time, the causality role of multiple factors while performing an affordable study due to its low cost and short duration. In addition, the power of our sample is pretty above of the optimal theoretically power calculated before doing any study (93.73% versus 80.00%). Finally, even though the study was not multicentric (it was performed in HUGTiP), it included patients of all over Catalonia because during weekends and non-working days, there is only one hospital on call in Catalonia to attend all the patients with SAH, and HUGTiP is one of them.

11. RESULTS

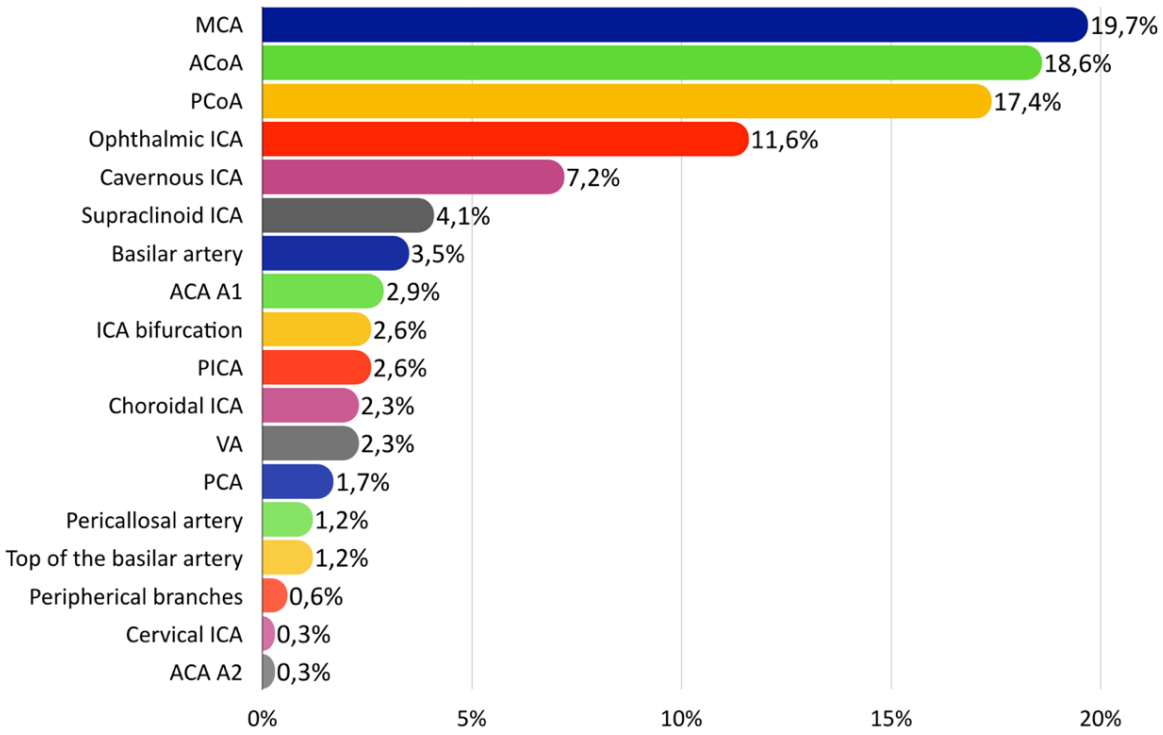
In order to make it more comprehensible, we have divided the results according to the objectives previously described.

11.1 MAIN OBJECTIVE

A total of 287 patients with 345 aneurysms were included to our study. The control group was formed with 170 unruptured aneurysms (49.3%) and the case group with 175 ruptured aneurysms (50.7%).

The median age of our patients was 54 years old and 235 (68.1%) were female. At the recruitment moment, 315 (91.8%) patients were asymptomatic and functionally independent (basal mRS=0) and only 6 (1.8%) had a basal mRS > 2. The presence of tobacco smoking (41.7%), hypertension (44.1%) and dyslipidemia (29.6%) were the most prevalent factors risk, and statins treatment (23.5%) and antiplatelet medication (14.2%) the most frequent ongoing medication.

Multiple aneurysms were found in 170 patients (49.4%). The most frequent aneurysms locations were MCA (19.7%), ACoA (18.6%), PCoA (17.4%) and ophthalmic ICA (11.6%) and the less frequent locations, peripherical branches (0.6%), cervical ICA (0.3%) and ACA A2 (0.3%).



ACA: anterior cerebral artery; ACoA: anterior communicating artery; ICA: internal carotid artery; MCA: middle cerebral artery; PCA: posterior cerebral artery; PCoA: posterior communicating artery; PICA: posterior inferior cerebellar artery; VA: vertebral artery.

Figure 7 Descriptive analysis: aneurysm location

Regarding aneurysm characteristics, 311 (90.1%) aneurysms were saccular, 329 (96.5%) did not presented thrombosis and 185 (54.7%) were multilobulated. The median size of the sac was of 6.01 mm and the median size of the neck of 3.29 mm with a mean sac-neck ratio of 2.96.

Although 261 (80.6%) patients did not present any alarm sign, having a daughter aneurysm (11.4%) and sentinel headache (5.2%) were the two most prevalent of them.

Table 4 Univariate analysis

	VARIABLE	ABSOLUTE FREQUENCY	RELATIVE FREQUENCY
DEMOGRAPHIC	**Age (median, IQR)**	54.00	[47.00 – 65.50]
	Gender		
	Female	235	68.1%
	Male	110	31.9%
HEALTH HISTORY DATA	**Basal mRS**		
	0	315	91.8%
	1	17	5.0%
	2	5	1.5%
	3	5	1.5%
	4	1	0.3%
	5	0	0.0%
	6	0	0.0%
	Tobacco smoking	144	41.7%
	Alcohol intake	20	5.8%
	Hypertension	152	44.1%
	Diabetes mellitus	22	6.4%
	Dyslipidemia	102	29.6%
	Previous ischemic stroke	32	9.3%
	Ischemic heart disease	21	6.1%
	Atrial fibrillation	11	3.2%
	Valvular hearth disease	4	1.2%
	Epilepsy	8	2.3%
	Allergies	35	10.1%
	Drug addiction	15	4.3%
	Previous traumatic brain injury	13	3.8%
	Surgery history	147	42.6%
	Hepatopathy	8	2.3%
ONGOING MEDICATION	**Birth control pills**	1	0.3 %
	Antiplatelet treatment		
	Antiplatelet treatment (all)	49	14.2%
	ASA	38	11.0%
	Clopidogrel	7	2.0%
	ASA + clopidogrel	2	0.6%
	Trifusal	2	0.6%

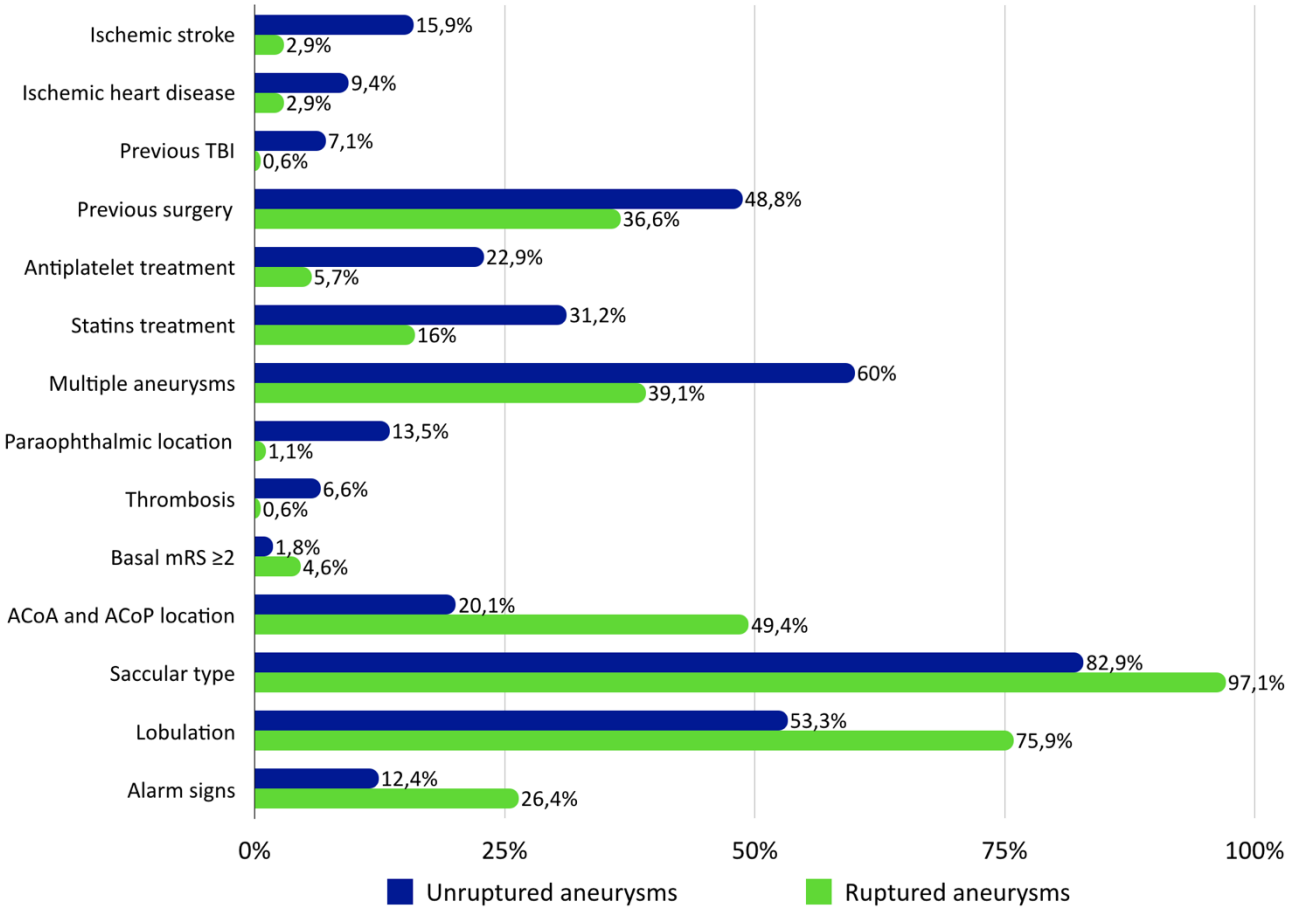
	Statins treatment		
	Statins (all)	81	23.5%
	Atorvastatin (all)	34	9.9%
	Atorvastatin 10mg	2	0.6%
	Atorvastatin 20mg	6	1.7%
	Atorvastatin 40mg	15	4.3%
	Atorvastatin 80mg	11	3.2%
	Fluvastatin (all)	3	0.9%
	Fluvastatin 20mg	2	0.6%
	Fluvastatin 40mg	1	0.3%
	Pravastatin (all)	2	0.6%
	Pravastatin 10mg	1	0.3%
	Pravastatin 20mg	1	0.3%
	Simvastatin (all)	42	12.2%
	Simvastatin 10mg	9	2.6%
	Simvastatin 20mg	28	8.1%
	Simvastatin 40mg	5	1.4%
	Oral anticoagulant intake	5	1.5%
	OAHA	17	4.9%
	Insulin	5	1.5%
ANEURYSM CHARACTERISTICS	**Ruptured**	175	50.7%
	Multiple aneurysms	170	49.4%
	Aneurysms number (mean ± SD)	1.92	± 1.21
	1	174	50.4%
	2	82	23.8%
	3 or more	89	25.8%
	Vascular territory		
	Cervical ICA	1	0.3%
	Cavernous ICA	25	7.2%
	Supraclinoid ICA	14	4.1%
	Ophthalmic ICA	40	11.6%
	PCoA	60	17.4%
	Choroidal ICA	8	2.3%
	ICA bifurcation	9	2.6%
	ACA A1	10	2.9%
	ACoA	64	18.6%
	Pericallosal artery	4	1.2%
	MCA	68	19.7%
	VA	8	2.3%
	PICA	9	2.6%
	Basilar	12	3.5%
	Basilar tip	4	1.2%
	PCA	6	1.7%
	Peripherical branches	2	0.6%
	ACA A2	1	0.3%

	Paraophthalmic location		
	Yes	25	7.2%
	No	320	92.8%
	ACoA or PCoA location		
	Yes	120	34.8%
	No	223	64.6%
	Aneurysm type		
	Saccular	311	90.1%
	Fusiform	20	5.8%
	Dissecting	7	2.0%
	Giant	6	1.7%
	Pseudoaneurysm	1	0.3%
	Saccular		
	Yes	311	90.1%
	No	34	9.9%
	Thrombosis		
	No	329	96.5%
	Partial	11	3.2%
	Complete	1	0.3%
	Lobulation		
	No	124	36.7%
	Bilobulated	29	8.6%
	Multilobulated	185	54.7%
	Total lobulated aneurysm	214	63.3%
	Alarm signs		
	No	261	80.6%
	Sentinel headache	17	5.2%
	Daughter aneurysm	37	11.4%
	Contrast extravasation	3	0.9%
	Artery vasospasm	6	1.9%
	Sac (mm) (median, IQR)	6.01	[4.00 – 8.96]
	Neck (mm) (median, IQR)	3.29	[2.50 – 4.70]
	Sac-neck ratio	2.96	± 15.75

ACA: anterior cerebral artery; ACoA: anterior communicating artery; ASA: acetylsalicylic acid; ICA: internal carotid artery; IQR: interquartile range; MCA: middle cerebral artery; mRS: modified Rankin Scale; OAHA: oral antihyperglycemic agents; PCA: posterior cerebral artery; PCoA: posterior communicating artery; PICA: posterior inferior cerebellar artery; SD: standard deviation; VA: vertebral artery.

In the bivariate analysis (*Table 5*), factors with a p value < 0.05 associated with **less risk of rupture** were (% unruptured versus ruptured; p value): history of previous ischemic stroke (15.9% vs 2.9%; p=<0.001), history of previous ischemic heart disease (9.4% vs 2.9%; p=0.011), previous TBI (7.1% vs 0.6%; p=0.002), surgery history (48.8% vs 36.6%; p= 0.021), antiplatelet treatment (22.9% vs 5.7%; p=<0.001), statins treatment (31.2% vs 16.0%; p=0.001), multiple aneurysms (60.0% vs 39.1%) p=<0.001), paraophthalmic location (13.5% vs 1.1%; p=<0.001) and aneurysm thrombosis (6.6% vs 0.6%; p=0.011).

In contrast, the factors statistically associated with a **higher risk of rupture** were (% unruptured versus ruptured; p value): basal mRS of ≥2 (1.8% vs 4.6%; p=0.009), ACoA and PCoA location (20.1% vs 49.4%; p=<0.001), saccular type (82.9% vs 97.1%; p=<0.001), lobulation (53.3% vs 75.9%; p=<0.001), presence of alarm signs (12.4% vs 26.4%; p=0.022), sac size (median size 6.05mm vs 6.01mm; p=<0.001) and neck size (median size 3.32mm vs 3.25mm; p=0.013).



ACoA: anterior communicating artery; mRS: modified Rankin Scale; PCoA: posterior communicating artery; TBI: traumatic brain injury

Figure 8 Factors with p value < 0.05 in the bivariate analysis

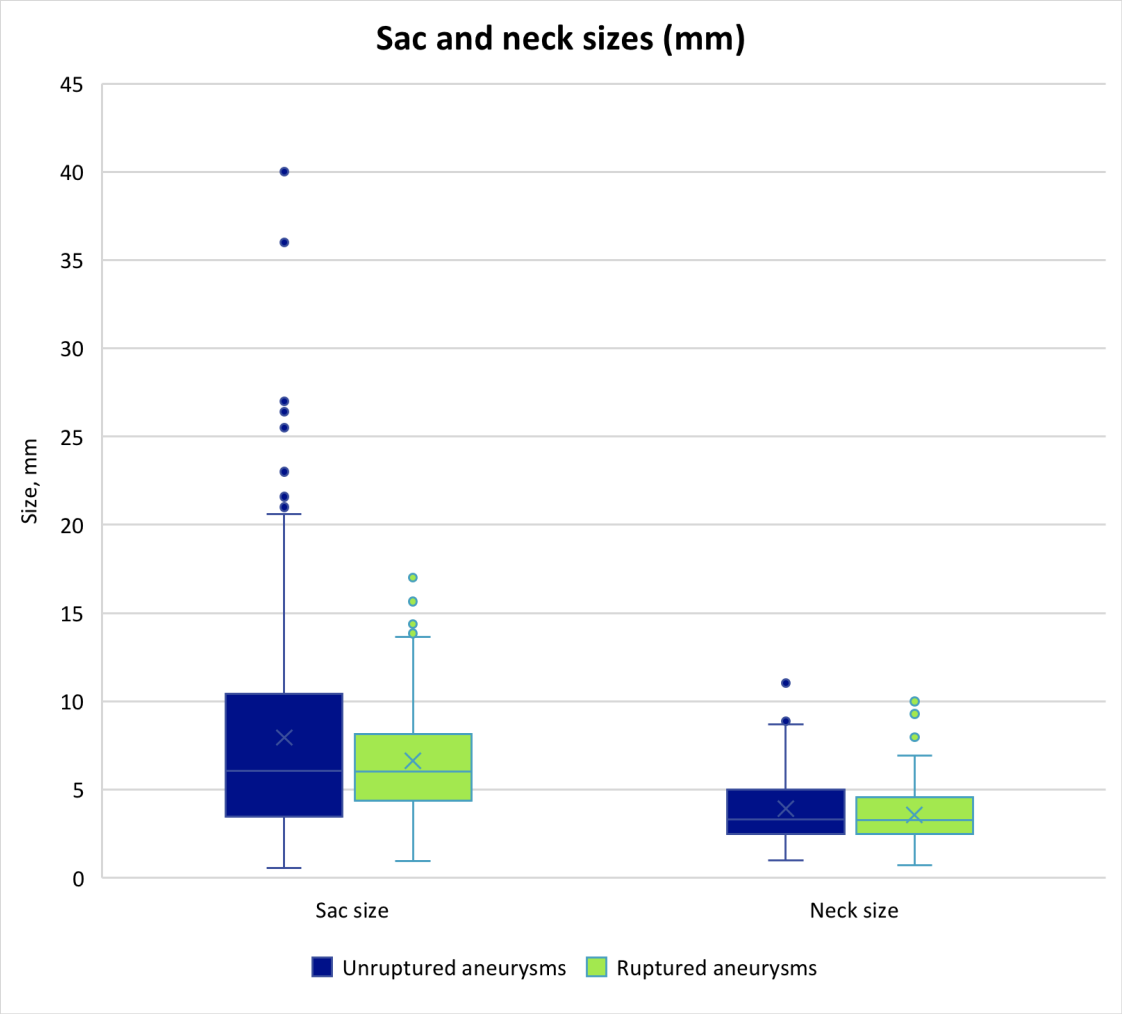


Figure 9 Bivariate analysis: sac and neck size in millimeters

Table 5 Bivariate analysis

	VARIABLE	UNRUPTURED ANEURYSM	RUPTURED ANEURYSM	P VALUE
DEMO-GRAPHIC	**Age, (median) years**	54.0 (46.8 – 65.0 IQR)	55.0 (47.0 – 66.0 IQR)	0.203
	Gender			0.963
	Men	54 (31.8%)	56 (32.0%)	
	Women	116 (68.2%)	119 (68.0%)	
HEALTH HISTORY DATA	**Basal mRS**			0.009
	0	152 (89.9%)	163 (93.7%)	
	1	14 (8.3%)	3 (1.7%)	
	2	0 (0.0%)	5 (2.9%)	
	3	3 (1.8%)	2 (1.1%)	
	4	0 (0.0%)	1 (0.6%)	
	5	0 (0.0%)	0 (0.0%)	
	6	0 (0.0%)	0 (0.0%)	

	Tobacco smoking	77 (45.3%)	67 (38.3%)	0.187
	Alcohol intake	11 (6.5%)	9 (5.1%)	0.598
	Hypertension	76 (44.7%)	76 (43.4%)	0.811
	Diabetes mellitus	12 (7.1%)	10 (5.7%)	0.609
	Dyslipidemia	53 (31.2%)	49 (28.0%)	0.518
	Previous ischemic stroke	27 (15.9%)	5 (2.9%)	<0.001
	Ischemic heart disease	16 (9.4%)	5 (2.9%)	0.011
	Atrial fibrillation	4 (2.4%)	7 (4.0%)	0.384
	Valvular hearth disease	2 (1.2%)	2 (1.1%)	0.977
	Epilepsy	5 (2.9%)	3 (1.7%)	0.449
	Allergies	19 (11.2%)	16 (9.1%)	0.532
	Drug addiction	8 (4.7%)	7 (4.0%)	0.748
	Previous TBI	12 (7.1%)	1 (0.6%)	0.002
	Surgery history	83 (48.8%)	64 (36.6%)	0.021
	Hepatopathy	5 (2.9%)	3 (1.7%)	0.449
	Birth control pills	1 (0.6%)	0 (0.0%)	0.310
ONGOING MEDICATION	**Antiplatelet treatment**	39 (22.9%)	10 (5.7%)	<0.001
	Statins treatment	53 (31.2%)	28 (16.0%)	0.001
	Oral anticoagulant intake	2 (1.2%)	3 (1.7%)	0.671
	OAHA	12 (7.1%)	5 (2.9%)	0.073
	Insulin	2 (1.2%)	3 (1.7%)	0.662
	Multiple aneurysms	102 (60.0%)	68 (39.1%)	<0.001
	Paraophthalmic location	23 (13.5%)	2 (1.1%)	<0.001
	ACoA or PCoA location	34 (20.1%)	86 (49.4%)	<0.001
	Saccular aneurysm	141 (82.9%)	170 (97.1%)	<0.001
	Thrombosis			0.011
	No	157 (93.5%)	172 (99.4%)	
	Partial	10 (6.0%)	1 (0.6%)	
	Complete	1 (0.6%)	0 (0.0%)	
	Lobulated aneurysm	89 (53.3%)	129 (75.9%)	<0.001
	Alarm signs			0.022
	No	141 (87.6%)	120 (73.6%)	
	Sentinel headache	5 (3.1%)	12 (7.4%)	
	Daughter aneurysm	13 (8.1%)	24 (14.7%)	
	Contrast extravasation	0 (0.0%)	3 (1.8%)	
	Artery vasospasm	2 (1.2%)	4 (2.5%)	
ANEURYSM CHARACTERISTICS	**Sac, (median) mm**	6.1 (3.5 – 10.4 IQR)	6.01 (4.36 – 8.14 IQR)	<0.001
	Neck, (median) mm	3.3 (2.5 – 5.0 IQR)	3.26 (2.49 – 4.57 IQR)	0.013
	Sac-neck ratio (mean)	2.21 (± 5.46 SD)	3.64 (± 21.17 SD)	0.240

ACoA: anterior communicating artery; IQR: interquartile range; mRS: modified Rankin Scale; OAHA: oral antihyperglycemic agents; PCoA: posterior communicating artery; SD: standard deviation; TBI: traumatic brain injury.

In the multivariate analysis (*Table 6*), we did a logistic regression. The factors independently associated with aneurysm rupture in the final model were:

- **Protective factors**: multiple aneurysms (OR 0.41, 95% CI 0.24-0.70, p=0.001), antiplatelet treatment (OR 0.23, 95% CI 0.09-0.59, p=0.002), statin treatment (OR 0.44, 95% CI 0.21-0.90, p=0.025) and paraophthalmic location (OR 0.15, 95% CI 0.03-0.72, p=0.017).
- **Risk factors**: age (OR 1.02, 95% CI 1.00-1.05, p=0.049), ACoA and PCoA location (OR 3.01, 95% CI 1.68-5.37, p=<0.001), saccular type (OR 9.19, 95% CI 1.05-80.74, p=0.045) and lobulation (OR 1.48, 95% CI 1.11-1.99, p=0.009).
- Gender (risk factor: female; OR 0.80, 95% CI 0.44-1.47, p= 0.473), sac size (risk factor: smaller size; OR 1.02, 95% CI 0.94-1.11, p=0.623) and neck size (risk factor: smaller size; OR 0.87, 95% CI 0.71-1.08, p=0.205) although they did not have a statistically significant p value, they were included in the model because there is evidence of their association in the literature.

Table 6 Multivariant analysis

VARIABLES	CRUDE OR (95% CI)	ADJUSTED OR (95% CI)	P VALUE
Age	1.11 (0.89 – 1.58)	1.02 (1.00 – 1.05)	0.049
Gender	0.99 (0.63 – 1.56)	0.80 (0.44 – 1.47)	0.473
Multiple aneurysms	0.43 (0.28 – 0.66)	0.41 (0.24 – 0.70)	0.001
Antiplatelet treatment	0.20 (0.10 – 0.42)	0.23 (0.09 – 0.59)	0.002
Statins treatment	0.42 (0.25 – 0.71)	0.44 (0.21 – 0.90)	0.025
Aneurysm in ACoA or PCoA	3.88 (2.40 – 6.27)	3.01 (1.68 – 5.37)	<0.001
Paraophthalmic location	0.07 (0.02 – 0.32)	0.15 (0.03 – 0.72)	0.017
Saccular aneurysm	6.99 (2.64 – 18.54)	9.19 (1.05 – 80.74)	0.045
Lobulated aneurysm	2.76 (1.73 – 4.39)	1.48 (1.11 – 1.99)	0.009
Sac size	0.64 (0.57 – 0.78)	1.02 (0.94 – 1.11)	0.623
Neck size	0.75 (o.67 – 0.96)	0.87 (0.71 – 1.08)	0.205

ACoA: anterior communicating artery; CI: coefficient interval; OR: odds ratio; PCoA: posterior communicating artery.

With the results of the logistic regression model, we have made an equation to create the **"ITARR SCORE: InTracerebral Aneurysm's Risk of Rupture SCORE"**, which using this equation will calculate the probability of rupture of every patient. In order to facilitate its use in the clinical practice, we have created an online calculator available on the following link:

http://isvgirona.net/aneurysm/calculator/

Equation: Intracerebral Aneurysm's Risk of Rupture SCORE was estimated using logistic regression. Coefficients and risk calculation are shown below. Let:

$$\begin{aligned} y \quad = \quad & -2.56 + 0.023\text{age} - 0.223 \times \chi_{\text{male}} - 0.890\chi_{\text{m.aneurysm}} \\ & -1.470\chi_{\text{antiplatelet}} - 0.827\chi_{\text{statin}} + 1.101\chi_{\text{commun. loc.}} \\ & -1.883\chi_{\text{paraoph.loc.}} + 2.218\chi_{\text{saccular}} + 0.395\chi_{\text{an.lob.}} \\ & +0.021\text{sac} - 0.137\text{neck} \end{aligned}$$

where $\chi_{\text{characteristic}}$ is **1** if characteristic holds or **0** if not.

Then, the probability of intracerebral aneurysm, r, is given by equation:

$$r = \frac{1}{1 + e^{-y}}$$

Figure 10 Equation of ITARR SCORE

Intracerebral Aneurysm's Risk of Rupture SCORE

Covariates

Age (years): 54

Sex
(•) Woman ( ) Man

Multiple Aneurysm
(•) No ( ) Yes

Antiplatelet treatment
(•) No ( ) Yes

Statin
( ) No (•) Yes

Aneurysm location
(•) Anterior or posterior communicating artery
( ) Paraophthalmic location
( ) Other locations

Saccular aneurysm
( ) No (•) Yes

Aneurysm lobulation
(•) No ( ) Yes

Sac size (mm): 5

Neck size (mm): 3

Probability of aneurysm rupture

Clean form

Probability in percentage: 71%

For example, a 54 years old woman, treated with simvastatin due to dyslipidemia, that has been diagnosed of a single, saccular, non-lobulated intracerebral aneurysm located in the ACoA with a sac diameter of 5 mm and a neck of 3 mm, has a **probability of rupture of 71%**.

Figure 11 ITARR SCORE, online calculator

11.2 SECONDARY OBJECTIVES

11.2.1 Descriptive analysis of diagnosis, treatment and follow-up variables

The cause of diagnosis of our sample population was mostly due to aneurysm rupture (50.4%), being an incidental finding (16.8%) and headache (11.6%) the second and third cause respectively.

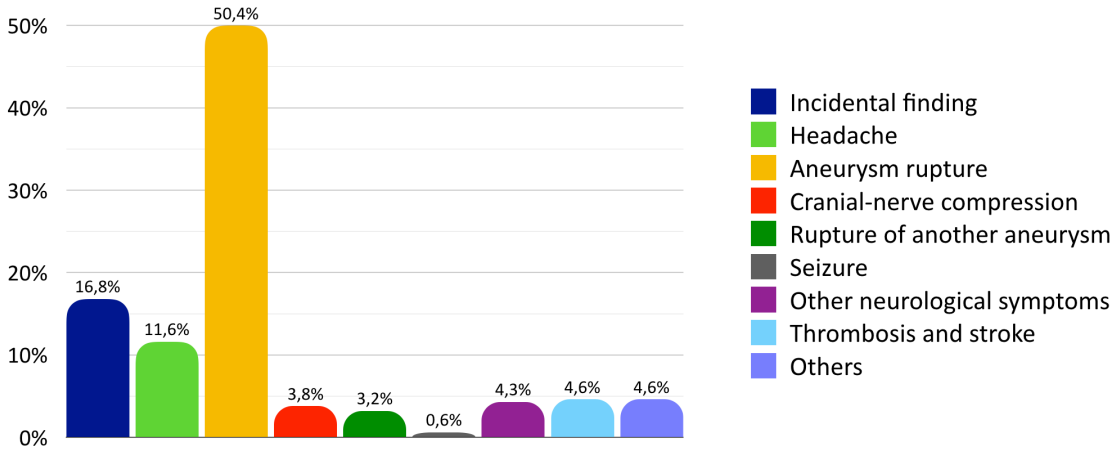


Figure 12 Descriptive analysis: cause of diagnosis

Table 7 Univariate analysis: causes of diagnosis

CAUSE OF DIAGNOSIS	ABSOLUTE FREQUENCY	RELATIVE FREQUENCY
Incidental finding	58	16.8%
Headache	40	11.6%
Aneurysm rupture	174	50.4%
Cranial-nerve compression	13	3.8%
Rupture of another aneurysm	11	3.2%
Seizure	2	0.6%
Other neurological symptoms	15	4.3%
Thrombosis and stroke	16	4.6%
Others	16	4.6%

The classifications and scales performed to assess the initial clinical status of the patients during their hospital admittance were the Glasgow Coma Scale, the Hunt Hess scale and the World Federation of Neurosurgeons classification.

As shown in the table below (*Table 8*), 84.2% of patients arrived at the hospital with a GCS grade of ≥ 13 and only 7% had a GCS grade ≤6. Using the HH scale, 59.7% had a grade I, and only 7% had a HH scale grade of V. With the WFNS classification, 71% of patients were on grade I while 7.6% were on grade V.

Table 8 Univariate analysis: initial clinical status

VARIABLE		ABSOLUTE FREQUENCY	RELATIVE FREQUENCY
INITIAL CLINICAL STATUS	**GCS grade**		
	3	12	3.5%
	4	8	2.3%
	5	2	0.6%
	6	2	0.6%
	7	7	2.0%
	8	8	2.3%
	9	5	1.5%
	10	1	0.3%
	11	4	1.2%
	12	3	0.9%
	13	12	3.5%
	14	30	8.8%
	15	248	71.9%
	HH scale		
	I	179	59.7%
	II	45	15%
	III	32	10.7%
	IV	23	7.7%
	V	21	7%
	WFNS classification		
	I	225	71%
	II	26	8,2%
	III	15	4.7%
	IV	27	8.5%
	V	24	7.6%

GCS: Glasgow Coma Scale; HH: Hunt and Hess scale; WFNS: World Federation of Neurosurgeons classification

At hospital admittance, a brain CT was done in 187 patients (61.7%). The absolute and relative frequencies of the findings on those CT are in the table below (*Table 9*):

Table 9 Univariate analysis: findings on the admittance CT

ADMITTANCE CT FINDINGS	ABSOLUTE FREQUENCY	RELATIVE FREQUENCY
No brain CT	116	38.3%
Normal	14	4.6%
Cisternal bleed	56	18.5%
Intraventricular bleed	84	27.7%
Visible aneurysm	7	2.3%
Cerebral infarction	3	1%
Hematoma	15	5%
Hematoma that requires surgical evacuation	3	1%
Hydrocephaly	5	1.7%

CT: computed tomography.

The Fisher CT grade showed that 62 patients (26.9%) had no blood in the CT image, 13 (5.7%) a diffuse deposition or thin layer of blood of <1mm thick, 34 (14.8%) localized clots and/or vertical layer of blood of ≥1mm thickness and 121 (52.6%) diffuse or absent subarachnoid blood with intracerebral or intraventricular clots.

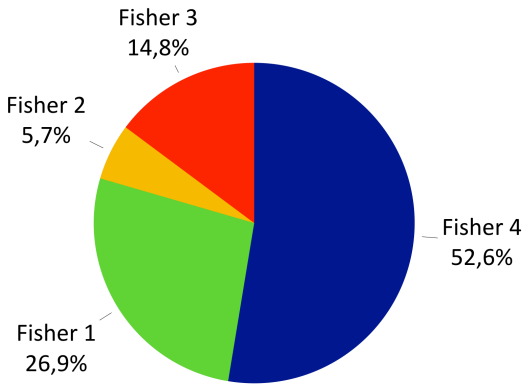


Figure 13 Descriptive analysis: Fisher CT grade by groups

Table 10 Univariate analysis: Fisher CT grade

FISHER CT GRADE	ABSOLUTE FREQUENCY	RELATIVE FREQUENCY
Group 1	62	26.9%
Group 2	13	5.7%
Group 3	34	14.8%
Group 4	121	52.6%

The great majority of patients needed to be admitted to the ICU or SICU (91.3%) during a mean of 5.20 days (±5.36 SD).

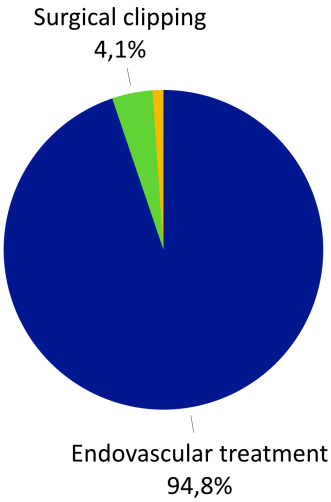


Figure 14 Endovascular treatment versus surgical treatment

A total of 14 patients (4.1%) underwent a surgical clipping while 327 patients (94.8%) underwent an endovascular treatment: 209 (60.6%) were treated with colis, 63 (18.3%) with coils + stent, 1 (0.3%) only with stent, 33 (9.6%) with a flowdiverter stent, 19 (5.5%) with flowdiverter stent + coils and 2 (0.6%) with liquid embolic agents (as onyx and hystocril). These treatments were successful (complete exclusion) in 278 cases (82.0%

The mean dose of heparin used in patients who underwent endovascular treatment was of 8743.30 Ul/kg (± 4270.93 SD), and their average basal glycemia was 112.42mg/dl ± 28.49 SD.

A total of 39 participants (12.2%) presented vasospasm, appearing mostly in the 5th day (mean 5.37 days ± 5.36 SD). Only 48 patients (14.8%) presented an angiography complication, being the most frequents an arterial rupture with contrast extravasation (4.3%) and a distal embolism (4.0%), without consequences in 91.5% of them.

The most prevalent general complications during the first 72 hours after the treatment were having a new stroke (3.0%), respiratory infection (1.9%) and symptomatic intracerebral hemorrhage (1.5%). Although 84.4% did not present any complication during this period, a total of 9 patients died (2.9%) during the first 72 hours, and 11 (3.8%) during the first week.

The mRS calculated at 7 days or in the moment of the patient discharge is shown in the following figure:

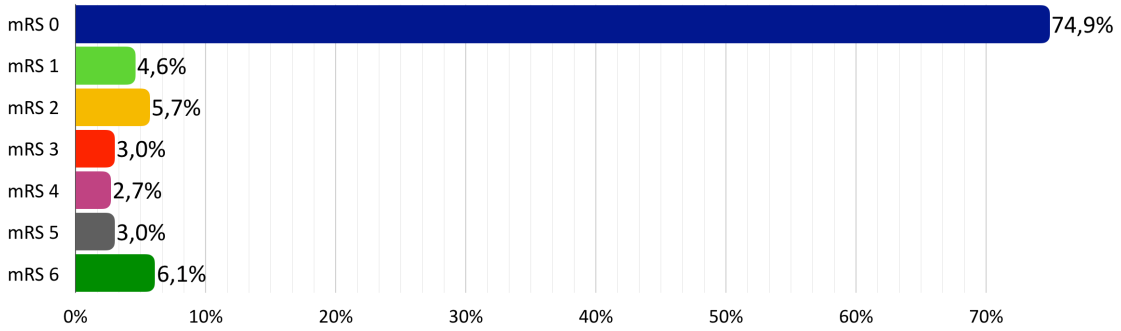


Figure 15 Descriptive analysis: mRS at 7 days or discharge

Table 11 Univariate analysis: Treatment and complications

	VARIABLE	ABSOLUTE FREQUENCY	RELATIVE FREQUENCY
TREATMENT AND COMPLICATIONS	**Addmitance to ICU/SICU**	303	91.3%
	Days in ICU or SICU (mean ± SD)	5.20	± 9.61
	Type of treatment		
	Coils	209	60.6%
	Coils + stent	63	18.3%
	Stent in stent	1	0.3%
	Flowdiverter stent	33	9.6%
	Flowdiverter stent + coils	19	5.5%
	Liquid embolic agents	2	0.6%
	Surgical clipping	14	4.1%
	Others	4	1.2%
	Closure		
	Complete exclusion	278	82.0%
	Exclusion of >95%	16	4.7%
	Exclusion of 90-95%	7	2.1%
	Exclusion of 50-89%	3	0.9%
	Flowdiverter changes	34	10.0%
	Without changes	1	0.3%

Heparin dose (mean ± SD)	8743.30	± 4270.93
Vasospasm	39	12.2%
Day of vasospasm (mean ± SD)	5.37	± 5.36
Basal glycemia (mean ± SD), mg/dl	112.42	± 28.49
Angiography complications		
No angiography complications	277	85.2%
Arterial rupture with contrast extravasation	14	4.3%
Arterial dissection	1	0.3%
Distal embolism	13	4.0%
Inguinal hematoma	2	0.6%
Vasospasm that needed treatment	8	2.5%
Embolization material complication	2	0.6%
Thrombosis	6	1.8%
Thrombosis + arterial occlusion	2	0.6%
Complication consequences		
Non-consequence	161	91.5%
Transient neurological deficit	13	7.4%
Permanent neurological deficit	1	0.6%
Death	1	0.6%
General complications first 72h		
No complications	229	84.8%
Symptomatic ICH	4	1.5%
Progressive stroke	3	1.1%
Death	1	0.4%
New stroke	8	3.0%
Auricular fibrillation	1	0.4%
Aspiration pneumonia	4	1.5%
Respiratory infection	5	1.9%
Peripheral embolism	1	0.4%
Acute urine retention	1	0.4%
Epileptic seizure	3	1.1%
Malignant stroke	1	0.4%
Coma	1	0.4%
Respiratory failure	2	0.7%
Medullar ischemia	1	0.4%
Intestinal ischemia	1	0.4%
Hepatic failure	1	0.4%
Other complications	3	1.1%
Death first 72h	9	2.9%
Mortality first 7 days	11	3.8%

	mRS at 7 days or discharge		
	0	197	74.9%
	1	12	4.6%
	2	15	5.7%
	3	8	3.0%
	4	7	2.7%
	5	8	3.0%
	6	16	6.1%

HT: hypertension; ICH: intracerebral hemorrhage; ICU: intensive care unit; mRS: modified Rankin Scale; SD: standard deviation; SICU: semi-intensive care unit.

During the follow-up, a total of 29 patients (11.0%) at 3 months still had a poor mRS (<2). The mortality during this period of time was of 6.6%.

The 6-months angiography control confirmed a complete occlusion on 122 patients (70.1%) and 20 (11.5%) with repermeabilization. In the 1-year follow-up angiography, it decreased to 13 patients (10.3%).

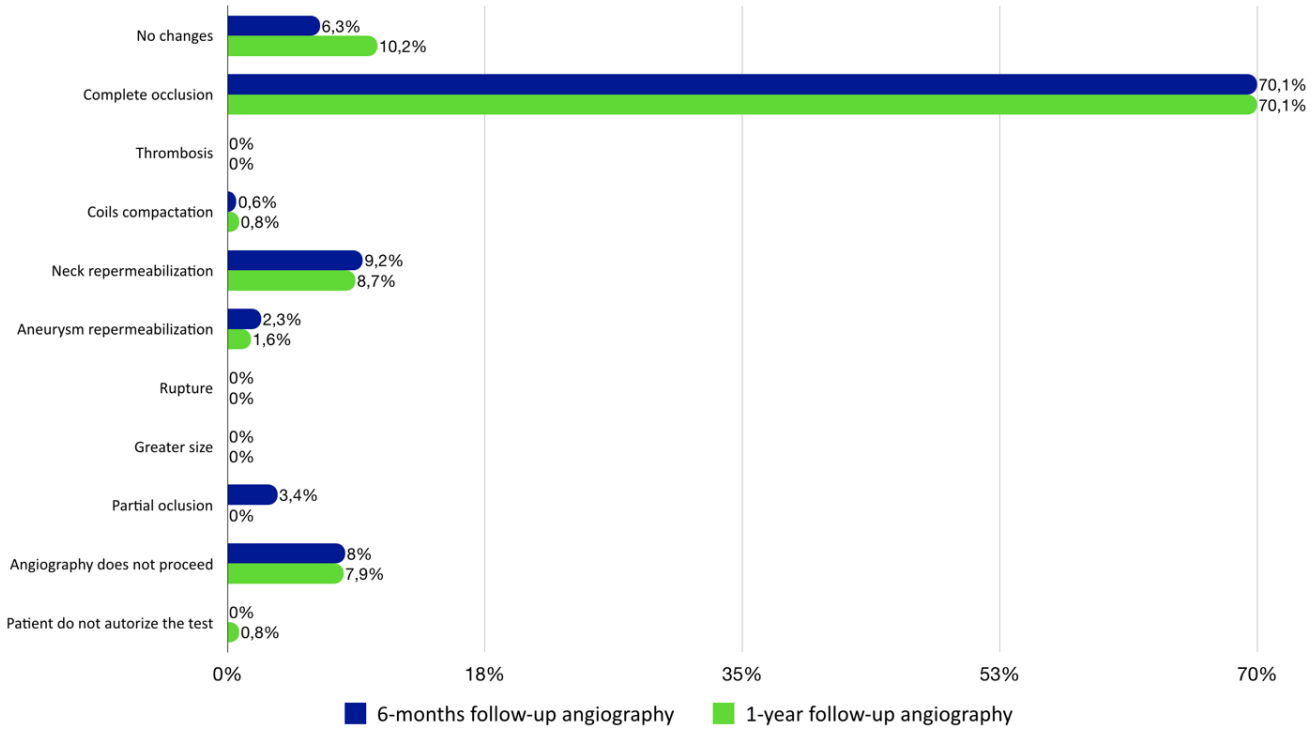


Figure 16 Angiography follow-up

Table 12 Univariate analysis: follow-up

	VARIABLE	ABSOLUTE FREQUENCY	RELATIVE FREQUENCY
FOLLOW-UP	**Poor outcome (3 months mRS > 2)**	29	11.0%
	Mortality 3 months	15	6.6%
	6-months follow-up angiography		
	No changes	11	6.3%
	Complete occlusion	122	70.1%
	Thrombosis	0	0.0%
	Coils compaction	1	0.6%
	Neck repermeabilization	16	9.2%
	Aneurysm repermeabilization	4	2.3%
	Rupture	0	0.0%
	Greater size	0	0.0%
	Partial occlusion	6	3.4%
	Angiography does not proceed	14	8.0%
	Patient do not authorize the test	0	0.0%
	1-year follow-up angiography		
	No changes	13	10.2%
	Complete occlusion	89	70.1%
	Thrombosis	0	0.0%
	Coils compaction	1	0.8%
	Neck repermeabilization	11	8.7%
	Aneurysm repermeabilization	2	1.6%
	Rupture	0	0.0%
	Greater size	0	0.0%
	Partial occlusion	0	0.0%
	Angiography does not proceed	10	7.9%
	Patient do not authorize the test	1	0.8%

mRS: modified Rankin Scale.

11.2.2 Statins treatment

An overall of 81 participants (23.5%) were under statins treatment. The following figures, describe the type of statin and their dose, being more frequent the treatment with simvastatin (12.2%) and the dosage of 20 mg (10.7%):

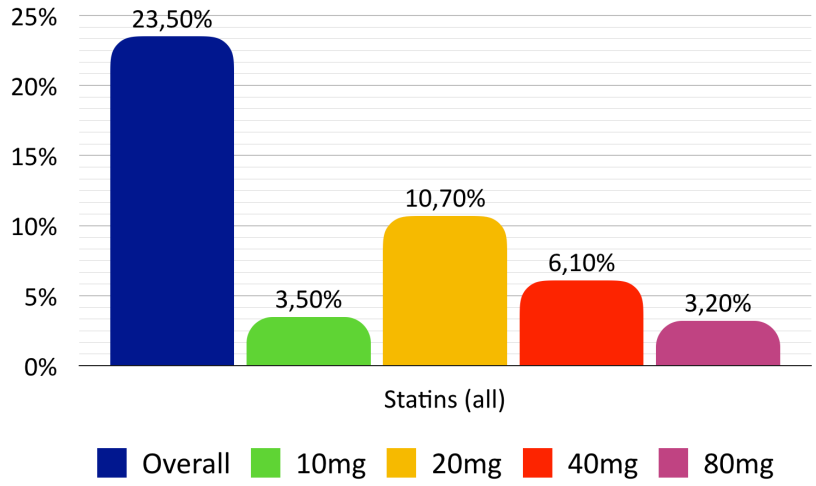


Figure 17 Descriptive analysis: statins by dose

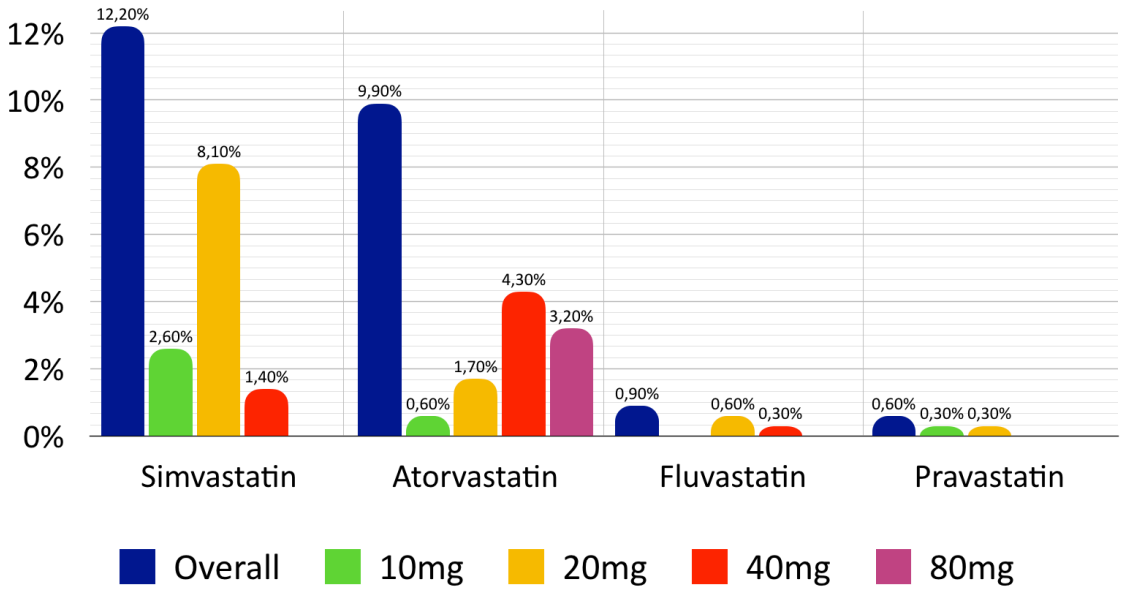


Figure 18 Descriptive analysis: statins by type and dose

As explained in the bivariate and multivariate analysis of the main aim of the study, statins (all) are a protective factor of rupture, with an adjusted OR of 0.44 (95% CI 0.21-0.90) and a p value of 0.025 in the multivariate analysis.

When studied stratified by type and dose, the p valor of the bivariate analysis is 0.038 instead of 0.001 (p value of overall statins in the bivariate analysis).

Table 13 Bivariate analysis: statins type

VARIABLE	UNRUPTURED ANEURYSM	RUPTURED ANEURYSM	P VALUE
STATINS TREATMENT			0.038
No statin treatment	117 (68.8%)	147 (84.0%)	
Atorvastatin			
Atorvastatin 10mg	1 (0.6%)	1 (0.6%)	
Atorvastatin 20mg	4 (2.4%)	2 (1.1%)	
Atorvastatin 40mg	13 (7.6%)	2 (1.1%)	
Atorvastatin 80mg	8 (4.7%)	3 (1.7%)	
Fluvastatin (all)			
Fluvastatin 20mg	0 (0.0%)	2 (1,1%)	
Fluvastatin 40mg	0 (0.0%)	1 (0.6%)	
Pravastatin (all)			
Pravastatin 10mg	0 (0.0%)	1 (0.6%)	
Pravastatin 20mg	1 (0.6%)	0 (0.0%)	
Simvastatin (all)			
Simvastatin 10mg	5 (2.9%)	4 (2.3%)	
Simvastatin 20mg	18 (10.6%)	10 (5.7%)	
Simvastatin 40mg	3 (1.8%)	2 (1.1%)	

In order to verify whether there were differences between the two most frequent types of statins (atorvastatin and simvastatin), or difference in the dosage, we group them (atorvastatin versus another statin; simvastatin versus another statin; less than 40mg versus 40 mg or more).

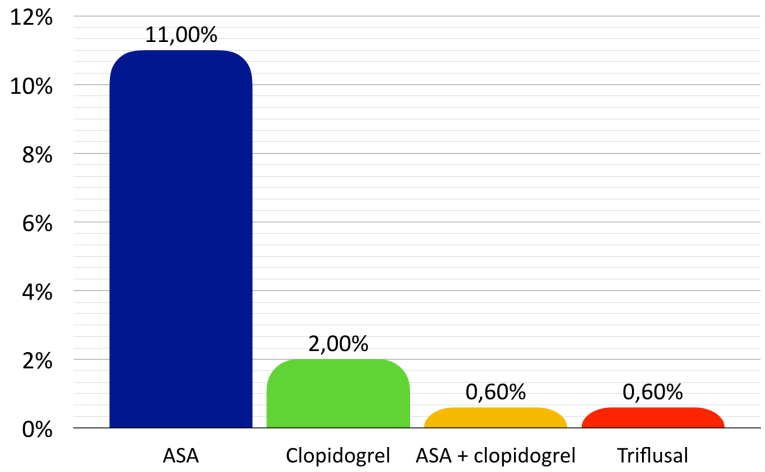
A bivariate analysis was performed and found that do not exist statistically differences between them:

Table 14: Bivariate analysis: statins stratified by groups

VARIABLE	UNRUPTURED ANEURYSM	RUPTURED ANEURYSM	CRUDE OR (95% CI)	P VALUE
Atorvastatin	26 (49.1%)	8 (28.6%)	0.42	0.076
Another statin	27 (50.9%)	20 (71.4%)	(0.16 – 1.11)	
Simvastatin	24 (50.0%)	15 (55.6%)	1.25	0.644
Another statin	24 (50.0%)	12 (44.4%)	(0.49 – 3.22)	
< 40 mg	29 (54.7%)	20 (71.4%)	0.48	0.143
≥ 40 mg	24 (45.3%)	8 (28.6%)	(0.18 – 1.29)	

11.2.3 Antiplatelet treatment

A total of 49 participants (14.2%) were under antiplatelet treatment at the moment of the diagnosis (*Table 5*): 38 with ASA (11%), 7 with clopidogrel (2.0%), 2 with a dual therapy of ASA + clopidogrel (0.6%) and 2 with triflusal (0.6%):



ASA: Acetylsalicylic acid
Figure 19 Descriptive analysis: antiplatelet treatment

A bivariate analysis was performed, showing a crude OR of 0.20 and a statistically significative p value of <0.001.

Table 15: Bivariate analysis: antiplatelet treatment

VARIABLE	UNRUPTURED ANEURYSM	RUPTURED ANEURYSM	CRUDE OR (95% CI)	P VALUE
Antiplatelet treatment	39 (22.9%)	10 (5.7%)	0.20 (0.10 – 0.42)	<0.001

In the multivariate analysis, as we showed above, a logistic regression model was performed confirming that the therapy with antiplatelet drugs has a protective effect in intracerebral aneurysms, having less risk of rupture (p value 0.002).

Table 16 Multivariate analysis: antiplatelet treatment

VARIABLES	ADJUSTED OR (95% CI)	P VALUE
Antiplatelet treatment	0.23 (0.09 – 0.59)	0.002

12. DISCUSSION

In this case-control study, we have created the **ITARR SCORE** (InTracerebral Aneurysm's Risk of Rupture SCORE), a new tool useful for psysicians to decide the correct management of patients who have been diagnosed of an unruptured intracerebral aneurysm and are being evaluated to decide which is the best medical, endovascular or surgical treatment they should receive. Through patients age, gender, ongoing medication (antiplatelet and statins drugs) and aneurysm's characteristics (number of aneurysms, location, type, shape and size), this SCORE is able to calculate the risk of rupture of every unruptured intracerebral aneurysm.

Nowadays, there are two scores that evaluate their risk of rupture and recommend which treatment should be performed to prevent aSAH. However, its use in practical medical decisions is not well established.

The PHASES SCORE (60), developed using data from 6 cohort studies, assessed the possible relationship between patient's characteristics (sex, age, hypertension, smoking status, previous SAH, number of aneurysms and geographical location) and aneurysm's features (size and location) with the risk of rupture at 5 years. The final score model did not include sex, smoking and multiple aneurysms, which had a p value of >0.20.

In contrast, the UIATS model (62) was created by 69 cerebrovascular specialists throughout a Delphi consensus instead of published data of well stablished risk factors, and included, apart from the ones in the PHASES score, life expectancy, clinical symptoms related to UIA, comorbid diseases and morphology of the aneurysms. The final punctuation, instead of saying the risk of rupture they have, it makes a recommendation for conservative management or surgical or endovascular treatment.

Although our score is not the only one developed for patient with UIA, in our knowledge, it is the first that has also studied, apart from aneurysm characteristics, other possible confounders factors and diseases as well as ongoing medication, including the role of statins and antiplatelet therapies, two factors that some studies have recently showed their protective role in aneurysm's rupture (53,57,58).

The results of our case-control study, after doing both bivariate and a multivariate analysis, conclude which factors were independently statistically significant, with a probability value of <0.05. It showed a significantly inverse association between rupture and having multiple aneurysms, previous antiplatelet and statins drugs use and paraophthalmic carotid location. In contrast, patients age, ACoA and PCoA locations, saccular shape and lobulated aneurysms, were found as independent risk factors for aneurysm rupture.

Patients **age** has been associated with a higher risk of rupture, being older patients more likely to present aSAH than the young ones. Until now, studies showed a tendency but not a firm relationship, with p values of > 0.05 (19). However, in our study, with the logistic regression, we obtained a statistical association (OR 1.02, 95% CI 1.00 – 1.05, p=0.049) confirming the results we expected to find.

Although the proportion of women within the case group (ruptured aneurysms) and the control group (unruptured aneurysms) in our study present no differences, we still used this variable in the regression logistic model, because some studies have confirmed the association between **female gender** and a higher prevalence of aSAH, showing a prevalence ratio, compared with men, that ranged between 1.1 (95% CI 0.6 – 1.8) and 2.2 (95% CI 1.3 – 3.6) (28,60).

Hostettler et al. (19) and Greving et al. (60) did not conclude that having **multiple aneurysms** is independently associated with risk rupture and showed a tendency that more than one aneurysm increases the risk of rupture. In our study we demonstrate that actually it is a protective factor (OR 0.41, 95% CI 0.24-0.70, p=0.001). This matches with the results of Choi et al. (22) where multiplicity was also statistically associated with less risk of rupture.

In agreement with García-Rodríguez et al. (24) and Chalouhi et al. (53) studies, our results show a lower risk of aSAH among patients who are being treated with **antiplatelet drugs**, with an OR 0.23 (95% CI 0.009 – 0.59). These results could be explained with the role that inflammation has in aneurysm formation, growth and rupture. Currently, there are several studies and trials investigating its effect versus placebo, as the ARREST study (Aneurysm Rupture Reduction and Expansion Stabilization Trial).

Our findings regarding to treatment with **statins drugs** is in accordance with the results of Can et al. (58) and Yoshimura et al. (57), where an inversely relationship between statins use and aneurysm formation, growth and rupture was demonstrated. In our study, we did not find statistically differences between different types of statins nor doses, although atorvastatin was more common in the unruptured group, and actually, when compared versus other statins, showed a tendency of protection (OR 0.42, 95% CI 0.16 – 1.11, p= 0.076). However, statins treatment in general (different statins and doses altogether) have statistically proven to be a protective factor of rupture (OR 0.44, 95% CI 0.21 – 0.90, p=0.025).

ISUIA study (26) proved that the 5-year cumulative rates of rupture differ with the **size and the location of the aneurysm**, having, same size aneurysms, different rates of rupture if they are located in different arteries. Our results showed that the ACoA and the PCoA aneurysm locations are a risk factor for aSAH (OR 3.01, 95% CI 1.68-5.37, p=<0.001), while aneurysms with a

paraophthalmic location is a protective factor (OR 0.15, 95% CI 0.03-0.72, p=0.017) for aSAH. We could not demonstrate a significant relationship with the size, but, as our results agreed with other studies where smaller aneurysms were associated with greater rates of rupture, we also include this factor to the final regression model (19).

Taking into account that **saccular aneurysm** is the most frequent type of intracerebral aneurysms, we carried out a bivariate and multivariate analysis evaluating the relationship between aSAH and the presence of saccular aneurysm type and we found, in both tests, statistically differences showing that it constitutes a risk factor for rupture. Unlike the other available scores (PHASES (60) and UIATS (62)) which cannot be used in non-saccular aneurysms, our score also predicts the rupture risk of the other types (fusiform, pseudosaccular, dissecting…).

The last factor with statistically signification in our regression model was the aneurysm **lobulation**, which was associated with a higher risk of rupture (OR 1.48, 95% CI 1.11-1.99, p=0.009). Although there is not much evidence between lobulation and aneurysmatic rupture, Backes et al. (23) found that irregularly shaped aneurysms (including lobulated aneurysms) are a risk factor for aneurysm growth with a RR of 2.32 (95% CI, 1.46–3.68). A possible hypothesis to explain our findings (greater rupture) is that due to this irregular growth, they have fewer stable walls, increasing their risk of rupture. It could correlate with aneurysm inflammation (53).

All these factors have been included in our predictive SCORE which, after being validated in a prospective study, we believe it will be useful at daily clinical practice to correctly decide the best treatment and medical management of patients with UIA.

13. CONCLUSIONS

In general terms, and taking into account the hypothesis and objectives proposed at the beginning of this work, we can conclude:

» The ITARR SCORE is an easily applicable tool that calculates the lifetime probability of rupture of intracerebral aneurysms.

» The most frequent location of intracerebral aneurysms is the MCA (19.7%), followed by ACoA (18.6%) and the PCoA (17.4%), being more common in women (68.1%). Statins intake was present in 23.5% of patients and antiplatelet drugs in 14.2%. Endovascular treatment was performed in 94.8%. At 3 months, the mortality rate was of 13.3% and poor outcome (mRS >2) in 11.0% of patients.

» Intracerebral aneurysm risk factors for rupture are: aging, women, aneurysm located in the ACoA or PCoA, the saccular type and presenting lobulation.

» Protective factors associated with intracerebral aneurysm rupture are: having multiple aneurysms, ongoing treatment with antiplatelet and/or statins drugs, paraohpthalmic location and increasing size of sac and neck.

» Statins drugs reduce the risk of rupture, without statistically differences between types of statins neither dosage.

» Antiplatelet drugs use reduces the risk of rupture in comparison with patients who do not intake them.

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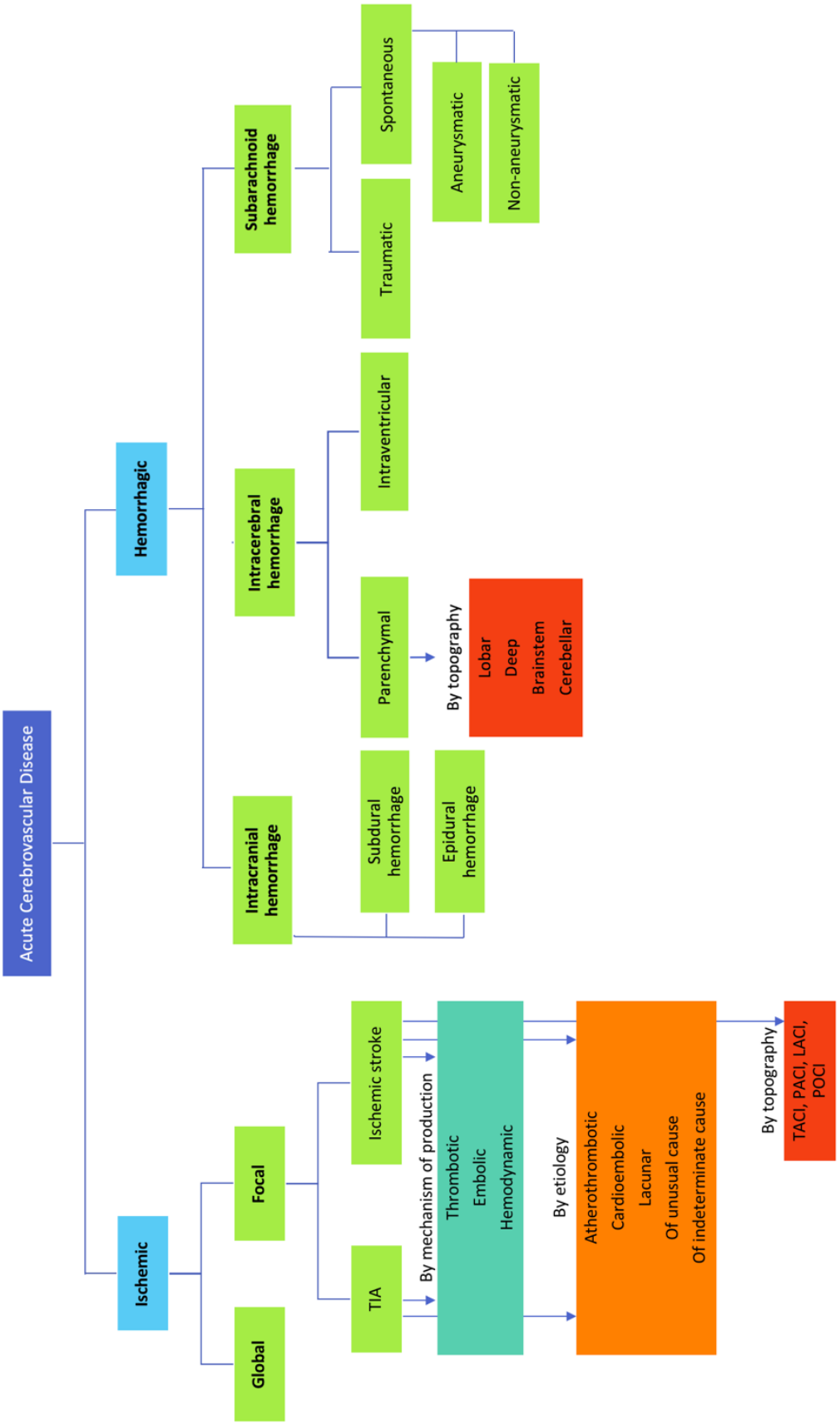
15. ANNEXES

15.1 ANNEX 1: CVD'S CLASSIFICATION



TIA: Transient ischemic attack; TACI: Total anterior circulation infarct; PACI: Partial anterior circulation infarct; LACI: Lacunar infarct; POCI: Posterior circulation infarct

Figure 20 Acute cerebrovascular disease by its nature. Adapted from (4)

15.2 ANNEX 2: CVD'S EPIDEMIOLOGY

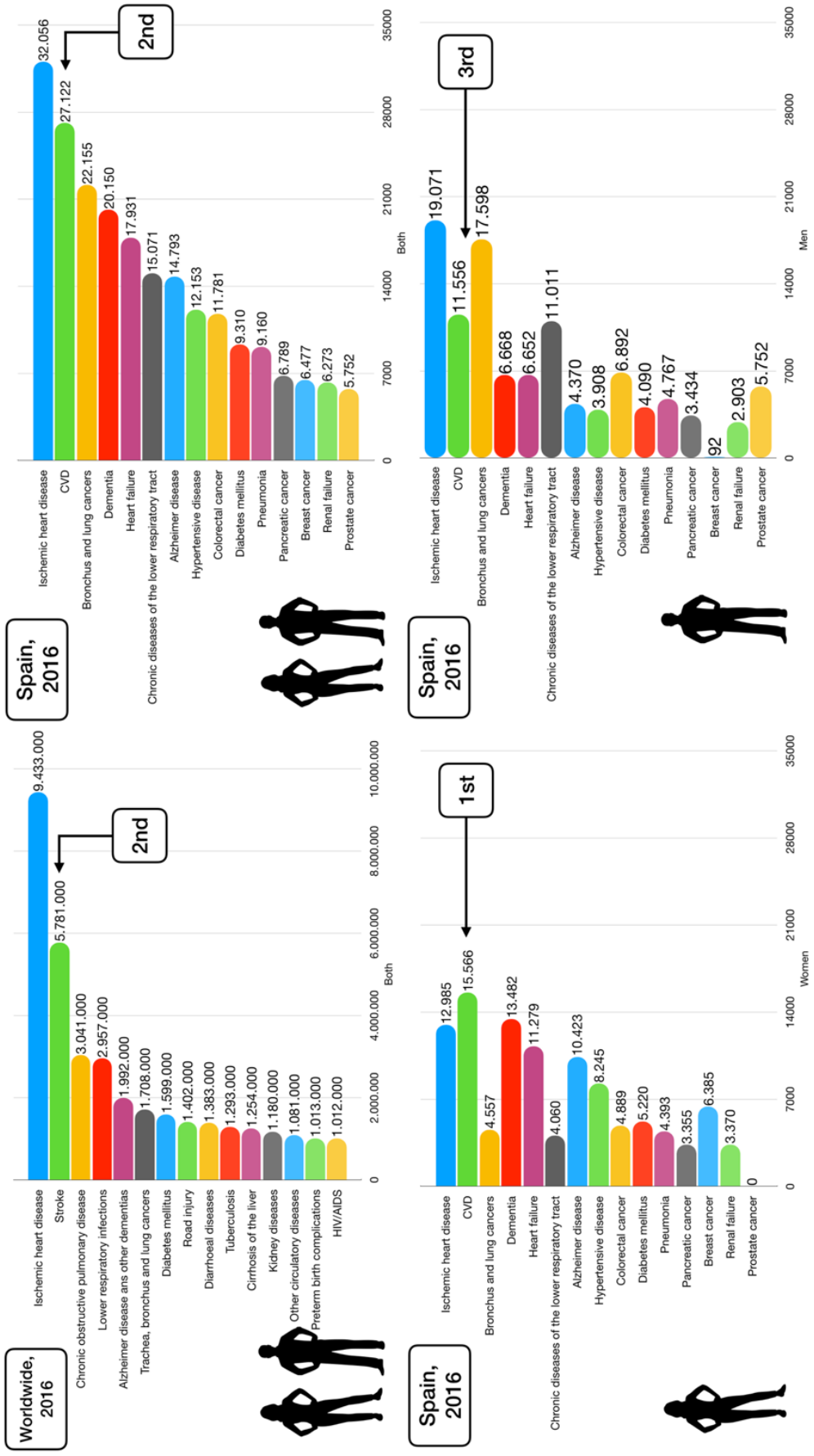


Figure 22 *Number of deaths of the leading causes of death in 2016, Worldwide and Spain. Data obtained from* (11,12)

15.3 ANNEX 3: SUBARACHNOID HEMORRHAGE ETIOLOGIES

Table 17 Etiology of subarachnoid hemorrhage. Adapted from (7,18).

1. **Traumatic brain injury**
2. **Intracerebral aneurysm**
   - Congenital
   - Acquired
   - Arteriosclerotic
   - Infectious
   - Neoplasic
   - Dissecting
   - Traumatic
   - Post radiation
   - Inflammatory
3. **Vascular malformation**
   - Brain arteriovenous malformation
   - Venous angioma
   - Cavernous angioma
   - Capillary telangiectasia
4. **Others wall vascular alterations**
   - Arteriosclerosis
   - Inflammatory (connective diseases)
   - Infections (sepsis, parasites, bacterial endocarditis, meningoencephalitis)
   - Drugs: cocaine, amphetamines, heroin
   - Medicines: phenylephrine, sildenafil
   - Arterial dissection
5. **Coagulation alteration**
6. **Anticoagulant treatment** (heparin, acenocoumarol)
7. **Hematological diseases** (leukemia, disseminated intravascular coagulation, sickle cell anemia)
8. **Brain tumors:** primary tumors (glioma), metastatic tumors, pituitary apoplexy, hemangioblastoma
9. **Cerebral venous thrombosis**
10. **Intracerebral hemorrhage**
11. **Perimesencephalic**
12. **Iatrogenic neurosurgical lesions** (after cranial and spinal surgeries)
13. **Reversible cerebral vasoconstriction syndrome**
14. **Cerebral amyloid angiopathy**
15. **Unknown cause**

15.4 ANNEX 4: HUNT AND HESS SCALE

According to the patient's clinical condition, the Hunt and Hess scale is able to predict the surgical risk of patients who have a ruptured intracerebral aneurysm that led to a SAH. HH grading is correlated with mortality: with a grade I HH punctuation the risk of dying is minimum while is maximum when it is 5 (69).

Table 18 Hunt and Hess Scale. Extracted from (69)

Category*	Criteria
Grade I	Asymptomatic, or minimal headache and slight nuchal rigidity
Grade II	Moderate to severe headache, nuchal rigidity, no neurological deficit other than cranial nerve palsy
Grade III	Drowsiness, confusion or mild focal deficit
Grade IV	Stupor, moderate to severe hemiparesis, possibly early decerebrate rigidity and vegetative disturbance
Grade V	Deep coma, decerebrate rigidity, moribund appearance
***** Serious systemic disease such as hypertension, diabetes, severe arteriosclerosis, chronic pulmonary disease, and severe vasospasm seen on angiography, result in placement of the patient in the next less favorable category.	

15.5 ANNEX 5: GLASGOW COMA SCALE

In order to correctly define, classify and also compare patients with impaired consciousness and coma, we have to use the GCS, a neurological reliable and objective scale. It evaluates three aspects of the patient's behavior (motor response, verbal response and eye opening, individually evaluated) and give points for each response. The worst GCS punctuation is 3, meaning deep unconsciousness, and the best score is 15 (70).

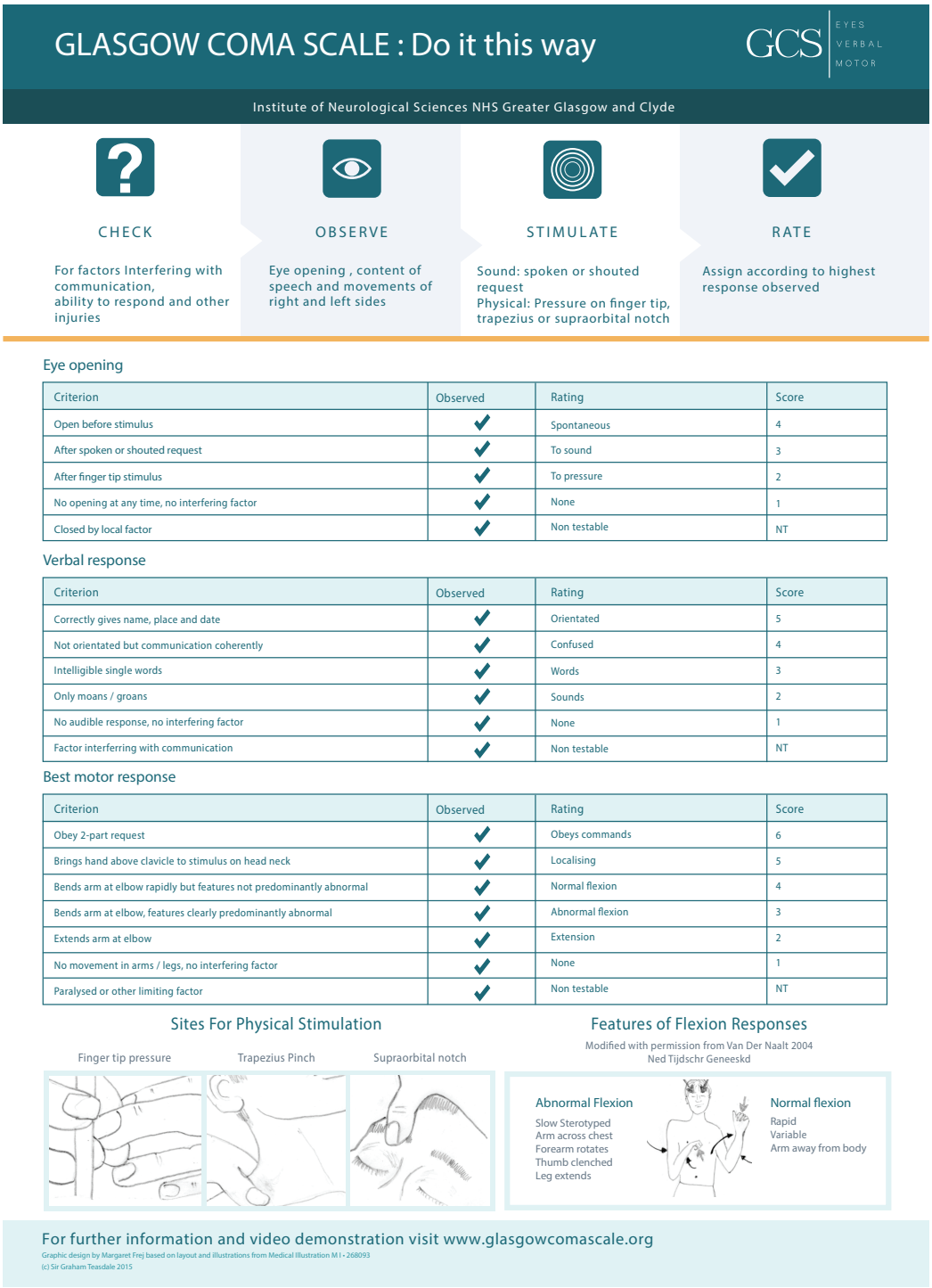


Figure 23 Glasgow Coma Scale. Obtained from (71)

15.6 ANNEX 6: WORLD FEDERATION OF NEUROSURGEONS CLASSIFICATION

The WFNS classification is a grading scale for patients with SAH. It is able to estimate their prognosis using the two most important prognostic factors (72):

- Consciousness level: it is useful to predict death and disability risk. WFNS use the GCS to evaluate it.
- Presence or absence of hemiparesis and/or aphasia: it can predict only the disability risk in patients who survive the SAH. It is considerate only in the three first grades.

Table 19 WFNS SAH grading scale. Extracted from(72)

Grade	GCS	Motor deficit
I	15	-
II	14-13	-
III	14-13	+
IV	12-7	±
V	6-3	±

15.7 ANNEX 7: FISHER CT GRADING SCALE

The Fisher CT grading scale classifies, using a brain CT image, the patients who have had a SAH into four groups depending on the presence, amount and location of the bleed they have.

Table 20 Fisher CT grading scale. Exported from (73)

Fisher CT grading scale	
Group 1	No blood detected
Group 2	Diffuse deposition or thin layer with all vertical layers of blood (interhemispheric fissure, insular cistern, ambient cistern) less than 1 mm thick
Group 3	Localized clots and/or vertical layers of blood 1 mm or greater in thickness
Group 4	Diffuse or no subarachnoid blood, but with intracerebral or intraventricular clots

15.8 ANNEX 8: MODIFIED RANKIN SCALE

The mRS is a clinical scale used in patients who have had a stroke. Considering the activities that the patients were able to do before the stroke and the symptoms and the activities that are able to do after the stroke, the mRS measures the overall independence they have, regardless the neurologic deficit they suffer (65,66).

Table 21 Modified Rankin Scale (mRS). Extracted from (65,66)

Modified Rankin Scale (mRS)	
0	No symptoms at all
1	No significant disability despite symptoms: able to carry out all usual duties and activities
2	Slight disability: unable to carry out all previous activities but able to look after own affairs without assistance
3	Moderate disability: requiring 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 requiring constant nursing care and attention
6	Death

15.9 ANNEX 9: INFORMED CONSENT FORM

UNITAT DE NEURORADIOLOGIA INTERVENCIONISTA

DOCUMENT DE CONSENTIMENT INFORMAT.
INCLUSIÓ EN EL REGISTRE D'ANEURISMES CEREBRALS.

Nom i cognoms del pacient: .....

Nom i cognoms del metge que informa: .....

Des de la secció de Neuroradiologia Intervencionista de l'Hospital Germans Trias i Pujol es realitza un registre prospectiu de tots el casos d'aneurismes cerebrals diagnosticats a la nostra unitat mitjançant arteriografia cerebral.
A vostè li hem diagnosticat aquesta malaltia, un aneurisma cerebral, que es tracta d'una malformació arterial que consisteix en una dilatació anòmala de l'artèria amb un potencial risc de ruptura i per tant, de presentar un tipus d'hemorràgia cerebral anomenada hemorràgia subaracnoïdal, amb una alta morbimortalitat.
En aquest moment, vostè ja he rebut tota la informació referent a la seva malaltia i ha estat informat de les possibles opcions de tractament així com del tipus de seguiment que rebrà.

Ens adrecem a vostè amb la intenció de que formi part d'aquest registre.

L'objectiu del registre és estudiar els possibles factors de risc associats a la ruptura de l'aneurisma cerebral, i els factors associats a un menor risc de ruptura, considerats protectors.

Aquest registre consisteix en una base de dades d'ús restringit pels membres de la nostra Unitat amb les dades els pacients inclosos de forma totalment anonimitzada.

La finalitat del registre és poder tenir la màxima evidència científica per identificar de forma òptima els pacients que es puguin beneficiar d'un tractament endovascular o quirúrgic de l'aneurisma, així com identificar factors de risc modificables que puguin condicionar la ruptura de l'aneurisma.

L'ús de la informació derivada del present registre serà exclusivament amb motivació científica.

Declaració del pacient:

- He rebut informació sobre el registre, la seva finalitat, forma de incloure les meves dades i l'ús intrahospitalari i confidencial de la informació inclosa.
- Estic satisfet amb la informació rebuda, he aclarit els meus dubtes i he pogut fer totes les preguntes que he considerat necessàries.

Data i signatura del metge que informa:

Data i signatura del pacient:

Data, nom i signatura del representant en cas de ser necessari:

En cas de revocació del consentiment, data i signatura:

CONSENTIMENT INFORMAT. REGISTRE D'ANEURISMES CEREBRALS