Universitat de Girona

Evaluation of a prognostic score for the identification of patients with poor prognosis in cerebral venous thrombosis

A MULTICENTRIC PROSPECTIVE COHORT STUDY PROTOCOL

FINAL DEGREE PROJECT

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ABBREVIATIONS

- **CVT**: Cerebral venous thrombosis
- **DVP**: Deep venous thrombosis
- **CSF**: Cerebrospinal fluid
- **BBB**: Blood-brain barrier
- **ICP**: Intracranial pressure
- **IIH**: Isolated intracranial hypertension
- **SSS**: Superior sagittal sinus
- **MR**: Magnetic resonance
- **MRV**: Magnetic resonance venography
- **CT**: Computed tomography
- **CTV**: Computed tomography venography
- **DSA**: Digital subtraction angiography
- **SE**: Spin-echo
- **FLAIR**: Fluid attenuated inversion recovery
- **GRE**: Gradient-recalled
- **SW**: Susceptibility-weighted
- **MSE**: Magnetic susceptibility effect
- **MIP**: Maximum-intensity projections
- **DWI**: Diffusion-weighted imaging
- **ADC**: Apparent diffusion coefficient
- **BTI**: Black-blood thrombus imaging
- **DANTE**: Delayed alternating with nutation for tailored excitation preparation methods
- **TOF**: Time-of-flight
- **PC**: Phase-contrast
- **CE**: Contrast-enhanced
- **US**: Ultrasonography
- **ACA**: Anterior cerebral artery
- **DTH**: Descending transtentorial hernia
- **PCA**: Posterior cerebral artery
- **ATH**: Ascending transtentorial hernia
- **SCA**: Superior cerebellar artery

- **PICA**: Posterior inferior cerebellar artery
- **MCA**: Middle cerebral artery
- **LMWH**: Low molecular weight heparin
- **UFH**: Unfractioned heparin
- **INR**: International normalized ratio
- **rTPA**: Recombinant tissue plasminogen activator
- **ACT**: Activated clotting time
- **RCT**: Randomized controlled trial
- **mRS**: Modified Rankin Scale
- **IL-6**: Interleukin 6
- **NLR**: Neutrophil-lymphocyte ratio
- **CRP**: C reactive protein
- **SII**: Systemic immune-inflammation index
- **ML**: Machine learning
- **AI**: Artificial intelligence
- **GCS**: Glasgow Coma Scale
- **CIE-10**: *Clasificación international de enfermedades 10ª revisión*
- **CBC**: Complete blood count
- **EDTA**: Ethylenediaminetetraacetic acid
- **WHO**: World Health Organization
- **ICD**: International Classification of Diseases
- **NIHSS**: National Institutes of Health Stroke Scale
- **MoCA**: Montreal Cognitive Assessment

ABSTRACT

Background: Cerebral venous thrombosis (CVT) is a disease with a low incidence but higher incidence rates among young adults, pregnant women and new-bourns. It generally has a good prognosis, but a significant number of deaths and important sequels, due to the limited management of patients who don't respond to anticoagulants, the standard treatment. Endovascular treatments have shown promising results in these patients, but are nowadays only performed in very deteriorated patients with low chance of survival. An early identification of patients with cerebral venous thrombosis with high risk of deterioration would allow for a better adjustment of the clinical following and monitoring, or even performing earlier endovascular treatments, improving the overall prognosis of the disease.

Objectives: The aim of this study is to derive and validate a prognostic score to quickly recognise these patients. Secondarily, the study will investigate if the prognostic factors vary in pregnant women or new-bourns population subgroups.

Methods: A national multicentric prospective cohort study will be performed with a sample formed by 983 men and 667 women with cerebral venous thrombosis. Clinical, imaging and laboratory variables will be collected from each patient, and a logistic regression analysis will be used to develop predictive model for death or disability that will be submitted to validation analysis.

Keywords: Cerebral venous thrombosis, cerebral sinus thrombosis, endovascular treatments, early identification, prognostic score, predictive model

INTRODUCTION

Cerebral venous thrombosis (CVT) is an infrequent entity with several distinctive features. It is a rare cause of cerebral stroke[1], it is considered an unusual location thrombosis[2,3] and, unlike deep venous thrombosis (DVP), it affects a low-middle age population group. Besides, the pathophysiology also differs from DVP, since there is no involvement of the gravitational factor. Although it's good prognosis, there is a considerable mortality (especially in acute phase) and also sequelae such as disability.

1. Epidemiology

The incidence of CVT has increased since first data was published. It was initially extrapolated from an autopsy study, establishing an incidence of 0.1-0.2 cases/100.000/year[4,5], and the increase was confirmed through estimates from observational studies[5–8].

A prospective cohort study in Holland established an incidence of 1.32/100000 inhabitants/year, which raised to 2.78 in the women group between 31-50 years old. Two more recent studies increased the incidence to 1.57 and 1.75/100000 inhabitants/year, respectively[9,10]. This progressive enlargement is probably related to technical improvement and accessibility of imaging techniques, which allows an earlier diagnosis and less severe cases. There is an ongoing meta-analysis that will establish more precisely the epidemiologic characteristics of the CVT[11].

The higher incidence rates are found in new-borns[12], young adults and women[13–15]. It is also more frequent in low-income countries, in correlation with high maternity[16], and also in Asian countries[17].

2. Aetiology

Cerebral venous thrombosis is a multicausal disease that usually involves an interaction of several risk factors (*Table 1*). The most common ones are the prothrombotic states, affecting up to 40% of the patients, and include G20210A prothrombin polymorphism (11.8%)[18], factor V Leyden mutation (10.7%)[19], antiphospholipid syndrome or protein C, S and antithrombin III deficiencies[13,14,20–23] and hyperhomocysteinemia[23].

The second most important group of risk factors is the hormone-related, which justifies the predominance in women[24], and includes oral contraception, pregnancy, puerperium and substitutive hormonal therapy[25]. Oral contraception is the most common one, and it raises almost 7 times the risk of CVT[26], particularly in combination with overweight, obesity[27,28] or in hereditary thrombophilia carriers[29,30].

Infectious causes are also important, and represent 2-12% of cases in adults[14]. The most commonly related infections are otitis, mastoiditis and sinusitis[13,14]. The cavernous sinus thrombosis, a rare but severe form of CVT, is usually caused by infections of the face skin[31–33].

Cancer has also been established as a risk factor for CVT[34], principally due to its hypercoagulative state[35], but also to local compression effect, invasion or in association of local or systemic infections. Other malignancy-related risk factors are some antineoplastic treatments (L-asparaginase[36,37], hormone-based therapy in breast cancer[38–40]) or as a paraneoplastic event[41]. Anaemia was also found to increase CVT risk[42,43].

Most of CVT cases are caused by systemic conditions that generally increase the formation of venous thrombus, but there are also local factors such as brain tumours, vascular malformations, local infections, head trauma and some invasive procedures (neurosurgery, jugular catheterizing, irradiation, lumbar puncture)[44,45].

It is remarkable that an important portion of patients (6-24%) remain unknown aetiology or risk factors, that can manifest weeks or months after the acute phase[13,14,21,22]. Therefore, it is recommended to do an active research of the cause.

Recently an association between coronavirus disease 19 (COVID-19) infection and CVT has been suggested, in relation with the demonstrated increasing of other types of

venous thromboembolisms. Some case reports and case series have been published, but there is still not enough evidence to establish a clear association[46,47].

***Table 1**. Risk factors and associated conditions for cerebral venous thrombosis[69].*

Permanent risk factors	Transient risk factors
• Genetic thrombophilia: prothrombin G20210A mutation; factor V Leiden mutation; protein C deficiency; protein S deficiency; antithrombin deficiency	• Gender-related risk factors: oral contraceptives; pregnancy and puerperium; replacement hormonal therapy
• Hematological diseases: paroxysmal nocturnal hemoglobinuria; sickle cell disease or trait; polycythemia vera; essential thrombocythemia	• Infections: intracranial infection; ear, sinus, mouth, face and neck; systemic infectious disease (e.g., sepsis, endocarditis, tuberculosis, HIV)
• Malignancy: central nervous system; solid tumor outside the CNS; leukemia and lymphoma	• Systemic conditions: severe dehydration; severe anemia; diabetic ketoacidosis
• Vasculitis and related disorders: antiphospholipid syndrome; Behçet's disease; systemic lupus erythematosus; Sjögren's syndrome; Wegener's granulomatosis; temporal arteritis; thromboangiitis obliterans	• Drugs: hormone therapy (glucocorticoids, androgens); chemotherapy (L-asparaginase, cyclosporine); hormonal therapy (tamoxifen); angiogenesis inhibitors (thalidomide); hemostatic treatments
• Inflammatory and other conditions: inflammatory bowel disease; sarcoidosis; nephrotic syndrome; thyroid disease	• Mechanical causes: head trauma; lumbar puncture; myelography; jugular catheter occlusion; neurosurgical procedures; irradiation
• Intracranial causes: meningioma; dural fistula	

3. Physiopathology

The pathology process that follows CVT is not entirely established[45,48]. It is known that the development of the venous thrombosis is related to a local or systemic aetiology and is based on a disbalance between prothrombotic and thrombolytic processes, in favor of the first[45,49]. According to the affected location, there are two physiopathologic mechanisms, that often occur simultaneously:

- If the thrombotic occlusion takes place in a cerebral sinus, the main impairment affects the cerebrospinal fluid (CSF) absorption due to Pacchioni granulations dysfunction, which are arachnoid intra-sinus protrusions that facilitate CSF transport from the subarachnoid space to blood. The direct consequence of this obstruction is the raise of intracranial pressure (ICP)[45,48]

- If the occlusion affects a cortical vein, there is an obstruction of the venous drainage of the adjacent cerebral tissue. This mechanism is dependant of the existence of

collateral circulation, very variable among individuals[48,50], which allows compensation to pressure changes. If this compensation is insufficient, the venous and capillary pressure increases and may end up with a blood-brain barrier (BBB) disruption, vasogenic edema[48,51] and plasma leak to the interstitial space, contributing to the ICP raise

The process can often start with the occlusion of a cerebral sinus and extent to a cortical vein, combining the physiopathological process and worsening the prognosis[52,53].

Intracranial hypertension can result in low brain perfusion and disfunction of the energetic metabolism. The failure of ATPase Na^+/K^+ pump will produce entry of intracellular water and cytotoxic edema[48].

It can also origin a venous subarachnoid haemorrhage, an infrequent presentation. Some hypothesis suggest blood extravasation can be produced by an inflammatory increase of vascular permeability caused by a venous brain infarction or superficial vein rupture, which are thin veins without muscular fibres or valves to allow blood collection[54,55].

CVT has a very variable evolution, but there is usually a gradual worsening in relation with the progression and propagation of the thrombus and/or the failure of compensation mechanism, such as collateralization[50,53].

However, the number of patients that fully or partially recover indicates metabolic and functional brain damage is reversible and, unlike arterial ischemic disease, there is a longer time window[48].

4. Clinical features

The clinical onset of CVT is highly variable, from mild signs to a stroke-like syndrome. It can be classified as acute (< 2 days), subacute (2-30 days) or chronic (> 30 days), being the subacute the most frequent one[13,20,22]. In spite of the variability, signs and symptoms can be group in onset syndromes[56], that are often incomplete or overlapped:

- **Isolated intracranial hypertension syndrome** (IIH): It is the most common one, typically with a chronic onset, and it usually consists in isolated headache (the most common symptom globally), but it can also occur with vomiting, papilledema, decreased visual acuity (blind point or concentric restriction of peripheric visual fields), tinnitus and VI cranial nerve palsy[20–22]. Headache is more frequent in women and young patients, and is an intracranial hypertension-like (severe, global, progressive, worsening with Valsalva manoeuvres and in laying down position)[57]

- **Focal syndrome**: Variable motor or sensitive focal impairments (paresis, aphasia, cerebellar signs) or epileptic seizures (partial or generalized) that can evolve to status epilepticus[13,14,20–22,58]

    - Acute seizures occur within the first 14 days of diagnosis, and appear in 6.9-76% of patients, especially in severe cases and in pregnancy[59]. It has also been correlated with supratentorial haemorrhagic lesions, frontal-parietal involvement or cortical thrombosis[60–62]

    - Late seizures appear after the first 14 days of diagnosis, and are less frequent (4-16%). The most important predictor factor is the existence of acute seizures[59]

    - Status epilepticus is defined as a seizure with $\geq$ 5 minutes of continuous clinical and/or electrographic seizure activity or recurrent seizure activity without recovery between seizures[63]

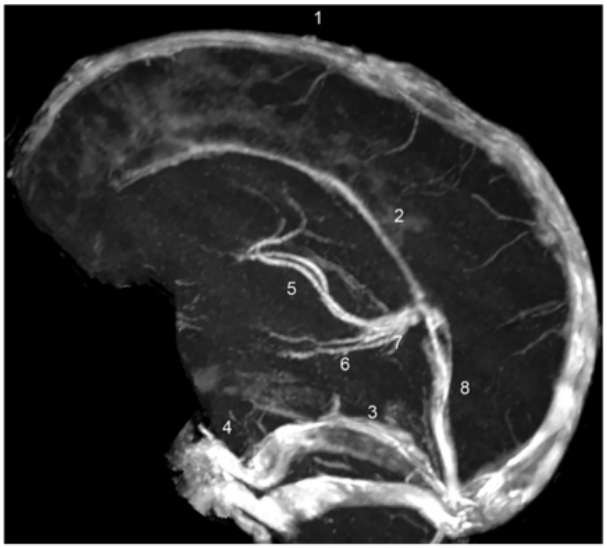
- **Encephalopathy syndrome**: The worst prognosis onset syndrome[64]. There is decreased consciousness (even coma, which is related with multiple sinus occlusion) and mental status disorders such as delirium, apathy or dysexecutive symptoms, bilateral or multifocal neurological signs and/or seizures[13,14,20–22]. It is more frequent in aged patients[65]

- **Cavernous sinus syndrome**: Usually caused by septic thrombosis from local infections (face or paranasal sinus). Patients have headache, orbital pain, chemosis, proptosis, diplopia and oculomotor paralysis[31–33]

One of the factors that justifies the variability of onset is the difference in the number and location of affected sinus. Patients with IIH usually have more extensive thrombosis because of the slow progression and compensation mechanisms, with predomination of a global drainage disorder. On the other hand, focal signs are associated with a less extensive thrombosis based on a sudden obstruction of local venous drainage, with consequently worse outcome[66].

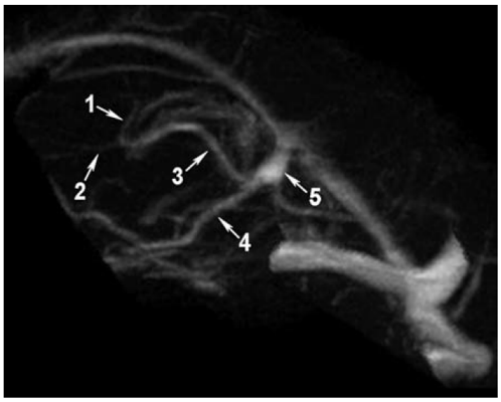
The superior sagittal sinus (SSS) is the most commonly affected, followed by the transverse and sigmoid sinus (***Figure 1***). Multiple sinus involvement is frequent[14,67]. The isolated cortical thrombosis is an unusual kind related to cerebral haemorrhagic infarction[68]. Another distinctive kind is thrombosis of the deep cerebral venous system (***Figure 2***), which is associated with bad evolution[20]. There is an ongoing meta-analysis that will determine more precisely the difference onset modes according to the occluded vessel or sinus[11].

Figure 1*. Sagittal contrast-enhanced maximum intensity projection MR venogram showing the dural sinuses and the deep venous system[79].*



Superior sagittal sinus (1), inferior sagittal sinus (2), transverse sinuses (3), sigmoid sinuses (4), internal cerebral veins (5), Rosenthal veins (6), vein of Galen (7), and straight sinus (8).

Figure 2*. Lateral MIP image from contrast-enhanced MR venography shows the major components of the deep venous system[76].*



Thalamostriate vein (1), septal vein (2), internal cerebral vein (3), basal vein (Rosenthal vein) (4), and vein of Galen.

5. Diagnosis

The diagnostic confirmation of CVT is based on the demonstration of the existence of the thrombus in the cerebral veins or sinuses. The techniques that have proved this capability are the magnetic resonance imaging (MR) and MR-venography (MRV), the computed tomography (CT) and CT-venography (CTV), and the digital subtraction angiography (DSA)[69,70].

5.1. Magnetic resonance imaging

***Table 2**. MR imaging signs of cerebral venous thrombosis.*

Direct signs	Indirect signs
- Direct view of the venous thrombus (variable intensity) - Empty delta sign: Triangular enhancement area with central attenuation*	- Cerebral venous infarction - Intracranial haemorrhage - Signs of raised ICP: Third ventricle collapse, obliteration of basal cisterns, sulcal effacement - Collateral circulation - Brush sign: Prominent flow to medullar deep veins, associated with thrombosis of the straight sinus or deep venous system - View of emissary veins

** in contrast-enhanced sequence*

Standard or spin-echo (SE) sequences (T1/T2) (***Figure 3***) are useful to detect thrombus enhancement because of its blood degradation products (deoxyhaemoglobin, methaemoglobin, hemosiderin)[71]. Therefore, the thrombus has a different enhancement according to the degradation phase[72–74]:

- On first 5 days after the thrombus formation, the signal is isointense in T1 and hypointense in T2 due to high deoxyhaemoglobin concentration
- From day 6 to 15, the signal is hyperintense both in T1 and T2 due to high methaemoglobin concentration

- From day 15, the thrombus looks isointense in T1 and iso/hyperintense in T2. In patients with chronic onset, the diagnosis can be difficult because of recanalization, fibrosis, collateralization and slow flows of oxygenated blood[72,74–77]

The **fluid attenuated inversion recovery** (FLAIR) sequence is particularly useful in brain imaging since it removes the signal from the CSF, resulting in a T2-like image (grey matter brighter than white matter)[78].

MR is also useful to detect indirect signs with good sensibility such as parenchymal lesions or cerebral edema[75], and can be useful to indicate the probable sinus or venous occlusion according to the drainage territories[79] (***Figure 5***). Another indirect sign is the brush sign (***Figure 4***), an abnormally accentuated signal drop of the subependymal and deep medullary veins, that might be useful as a severity marker[80].

Figure 3*. Subacute CVT in a 27-year-old woman with a severe headache for 7 days. (a, b) Sagittal T1-weighted MR image (a) and axial T2-weighted MR image (b) show an area of abnormally increased signal intensity in the right transverse sinus (arrow in a, arrows in b)[79].*

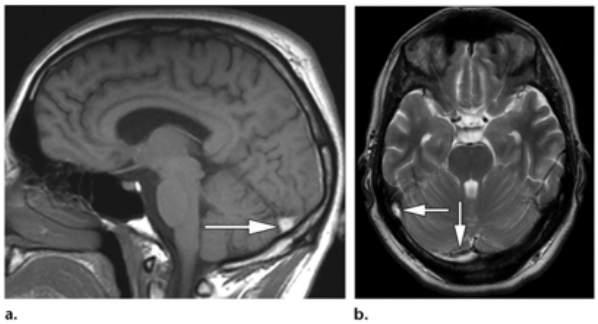


Figure 4*. Bilateral T2*WI-brush sign (D) in a patient with acute thrombosis of the superior sagittal sinus, bilateral transverse sinus, jugular vein, vein of Galen, straight sinus, and internal cerebral veins (C, MR venography). There is engorgement of the medullary veins bilaterally (arrows in D, T2*)[80].*

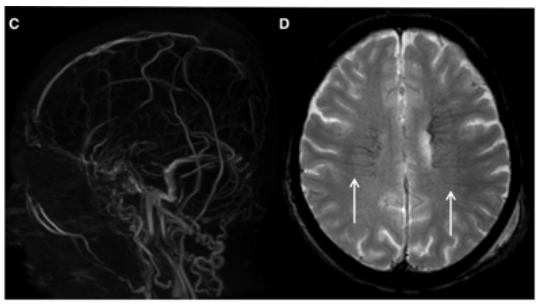
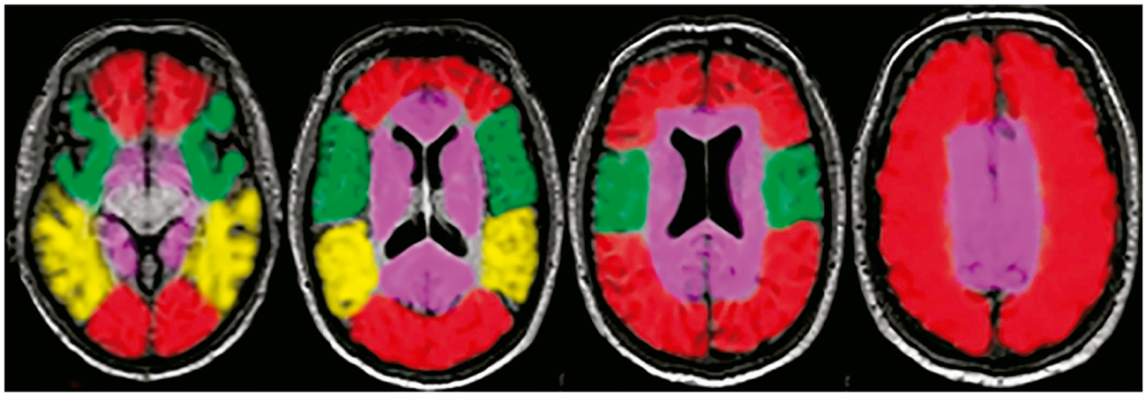


Figure 5*. Series of axial MR images with a color overlay represents the venous drainage territories. The cortical veins and superior sagittal sinus (red), middle cerebral veins and cavernous sinus (green), transverse sinus and Labbé vein (yellow), and deep cerebral veins (lilac) are shown. Hemorrhage or edema in these territories may be indicative of CVT of the corresponding dural sinus or vein[79].*



These sequences have proved a sensibility of 84-97% and a specificity of 28-96% in the diagnosis of CVT[81]. The main limitation is the difficult recognition of cortical thrombosis, especially when they are isolated[75].

The sequence **gradient-recalled echo** (GRE) (***Figure 6***) magnifies the enhancement by detection of degradation blood products, and is very useful in stages where the identification of the thrombus is unclear[75–77].

The **susceptibility-weighted** sequence (SW) is complementary to GRE and exaggerates the magnetic susceptibility effect (MSE) facilitating the identification of subtle thrombus, and it's also useful for visualizing venous stasis, collateral circulation and haemorrhages[75,77,81]. It is also the best sequence to identify isolated cortical thrombosis, especially using the maximum-intensity projections mode (MIP)[75,81].

The **diffusion-weighted** sequence (DWI) (***Figure 7***) can be useful in presence of edema to distinguish cytotoxic from vasogenic edema through apparent diffusion coefficient (ADC) levels (diminished and increased respectively) [75,77]. It is also valuable for the prognosis, since a diffusion restriction is associated with longer recovery time and less recanalization rates[82].

A recently tested sequence is the **black-blood thrombus imaging** (BTI), which supresses the blood signal and enables quick location of the thrombus, hyperintense and easily distinguishable from the surrounding tissue. It may be useful as a first-line technique since it doesn't require contrast administration and it can be used to measure the thrombus volume[83,84]. It has an adequate sensibility and specificity, especially in subacute thrombosis (there can be residual blood artefacts in acute or chronic), which increases with delayed alternating with nutation for tailored excitation preparation methods (DANTE)[85].

***Figure 6**. Gradient recalled echo (a) or susceptibility weighted images (b) can be very useful adjunctive sequences for demonstrating clots within dural venous sinuses or cortical veins. In a, there is blooming artifact from clot within the SSS and cortical veins. In b, there is extensive SSS and cortical vein thrombosis mixed with subarachnoid hemorrhage[75].*

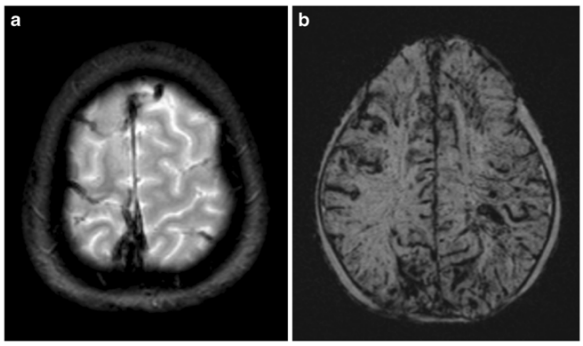
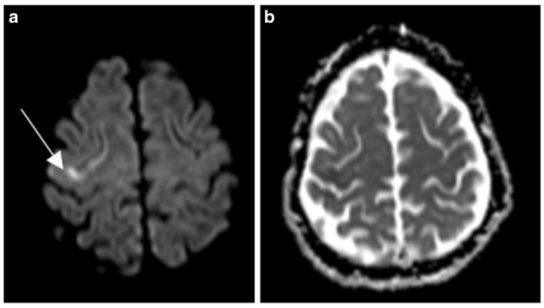


***Figure 7**. Axial ADC (a) and DWI (b) maps demonstrate mixed diffusion signal in the right parietal lobe. There is very cortical diffusion restriction (arrows) but elevated diffusion in adjacent subcortical matter. This pattern is highly atypical of arterial infarction and instead consistent with vasogenic edema syndrome as seen in CVT[75].*



5.2. MR-venography

These sequences are useful not only for the location and confirmation of the thrombosis, but also to globally evaluate the venous cerebral territory and the presence of recanalization or collateralization.

***Table 3**. MRV imaging signs of cerebral venous thrombosis.*

Direct signs	Indirect signs
- Absence of flow in the affected sinus - Irregularity in the sinus walls (recanalization)	- Collateralization - Brush sign - View of emissary veins

5.2.1. Non-contrast sequences

They are also known as non-contrast MR-venography, and the most important ones are **time-of-flight** (TOF) and **phase-contrast** (PC) sequences.

The TOF sequence (***Figures 8 and 9***) is the most commonly used[75,77]. It is especially sensible for slow flows, and particularly with a perpendicular flow, making the coronal, axial and oblique plains very valuable. However, it is affected by void artefacts in locations with a flow parallel to the acquisition plain (a global assessment with other sequences is required)[76].

The PC sequence (***Figure 10***) use blood protonic flows to determine the direction and degree of the flow, but it is skill-based (speed gradients must be correctly adjusted) and it requires a long acquisition time, which raises the susceptibility to movement artefacts[76,77,86,87].

They have the advantage of not requiring intravenous contrast, but they are the MR-venography sequences with more false positive tests due to artefacts. However, the global diagnostic performance is high[87].

Figure 8. *Unenhanced 2D TOF coronal image demonstrates thrombus within the right transverse sinus (white arrow) and superior sagittal sinus (red arrow)[77].*

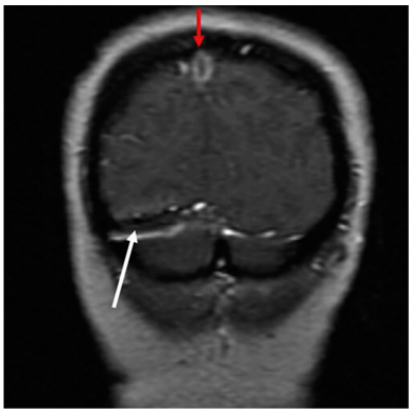


Figure 9. *2D TOF MRV (MIP) and demonstrating extensive superior sagittal sinus thrombosis[75].*

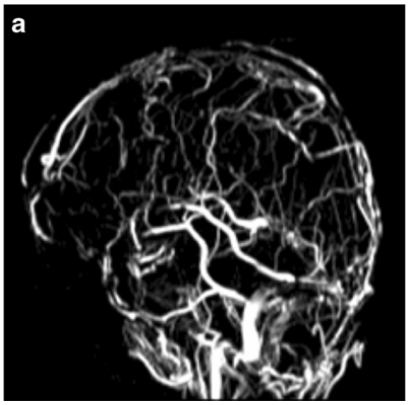
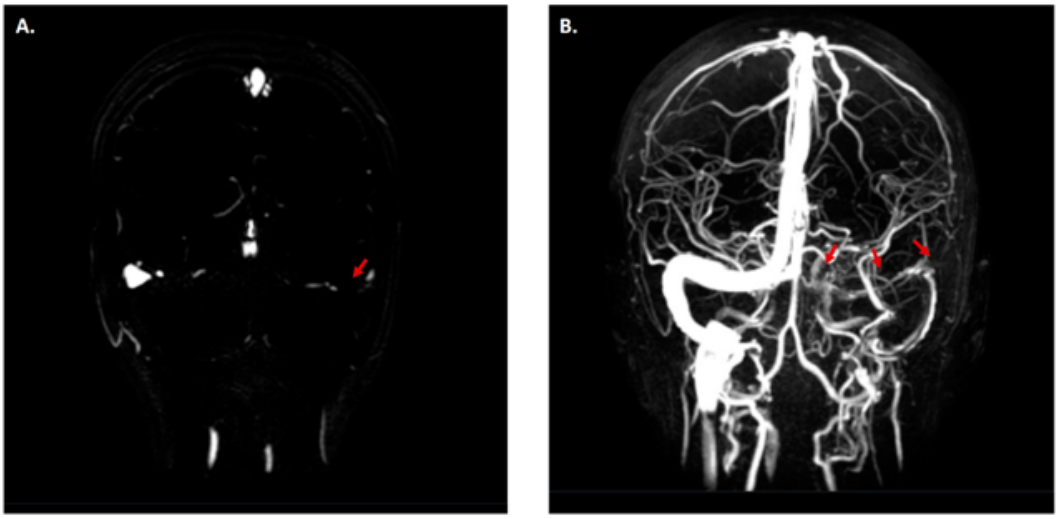


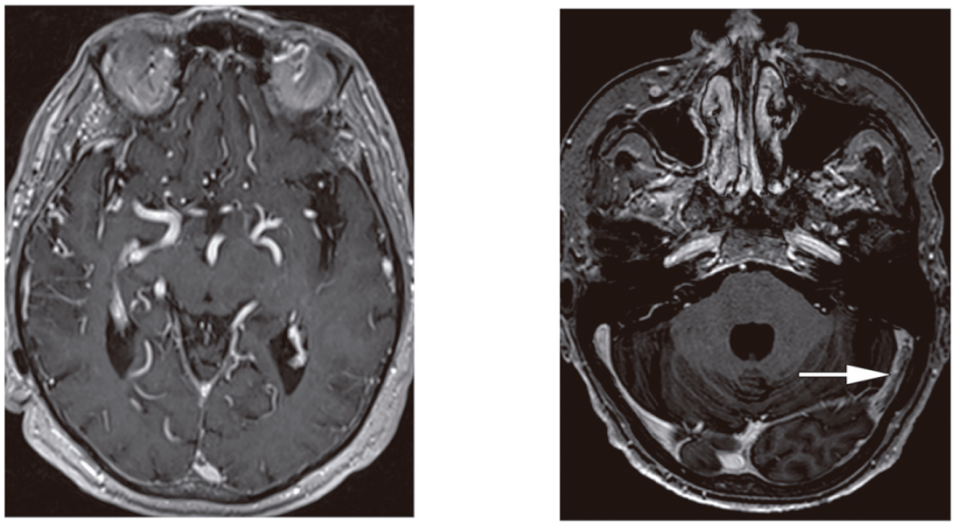
Figure 10. *Coronal Phase Contrast (PC) MR venography (MRV) image of a patient with acute sinus thrombosis of the left transverse and sigmoid sinus; A. Coronal PC MRV image and B. PC MRV maximum intensity projection (MIP) with absence of flow in the left transverse and sigmoid sinus (arrows)[81].*



5.2.2. Contrast sequences

The administration of intravenous paramagnetic contrast (contrast-enhanced MRV) (***Figure 11***) provides an excellent view of the venous cerebral structures and allows the distinction between thrombus and low flow[75,77,86], not being affected by flow artefacts, and has demonstrated a better diagnostic performance than TOF and PC[87]. It has a limitation in chronic thrombosis, where the thrombus can be enhanced by contrast simulating an open sinus[75].

Figure 11*. Axial contrast-enhanced MR venogram showing severe diffuse areas of cerebral venous engorgement (a) and a filling defect in the left transverse sinus (arrow)(b)[79].*



5.3. Computed tomography

Table 4*. CT imaging signs of cerebral venous thrombosis.*

Direct signs	Indirect signs
- Cord sign - Dense triangle sign - Empty delta sign*	- Haemorrhagic and non-haemorrhagic infarctions - Diffuse cerebral edema - Intraventricular haemorrhage - Subdural haematoma - Subarachnoid haemorrhage - Enhancement of the tentorium, falx cerebri or parenchymal tissue*

** in contrast-enhanced sequence*

It is a useful technique for patients with contraindications or inaccessibility to MR. It is usually performed in acute or subacute cases to make differential diagnosis with other neurologic acute pathology (tumours, subdural haematoma, abscesses)[75,77,81,86].

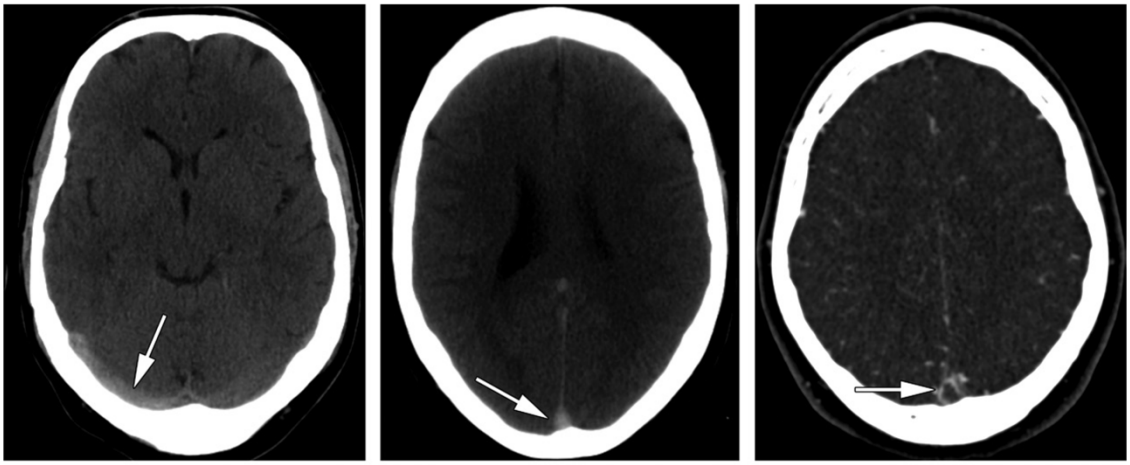
The CT is normal in 30% of patients, and most of the findings are not specific. The classic signs of CVT are the cord sign (hyperdense elongated image from a cortical thrombosis), the dense triangle sign (direct view of the thrombosis into the sinus) and the empty delta sign (triangular enhancement area with central opacification)[77,81,86,88] (***Figure 12***). It has been suggested that attenuation measure in the sinus may increase sensibility[89].

There are also indirect signs (60-80%)[81] that can raise the suspicion of CVT, such as focal or diffuse hypodensities in the white matter, intracranial haemorrhages, ventricular obliteration, dilatation of the trans-cerebral veins or contrast enhancement of the *falx cerebri* and tentorium in the contrast-enhanced (CE) sequence[75,77,81]. Parenchymal lesions can also reinforce the diagnosis, such as bilateral or multiple lesions, bilateral thalamic edema or small juxta-cortical haemorrhages[81].

The existence of non-haemorrhagic subcortical venous infarctions can help to locate the thrombus: thrombosis of the SSS affect bilaterally the frontal, parietal and occipital lobes close to the sinus; transverse sinus thrombosis concern principally temporal lobes; thrombosis of an internal cerebral vein or the straight sinus will affect deeper regions such as the thalamus[77,86].

The main limitations are the poor display of the base skull structures in 3D, the low resolution of the parenchymal lesions, the difficulty in detection of cortical and deep thrombosis, the contrast-related complications (allergies, kidney diseases) and the exposure to ionizing radiation. However, it has some advantages over MR such as the fast image acquisition (unstable or claustrophobic patients), lesser economic cost, absence of motion and flow artefacts and the possibility of examine patients with ferromagnetic devices[88,90].

***Figure 12**. Superior sagittal sinus and right transverse sinus CVT in a 27-year-old man with a headache and a history of cocaine abuse. (a, b) Axial nonenhanced CT images show areas of abnormal hyperattenuation that are consistent with CVT (arrow) in the right transverse sinus (cord sign)(a) and superior sagittal sinus (dense triangle sign)(b). (c) Axial contrast-enhanced CT image shows the empty delta sign (arrow)[79].*



5.4. CT-venography

***Table 5**. CTV imaging signs of cerebral venous thrombosis.*

Direct signs	Indirect signs
- Absence of enhancement on a vein or dural sinus	- Aberrant formation of collateral circulation - Prominent flow to medullary deep veins - View of emissary veins

The CT-venography is one of the most used techniques for the diagnostic confirmation due to its availability and cost-effectiveness. It is performed with intravenous contrast administration in bolus to achieve the enhancement of the cerebral venous system[81].

The sinus can be examined in the axial slices of helicoidal CT and reconstruction techniques can be used (such as MIP) to improve the view of the superficial and deep venous territory[77,86].

The diagnosis is established by observing a lack of sinus or venous filling (absence of flow). Indirect signs can also be assessed[81,86,88].

5.5. Digital subtraction angiography

It has a higher spatial resolution than MR and CT, but it is limited to patients with inconclusive or contradictory findings or when an invasive endovascular procedure is planned. The suggestive signs are the absence of view of the sinus or cortical veins, the intraluminal filling defects or delays and the angiographic evidence of venous congestion (thickening and tortuosity, inverse flow). It can assess the anatomy and the physiologic response (collateralization, venous phase alterations). The main limitations are the anatomical variances[77,86].

5.6. Ultrasonography

The utility of ultrasonography (US) is mainly the detection of hemodynamic changes caused by the venous occlusion through the Doppler mode. It has a low sensitivity in the confirmation of the thrombosis due to the limitations in the detection of slow flows, the distinction between arterial and venous flows, the limited angle access and the skill-based results[86].

The principal advantages are its good economic and technical accessibility and the possibility to repeat it as needed. It is especially useful in new-borns with open fontanelles since it's easier to locate the thrombus and detect haemorrhages, edema, venous infarcts, hydrocephalus and parenchymal changes[75].

The normalizing of the collateral venous flow, even without a observed recanalization, is associated with good prognosis[86].

5.7. Laboratory tests

There is no confirmatory test. It has been seen that increased levels of D-dimer reinforce the CVT diagnosis, and a recent study demonstrated a high sensibility (89.4%) on D-dimer > 500 μg/L. However, a negative result does not exclude CVT, since usually the delay in diagnosis on subacute or chronic onsets allow the D-dimer to return to normal levels (1-3 weeks)[70,91,92].

5.8. Choosing a diagnostic technique

Except for ultrasonography, all the imaging techniques have proved an adequate diagnostic performance[93], and the choice between them is principally based on the advantages and limitations of each and its adequacy to the case (*Annex 1*). For example, the CT is suitable for acute cases with a wide differential diagnosis and fast acting required. The MR gains importance in non-urgent situations because of the better resolution, or in CT contraindications such as pregnancy or iodine contrast allergies.

Within MR-venography sequences, it is not clearly established the best choice. The contrast-enhanced MR-venography is better in performance than the TOF and PC sequences[81], but it also has less availability and more cost, and requires the administration of intravenous contrast.

In conclusion, each health centre and professional should evaluate the more adequate test according to the availability, the experience in the techniques and the clinical situation.

5.9. Cerebral herniation

Recognising cerebral herniation is crucial in the management of patients with CVT, since it's a condition associated with early death[94]. Both CT and MR are useful to make the diagnosis. There are different patterns of intracranial brain hernias, that can occur separately or simultaneously[95,96]:

- **Subfalcine hernia** (midline shift or cingulate hernia): It is generally provoked by unilateral frontal, parietal or temporal lobe mass effect with medial direction, pushing the ipsilateral cingulate gyrus beneath the anterior *falx cerebri*. It can cause hydrocephalus due to obstruction of the foramen of Monro, cerebral infarct of the anterior cerebral artery (ACA) territory and focal necrosis of the cingulate gyrus. A midline shift < 5 mm is associated with good prognosis, and > 15 mm with bad prognosis

- **Descending transtentorial hernia (DTH)**: It is defined by the brain tissue migrating through the tentorial notch. It can be classified in lateral and central hernias, and the different types represent the progression of the descending transtentorial herniation. In cases with severe and abrupt herniation, perforating branches of the basilar artery can be affected, resulting in ischemia and haemorrhage in the brainstem (Duret haemorrhage), with a very poor prognosis

    - **Lateral hernia**: It involves the medial temporal lobe, that migrates downward through the tentorium incisura, and can be anterior or posterior

        - Anterior hernia: Usually caused by unilateral supratentorial lesions, the uncus is pushed over the free edge of the tentorium. It can originate compression of the third cranial nerve, the posterior cerebral artery (PCA) and the aqueduct of Sylvius causing mydriasis (blown pupil), temporal-occipital infarcts and hydrocephalus, respectively

        - Posterior hernia: It is originated by occipital and posterior temporal disease. The parahippocampal gyrus herniates downward into the posterolateral portion of the tentorial incisura. It can involve the tectum, resulting in Parinaud syndrome (vertical eye movement disability) and also affect the oculomotor nerve and PCA

    - **Central hernia**: The diencephalon, midbrain and pons get herniated downwards usually due to bilateral supratentorial disease, midline masses, severe edema or hydrocephalus. The most common complications are hydrocephalus and infarction of the PCA territory, and a progressive herniation may end up in decerebrate posturing, coma and death

- **Ascending transtentorial hernia (ATH)**: It is caused by a mass effect from the posterior cranial fossa with upward direction, that migrates the cerebellar vermis and hemispheres through the tentorial incisura. It can originate hydrocephalus due to aqueduct compression and infarctions of the superior portion of the cerebellum due to affectation of the superior cerebellar arteries (SCA)

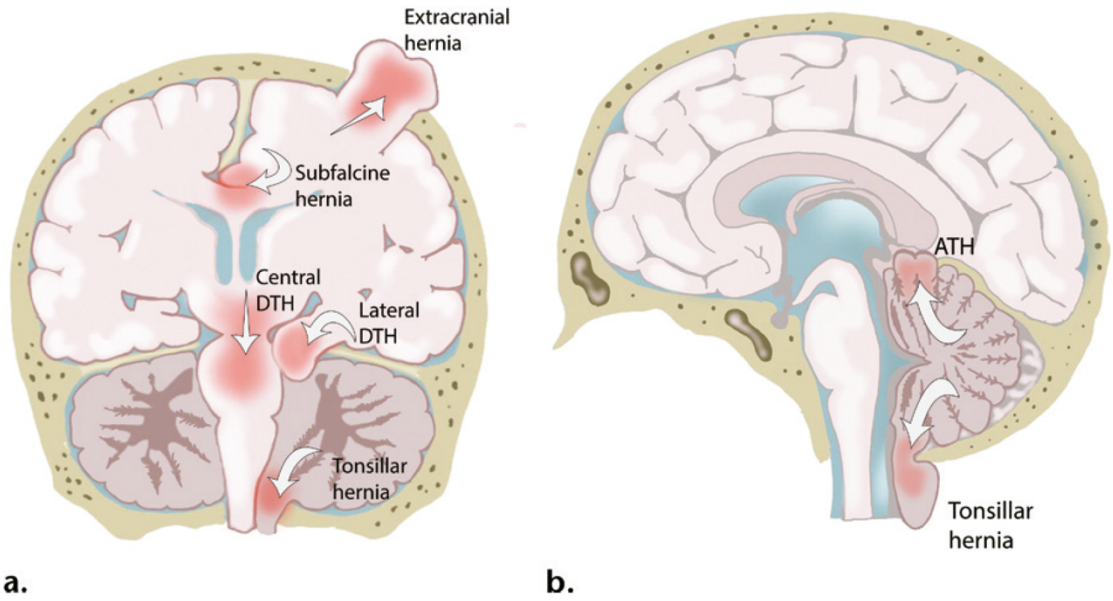
- **Tonsilar hernia**: It is a downwards herniation of the cerebellar tonsils through the foramen magnum into the cervical spinal canal, and it can be congenital (Chiari) or caused by an infratentorial or supratentorial mass effect. It can originate obstructive hydrocephalus and cerebellar infarcts due to compression of the posterior inferior cerebellar artery (PICA)

- **Transalar hernia**: It can be descending or ascending, and it is usually associated with subfalcine and transtentorial hernias

    - In the descending hernia, the frontal love gets displaced inferiorly and posteriorly over the sphenoid wing, and it is usually caused by frontal lobe disease. It can originate infarction of the middle cerebral artery (MCA) territory

    - The ascending hernia is characterized by a superior and anterior displacement of the temporal lobe across the sphenoid ridge, and is caused by a middle cranial fossa mass effect. It can originate infarction of the ACA and MCA territories

Figure 13. Drawings of different kinds of brain herniation in coronal (a) and sagittal (b) views[95].



ATH: ascending transtentorial hernia, DTH: descending transtentorial hernia.

6. Treatment

6.1. Anticoagulation

6.1.1. Acute phase

The standard treatment in the acute phase is the anticoagulation with heparin to prevent the extension of the thrombus and the pulmonary embolism and promote recanalization[70,97,98], and has proved its efficacy and safety versus placebo even with patients with haemorrhagic infarction[99,100]. It is preferred the use of low molecular weight heparin (LMWH) over unfractioned heparin (UFH) due to the better safety profile[99–102], but UFH can be used if there are contraindications to LMWH or if an imminent surgery is planned (allows a quick reversion of the anticoagulant effect)[98,103].

6.1.2. Recurrence prevention

The risk of thrombotic events after the first CVT is increased, with recurrence rates of 2-4% at 1 year, 6-10% at 2 years and 9-15% at 5 years[104,105]. Therefore, it is recommended an extended anticoagulant treatment with vitamin K antagonists.

There is lack of evidence about the period of treatment, and it is not well established. Guidelines advise following the general recommendations for venous extracranial thrombosis, with a period duration of 3 months in events secondary to a temporary cause and 6-12 months in idiopathic cases or with mild thrombophilic diseases. In patients with 2 or more events or with severe thrombophilic disease, an indefinite anticoagulation is recommended. The target international normalized ratio (INR) is between 2 and 3[70,98]. A study is being conducted to assess the period of anticoagulation that will better determine it specifically in CVT[106].

There is a discussion nowadays about the role of new direct oral anticoagulants in the treatment of CVT. The European guideline rejected its use on 2017 given the lack of evidence and the low quality of the existing one[103]. Nevertheless, several studies have been published since then proving the efficacy of these anticoagulants without an increased the risk of bleeding[107–111] (even diminishing it in one study[112]). There are also

3 ongoing studies (1 systematic review and 2 randomized control trials) that will provide more evidence about the efficacy and safety profile[113–115].

This new evidence, in conjunction with the improvement in quality of live, satisfaction and adherence to treatment compared to patients treated with vitamin K antagonists[116], raise the possibility of an impending adjustment of the guidelines recommendations in the next years.

6.2. Endovascular procedures

It is limited to patients with clinical worsening despite the anticoagulant treatment[70,98]. Its objective is to achieve complete or partial recanalization to restore the blood flow and relieve the symptomatology caused by venous congestion and intracranial hypertension, also preventing associated complications[117].

If a diagnostic confirmation is needed, or to have a better surgical planning, an arterial access can be performed to check the venous phase (DSA)[77]. For the venous access a 6-8 French long sheath is used (depending of the technique) into the femoral vein. The guide sheath is usually placed in the internal jugular vein and used as a guide to insert the material required for the technique[117,118].

6.2.1. Pharmacologic thrombolysis

The goal of the thrombolytic treatment is to dissolve the thrombus and achieve recanalization[117]. It can be used locally (directly on the thrombosed sinus) or systemically, and usually the first method is preferred since it allows to increase the target zone concentration and the contact of the thrombolytic agent with the thrombus and to reduce the used dose[118,119].

The local injection in bolus of a thrombolytic agent (recombinant tissue plasminogen activator or rTPA, urokinase, streptokinase) is performed. In some cases with large extension or if complete recanalization is not achieved, a microcatheter can be placed in the sinus for a continuous drip with angiographic checking at 12-24 hours[117,118]. The

treatment must be stopped if permeability has been fulfilled, if there is a clinical deterioration or if the maximum dose is reached[118,120].

Several studies have evaluated the safety and efficacy of the pharmacologic thrombolysis. The systemic thrombolysis has not proved its efficacy, and it has been associated with increase of bleeding risk[121]. Local thrombolysis has been suggested to have good efficacy and safety by some observational studies[120,122,123], while others have detected an increase in haemorrhage risk and limitations[118].

6.2.2. Mechanical thrombectomy

Mechanical thrombectomy requires systemic anticoagulation with intravenous unfractioned heparin to achieve an activated clotting time (ACT) of 250-300s[117] during the procedure, and it is also important the post-surgery anticoagulation to prevent re-occlusions[117].

Several techniques can be used for the treatment of CVT (***Figure 14***):

- **Direct aspiration thrombectomy**: It is the venous analogue of the arterial thrombectomy. Its use is frequent, especially in combination with thrombolysis techniques[117]. Nowadays an aspiration system with a wire separator is usually used, since it helps break the thrombus. It has good maneuverability[118,124]

- **Thrombectomy with stent retriever**: It can be used alone or combined with other techniques, such as pharmacological thrombolysis. It can also be used as a filter anchoring it while the aspiration thrombectomy is performed, or back it up directly inside the aspiration catheter to improve the thrombus capture[117]. It can achieve complete restoration of the flow quickly[118]

- **Balloon thrombectomy**: A balloon can be inflated at the thrombus location or pass next to it to back it up to an aspiration catheter or the guide catheter. It also can be performed with pharmacological thrombectomy. It has the advantage of being capable of treating stenotic lesions, and it can be used as a pre-stenting therapy, but it has a limited maneuverability and it may cause mechanic vascular damage[117,118,124]

- **Angiojet**: It is a catheter with thrombolytic hydrodynamic action (rheolytic thrombectomy) thanks to high speed saline jets that break the thrombus and facilitate suction[124]. It has been related to less recanalization rates and efficacy[117]. It has maneuverability limitations due to its size and rigidity[118]

- **Merci clot retriever**: It is a device with a twisted wire that gets anchored to the thrombus and pulled back. It also has been used to improve the thrombus exposition to thrombolytic agents, enlarging its exposed area with back and forward movements[118,124]

The existing studies about efficacy and safety are mostly based in case series, and suggest a good efficacy and reasonable safety profile in CVT with bad response to anticoagulation, but also highlight the need of randomized controlled trials (RCT) to make a strong recommendation[118,125–127].

6.2.3. Combined treatment

The combination of local pharmacological thrombolysis and mechanical thrombectomy has shown promising results, allowing the reduction of the thrombolytic dose and acceleration of the recanalization[118]. Some studies have proved its efficacy and safety, and propose its use in patients that don't respond to anticoagulants or with a quick deterioration[128–130]. These observational studies are based on severe cases with low chance of survival, which carries a bias that doesn't allow the guidelines to make a strong recommendation. Few studies highlight the improvement in efficacy in less severe patients, claiming for a system to select bad prognosis patients earlier to offer an early treatment[131].

The only existing randomized controlled trial had to be stopped since the results of the combined therapy were not better than anticoagulation (but also not worse). Nevertheless, it encouraged to continue the research in a bigger sample and to focus the treatment to a worse prognosis group[132].

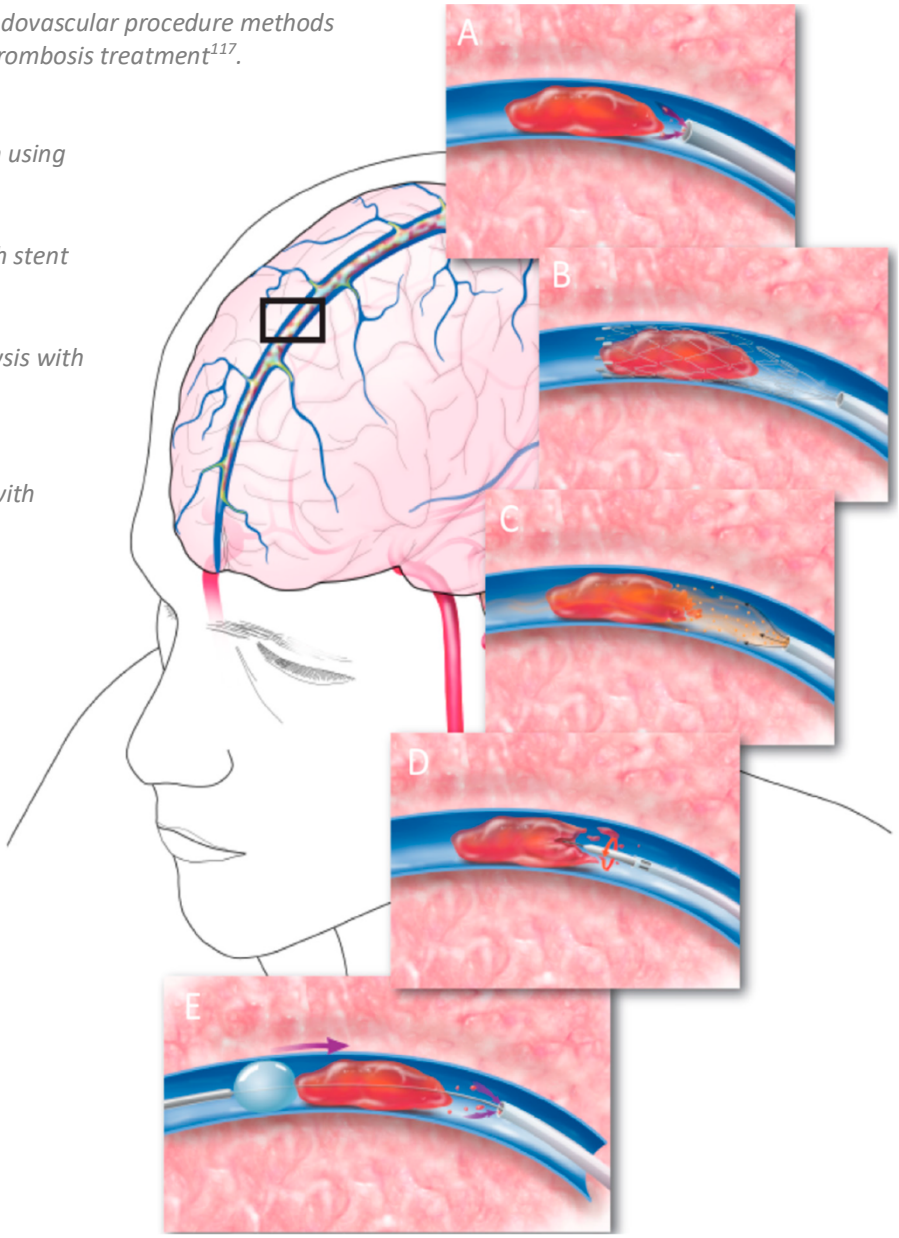
***Figure 14**. Some endovascular procedure methods for venous sinus thrombosis treatment[117].*

A: Direct aspiration using

B: Mechanical thrombectomy with stent retrievers

C: Direct thrombolysis with local injection of thrombolytics

D: Clot disruption with Angiojet irrigation



6.3. Intracranial hypertension treatment

Since the main cause of death in acute phase is transtentorial herniation[94], identifying signs of raising ICP signs is essential in these patients, including an intensive monitoring with invasive measurement and mechanical ventilation in patients with decreased level of consciousness[67,70,133].

The use of lumbar puncture or inhibitors of the carbonic anhydrase diuretics (acetazolamide, topiramate) to lower the CSF production have not shown a benefit in

the functional outcome, but may be useful to improve the symptoms in patients with IIH[103,134].

Corticoids reduce vasogenic edema, but also have a prothrombotic effect, and have not proved improvement in acute phase. Therefore, they are only recommended when there are associated inflammatory diseases[70,103].

A few methods can be used to diminish ICP, including the lower of the bed headboard to 30º, hyperventilation with $PaCO^2$ target of 30-35 mmHg or osmotic diuretics (with a careful use)[98]. The ventricular shunt has also been studied to reduce ICP, without good results[135].

Decompressive surgery with craniectomy is saved for patients with signs of cerebral herniation or treatment-resistant intracranial hypertension[70,103], and has proved to be a life-saving procedure often with good functional outcome results[136–139]. Haemorrhagic lesions, deep CVT[138] and bilateral lesions are poor prognosis factors[136].

6.4. Epileptic seizures treatment

The recommendations about the treatment of epileptic seizures are based on observational studies.

The prophylactic therapy with antiepileptic drugs is not recommended in all patients, but it must be considered in those with supratentorial lesions or focal neurological signs. The treatment is recommended in patients with acute seizures, and is usually maintained for 3-12 months to prevent recurrences[59,98,103].

6.5. Treatment of the associated conditions

It is essential to give an antibiotic treatment when there is a suspicion of associated bacterial infections[70]. Corticoids may be required in vasculitis or inflammatory diseases[70,103]. Cancer treatment must also be considered, since some antineoplastic drugs can have a prothrombotic effect[36,37,40].

7. Prognosis

The prognosis of the CVT is usually good, but a notable number of patients will have a bad outcome. The first days are highly variable, and a deterioration of neurological function, seizures or increase of the headache can occur. The death rate in acute phase is 5.6%, and it increases to 9.4% at discharge. Death or dependency occurs in 13.4% of patients at follow-up, while the complete recovery rate is 79-88%[20,140]. Mortality and invalidating sequels are more common above 64 years old[65], and also in new-borns[141–144]. There is a decrease in mortality these last years, probably related to the identification of less severe cases[145].

Death are normally produced by transtentorial herniation due to raise of ICP by a local mass effect or to multiple lesions with edema[94]. There are also deaths associated to other pathological complications (oncologic, septic), epileptic status or pulmonary embolism[14,22]. Death after the acute phase are usually caused by CVT complications or by underlying conditions[20].

7.1. Prognostic factors

A few studies have investigated about prognostic factors. The prognosis is determined by death or the functional outcome of the patients, and the modified Rankin Scale (mRS) (*Annex 2*) is used to establish it. A bad prognosis (death or dependency) is usually defined by a mRS ≥ 3, and a good prognosis (complete recovery) by a mRS ≤ 2. It is also frequent to stratify the results in the groups of complete recovery (mRS 0-1), partial recovery (mRS 2), disability (mRS 3-5) and death (mRS 6)[13,14,20,22,146].

- **Clinical factors**: They are the most studied factors. An association has been found between poor prognosis and age > 37 years old, male gender, Glasgow Coma Scale ≤ 9 (coma) on admission, mental status disturbance, fever, epileptic seizures, focal neurological sings and some comorbidities (central nervous system infection, malignancy, sepsis, drug addiction, connective tissue disease)[20,147–149]. Pregnancy and puerperium are associated with good prognosis[147], as well as IIH onset[20]

- **Imaging factors**: Some factors related to poor prognosis are the parenchymal involvement or intracranial haemorrhage on admission, the deep cerebral thrombosis, the existence of mass effect signs (especially midline shift) or brush sign[80], absence of recanalization[150], and presence and low quality of collateral paths[151,152]. An isolated thrombosis of the transverse sinus[13,58] and a fast recanalization are good prognosis factors, and have been associated to a regression of haemorrhagic lesions and decrease in the extension of non-haemorrhagic lesions[153,154]

- **Laboratory factors**: Until recently, laboratory factors were not studied as prognostic factors. Lately some studies have related poor prognosis with anaemia[155], natremia levels (in relation with hydration status)[156], elevated fasting blood glucose[157], a raise in inflammation blood biomarkers (interleukin 6 or IL-6, neutrophil-lymphocyte ratio or NLR, c reactive protein or CRP)[158] and the systemic immune-inflammation index (SII), typically used on some types of cancer[159]

7.2. Prognosis scales

There have been several attempts to make a scale or index capable of distinguishing patients with good or bad prognosis.

The first one was created in 2008 with data about prognostic factors from an observational prospective study. The index included age > 37, mental status disorder, coma, intracranial haemorrhage, deep cerebral thrombosis, central nervous system infection and malignancy. A retrospective cohort study with a limited sample was performed to validate the index, analysing the best cut-off score for prediction. They established that a result of ≥ 14 had a sensibility of 88% and a specificity of 70% to detect patients with poor prognosis, but the predictive value was low. The index was useful to predict good prognosis, but not good enough to predict bad prognosis[160].

Next year a similar score was made (ISCVT-RS) from data of the same study in combination with another observational prospective one, including in the index the factors of malignancy, coma, deep CVT, mental status disorder, male gender and

intracranial haemorrhage. The index was tested in to samples from the initial studies and achieved similar results as the first index, with a high sensibility (96.1%) but low specificity (13.6%)[161] for poor prognosis.

Two new scores were published in 2018. The first one (CVT-GS) considered new factors such as parenchymal lesion > 6 cm and bilateral Babinski sign, and also male gender, parenchymal haemorrhage and mental status disorder. This one achieved a better prediction of poor acute prognosis, with a 91.6% precision in prediction of death and 85.3% in prediction of poor prognosis (mRS > 2). However, it was not tested in other samples to assess external validation[162].

The second one was created from a retrospective study with a limited sample. This time the index included decreased consciousness, thrombocytopenia < $225x10^9$/L, natremia < 139 mEq/L, epileptic seizures, absence of oral contraceptives and involvement of > 3 sinus. This index was not tested afterwards in more samples[156].

7.3. Long-term impact

Patients that recover from a CVT have an increased risk of recurrence, especially those with a previous thrombotic event, with malignant blood diseases or with an unknown cause[105,163].

In spite of the high recovery rates, a large number of patients have residual symptomatology such as headache or fatigue. A cognitive and psychological impairment is frequent (depression, anxiety, mild cognitive and language deficiencies) and also difficulties in returning to normal working life[164–166].

This increases significantly the impact of the disease, considering it usually affects young individuals with a long expected working life.

8. Future paths in CVT approach

Technology and new approaches to the pathology study are constantly growing. New techniques are already being used in many fields to aid the clinical decision process and are becoming very valuable.

8.1. Biomarkers

Biomarkers are characteristics that are objectively measured as indicators of normal biological processes, pathological changes, or pharmaceutical responses to a therapeutic intervention. Imaging biomarkers can be obtained from different imaging techniques. Grading biomarkers are specifically related to a disease aggressiveness and prognosis.

The development of these biomarkers isn't simple, and must follow a clinical and technical validation process, including a definition of the proof of concept and mechanism, the standardized and optimized acquisition of anatomical, functional and molecular images, the analysis of the data my computed models, the adequate review of the results, the performing of the corresponding statistical measures and the testing of the efficacy and effectivity of the biomarker. However, when they are developed, imaging biomarkers become excellent aiding factors of the clinical process and can modify favourably the pathological course of a disease[167].

Until now, no biomarkers have been developed or investigated in relation with CVT, but we encourage the research since an objective and validated factor is required specially to determine its prognosis, since nowadays mostly clinical factors are considered, influenced by biological and environmental variables.

8.2. Radiomics

Radiomics is a closely related concept to imaging biomarkers, and is defined as the conversion of digital medical images into mineable quantitative high-dimensional data, that can be used to make hypothesis generation, testing and developing decision support tools. The imaging features can be tested as imaging biomarkers to potentially

aid in detection, diagnosis and assessment of prognosis, treatment or monitoring. The correlation of this mineable data with genomic patterns is known as radiogenomics, which is especially useful in oncology[168].

The use of radiomics is raising interests in many fields, and has a potential role in the investigation of CVT finding useful biomarkers to improve the clinical management of patients.

8.3. Machine learning

Machine learning (ML) is a branch of artificial intelligence (AI) that applies a learning algorithm to a set of data to learn and apply it to other data in order to make predictions. It is also related to radiomics and biomarkers, since validated biomarkers can be used as input features in the learning process. With an appropriate design of this algorithm, it can be very useful to quickly recognise specific conditions, and is already being used in some fields showing good results such as in predicting the occurrence of portosplenomesenteric vein thrombosis in patients with acute pancreatitis or in myocardial infarction prediction.

It has also been suggested that an AI software using parameters from diverse factors associated with thromboembolic disorders could be useful to predict individual risks in certain environmental and clinical conditions, assisting the clinical task[169,170]. There are no studies specifically about machine learning in CVT, but it could have an important role in the future especially on acute cases or rapid deterioration, when fast recognizing and acting is required.

JUSTIFICATION

Many factors make cerebral venous thrombosis to be a relatively unknown disease, and the most important ones are probably the low incidence and generally a good prognosis. However, young adults are one of the most affected groups, often causing sequels and work difficulties, and it also frequently affects pregnant women and new-borns, two particularly vulnerable groups, increasing the impact of the disease in the society.

The knowledge about its treatment is limited. General recommendations about venous thrombosis are usually followed, based on anticoagulant therapy as a standard treatment, which has a good effectivity. Nevertheless, the evidence is limited with patients that don't respond to this treatment. More aggressive measures have been suggested to have good results in these cases, such as an intensive early treatment of intracranial hypertension, endovascular therapy to remove or dissolve the thrombus or decompressive craniectomy to avoid the main cause of death, cerebral herniation.

Clinical guidelines recommend these treatments only in very severe patients when the anticoagulant treatment has failed. Therefore, these treatments are only performed in very deteriorated patients with low chance of survival, and some studies claim the need to make and early identification of patients with poor clinical evolution to be able to act before it’s too late.

Prognostic factors are the basic elements required for this identification. Clinical factors are the most well studied, but many imaging factors are also being established with the improvement of imaging techniques, such as early increased intracranial pressure signs. Lately some laboratory factors have been also related to bad prognosis.

There have been a few attempts to design a prognostic score to help with this early identification of patients with poor prognosis, but none of them have succeeded. Most are principally based on clinical factors and achieve a good distinction of patients with good prognosis, but are insufficient in the detection of bad prognosis.

A new approach to a prognostic score design is needed to be able to perform an early identification of bad outcome patients, that might have an important role in reducing the mortality and sequels of CVT by offering a more adjusted treatment to lower the impact the disease has in the patients and the society.

HYPOTHESIS AND OBJECTIVES

1. Hypothesis

The design of a cerebral venous thrombosis prognostic score can help identifying patients with a poor clinical evolution.

2. Objectives

- **Primary objective**: To determine clinical, imaging and laboratory factors associated with death or disability in patients with cerebral venous thrombosis (CVT) in order to design an accurate and valid prognostic score
- **Secondary objectives**
    - To calculate the weight of the identified CVT prognostic factors
    - To make a simple and useful tool to identify patients with bad CVT prognosis
    - To find out if the influence of the different prognostic factors is different in new-borns and in pregnant women

METHODOLOGY

1. Study design

The first part of the study consists on elaborating a national multicentric prospective cohort study in 75 tertiary health centres of Spain including patients with CVT confirmed by CT/CTV, MR/MRV and/or US (new-bourns). Clinical evolution will be the dependent variable as good (complete recovery) or bad (death or disability) outcome (mRS ≤ 2 or > 2, respectively), evaluated at discharge and at 6 months. Collection of clinical, laboratory and imaging data will be performed as independent variables, chosen due to a potential association with CVT evolution according to the existing evidence. A bivariate analysis using logistic regression will be performed for each independent variable, and then a multiple logistic regression model will be made to determine a predictive model for death or disability. An analysis of new-borns and pregnant women subgroups will be made to find out differences in the influence of the prognostic variables.

Then, the independent variables obtained will be used to design a risk stratification score, which will be submitted to a validation analysis.

2. Period of study

The study will have an approximate duration of 3.5 years (44 months), from May 2021 to December 2024.

3. Study population

Inclusion criteria	Exclusion criteria
- Cerebral venous thrombosis confirmed by CT/CT-venography and/or MR/MR-venography and/or US	- Subjacent disease with short-term bad prognosis - Non-signature of the informed consent

4. Sample calculation and sampling method

All variables with available data (number of exposed / non-exposed patients, classification according to mRS ≤ 2 / > 2) were tested to establish the minimum sample size to recognize a relative risk greater than or equal to 2, accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test and with an anticipated drop-out rate of 10% (*Annex 14*). Based on the existing knowledge, a relative risk ≥ 2 will be enough to obtain significant results at least in some of the variables. The calculations were made with the GRANMO sample size and power calculator program.

A sample size of 983 exposed and 667 non-exposed patients from the variable "male sex" was established (983 men / 667 women), with a total number of participants (N) of 1650 patients. Choosing the variables with the highest patient number requirements ensures the sample will be big enough to achieve representative results in all the variables.

A non-randomized consecutive sampling method will be used for the recruitment.

5. Variables of the study

5.1. Clinical and demographical variables

These variables will be evaluated and collected by an expert neurologist from each health centre.

On admission
- **Age**: As a quantitative continuous variable (years), obtained from the medical history - **Sex**: As a qualitative nominal variable (man / woman), obtained from the medical history - **Risk factors for CVT**: As qualitative nominal variables (any present / none present). They will be collected from the medical history by checking the specific *Clasificación internacional de enfermedades 10.ª revisión, modificación clínica, edición española* (*CIE-10*) codification, and the pharmacological risk factors will be obtained from the electronic drugs prescription. They can also be detected through clinical investigation and added during the clinical course or at discharge ○ **Primary thrombophilia**: As a qualitative nominal variable (G20210A polymorphism [D68.52] / factor V Leiden [D68.51] / antiphospholipid syndrome [D68.61] / protein C deficiency [D68.59] / protein S deficiency [D68.59] / antithrombin III deficiency [D68.59] / hyperhomocysteinemia [E72.11] / any primary thrombophilia [D68.59]) ○ **Gender-linked risk factors**: As a qualitative nominal variable (pregnancy [Z3A] / puerperium (pregnancy < 6 weeks ago) [Z3A] / oral contraception / hormone replacement therapy)

- **Central nervous system infection** [A80 - A89 / A39.0 / A39.81 / G00 / G01 / G02 / G04.01 / G04.2 / G04.31], **local infection** (head/neck) [H01.0 / H04.01 / H05.0 / H10.0 / H15.0 / H15.1 / H16.31 / H20.0 / H44.0 / H44.11 / H44.12 / H60.0 / H60.1 / H60.2 / H60.3 / H61.0 / H65 / H66 / H68.01 / H70.0 / H70.21 / H70.8 / I80.8 / J00 - J06 / J32 / J36 / J39.0 / J39.1 / K05.0 / K05.2 / K11.21 / K11.3 / K11.4 / K12.2 / K13.0 / K14.0 / L02.0 / L02.1 / L03.2 / L04.0]
- **Malignancy** [C00 - C96]
- **Traumatic aggression**: Head trauma [S00 - S09], recent invasive CNS procedure
- **Cerebral vascular malformations** [Q28.0 - Q28.3]
- **Vasculitis** [I77.6]
- **Inflammatory systemic disease** [M30 - M36]

On admission, during the clinical course and at discharge

- **Clinical evolution**: As a qualitative nominal variable (death or disability / partial or complete recovery). Measured with the modified Rankin Scale (mRS) (*Annex 2*). It is the **dependent variable** of the study. This is the only variable that will also be evaluated at 6 months
- **Glasgow Coma Scale (GCS) score**: As a quantitative discrete variable (3 - 15) and as a qualitative ordinal variable (> 8, ≤ 8) (*Annex 3*)
- **Time of onset, to admission, of diagnostic confirmation and to discharge**: As a quantitative continuous variable (days)
- **Headache**: As a qualitative nominal variable (present / not present), defined by the International Classification of Headache Disorders criteria for headache attributed to cerebral venous thrombosis (*Annex 4*)

- **Decreased visual acuity**: As a qualitative nominal variable (present / not present). The presence is defined by the World Health Organization's (WHO) International Classification of Diseases 11 (ICD) as any distance or near vision impairment (*Annex 5*)

- **Papilledema**: As a qualitative nominal variable (present / not present). The presence is defined by a Frisen grade ≥ 1 (*Annex 6*) through ophthalmologic examination

- **Diplopia**: As a qualitative nominal variable (present / not present). The presence is defined by the perception of 2 images from a single object (monocular or binocular)[171]

- **Decreased level of consciousness**: As a qualitative nominal variable (present / not present). The presence is defined by a National Institutes of Health Stroke Scale (NIHSS) 1a, 1b or 1c score ≥ 1 (*Annex 7*)

- **Altered mental status**: As a qualitative nominal variable (present / not present). The presence is defined by a Montreal Cognitive Assessment (MoCA) score of < 26/30 (*Annex 8*)

- **Aphasia**: As a qualitative nominal variable (present / not present). The presence is defined by a NIHSS 9 score ≥ 1 (*Annex 7*)

- **Paresis**: As a qualitative nominal variable (left hemiparesis / right hemiparesis / any paresis) (*Annex 7*)

    - Right hemiparesis is defined as NIHSS 5a and 6a scores ≥ 1
    - Left hemiparesis is defined as NIHSS 5b and 6b scores ≥ 1
    - Any paresis is defined as NIHSS 5a, 5b, 6a or 6b scores ≥ 1

- **Seizures**: As a qualitative nominal variable (focal / generalized / focal to bilateral tonic-clonic / status epilepticus / any seizure type) with the 2019

Manual de Práctica Clínica en Epilepsia from the *sociedad española de neurología (SEN)*[172] definitions:

- Focal seizures are defined as seizures that originate from a single cerebral hemisphere
- Generalized seizures are defined as seizures that originate from both cerebral hemispheres
- Focal to bilateral tonic-clonic seizures are defined as seizures that initially originate from a single cerebral hemisphere, and posteriorly from both hemispheres
- Status epilepticus is defined as a seizure with ≥ 5 minutes of continuous clinical and/or electrographic seizure activity or recurrent seizure activity without recovery between seizures[63]
- Any seizures type: Defined as any of the mentioned types, or unknown seizure type

5.2. Imaging variables

All variables are collected by an expert neuroradiologist. Variables will be collected from all the following available imaging techniques: MR/MRV, CT/CTV and ultrasonography. If more than one imaging technique is available, MR/MRV will be prioritized.

The protocol for MR/MRV includes the following sequences and projections: T1-SE sagittal and axial, T2-FLAIR axial, T2-TSE axial, T2-GRE axial, DWI axial and 2D-PC sagittal and axial. If required, 3D-CE dynamic and sagittal (single shot) sequences can be added.

The protocol for the CT includes the following sequences: Non-enhanced CT, CECT.

Evaluated at least on admission and at discharge

- **Parenchymal lesion type**: As a qualitative nominal variable (edema / infarct / haemorrhage / any)
    - **Cerebral edema**: Low density and loss of grey/white matter differentiation on unenhanced CT, increased T2 and FLAIR signal changes (hyperintensity) in MR[173]
    - **Cerebral infarct**: The imaging signs vary depending on the technique and the time of onset[174] (*Annex 9*). The main difference from arterial infarcts is the affected territory[79]
    - **Intracranial haemorrhage**: Acute blood is hyperdense in CT. The signal in MR is variable according to the time of onset, the size and the location of the bleed[175]
- **Parenchymal lesion location**: As a qualitative nominal variable (unihemispheric supratentorial / bihemispheric supratentorial / infratentorial / supra-infratentorial), globally and separately for each parenchymal lesion type
- **Parenchymal lesion size**: As a quantitative continuous variable (centimetres), globally and separately for each parenchymal lesion type, taking the highest diameter size
- **Thalamic and basal ganglia edema**: As a qualitative nominal variable (present / not present), and location as a qualitative nominal variable (unilateral / bilateral)
- **Sulcal effacement**: Existence as a qualitative nominal variable (present / not present), and characteristics as a qualitative nominal variable (focal unihemispheric / focal bihemispheric / diffuse unihemispheric / diffuse bihemispheric / infratentorial / supra-infratentorial)

- **Midline shift**: As a qualitative nominal variable (present / not present), as a qualitative ordinal variable (< 1 cm / > 1 cm) and as a quantitative continuous variable (millimetres)

- **Cerebral herniation**: As a qualitative nominal variable (subfalcine hernia / transtentorial lateral hernia / transtentorial central hernia / tonsillar hernia / transalar hernia / any herniation type). The definitions for each type can be found in section 5.9 of the Introduction[95,96]

- **Sinus occlusion**: As a qualitative nominal variable (superior sagittal sinus / right transverse sinus / left transverse sinus / straight sinus / deep venous system / sinus confluence / right sigmoid sinus / left sigmoid sinus / right jugular vein / left jugular vein)

- **Number of occluded sinus**: As a quantitative continuous variable (absolute number)

- **Hydrocephalus**: As a qualitative nominal variable (present / not present). The presence is defined by any the following imaging sings[176]:

    - Enlargement of the ventricular system
    - Rounding of the frontal horns
    - Bulging of the third ventricle floor
    - Periventricular interstitial edema

- **Mass effect signs**: As a qualitative nominal variable (any herniation type / any midline shift / compression of ventricles / sulcal effacement / obliteration of basal cisterns / any sign)

- **Brush sign**: As a qualitative nominal variable (present / not present)[80]

5.3. Laboratory variables

The analytic measurements will be performed by the laboratory department of each health centre. The variables will be evaluated by the neurologist of each health centre.

On admission, each day during the clinical course (at least) and at discharge
- **Haemoglobin concentration**: 3 - 5 mL of blood will be collected by venepuncture into a vacuum tube with anticoagulant (ethylenediaminetetraacetic acid or EDTA). A complete blood count (CBC) will be performed as soon as possible with the Beckman Coulter method to determine the haemoglobin concentration, the platelet count, the neutrophil number and the lymphocyte number[177]. Haemoglobin concentration will be reported as a qualitative nominal variable depending on the existence of anaemia (present / not present). Anaemia is defined by any type of anaemia (mild, moderate or severe) according haemoglobin levels WHO criteria (*Annex 10*) - **Platelet count**: Obtained from the CBC as a quantitative continuous variable (n x 10^3 cells/μL) - **Systemic immune-inflammation index (SII)**: Obtained from the CBC as a quantitative continuous variable. The SII is calculated from the blood cell count as platelet count (/L) x neutrophil number (/L) / lymphocyte number (/L) - **Neutrophil-lymphocyte ratio (NLR)**: Obtained from the CBC as a quantitative continuous variable. The NLR is calculated from the blood cell count as neutrophil number (/L) / lymphocyte number (/L) - **D-dimer levels**: 3 - 5 mL of blood will be collected by venepuncture in a vacuum tube with tri-sodium citrate (9:1 ratio), and mixed gently. Then, it will be centrifuged at 3500 rpm for 10 min and analysed with a turbidimetric

latex agglutination technique[178]. The results will be reported as a quantitative continuous variable (ng/mL)

- **Fasting blood glucose**: 3 - 5 mL of blood will be collected by venepuncture in a vacuum tube with glycolytic inhibitors (potassium oxalate, sodium fluoride). The blood will be centrifugated immediately at 1500 x g form 10 min, and the plasma (at least 1.5 mL) will be transferred to a vial and immediately analysed or refrigerated at - 70 ºC until the analysis. Fasting blood glucose will be calculated from the glucose reaction with the adenosine triphosphate (ATP) thanks to the hexokinase enzyme (HK)[179]. It will be reported as a qualitative nominal variable depending on the existence of hypoglycaemia (present / not present). Hyperglycaemia is defined by fasting blood glucose $\geq$ 6.1 mmol/L[157]

- **Natremia**: 3 - 5 mL of blood will be collected by venepuncture into a vacuum tube with anticoagulant (EDTA, heparin, citrate). The blood will be centrifugated to obtain 1 mL of serum or plasma (at least 0.5 mL). The serum will be immediately analysed with ion-selective electrode method or refrigerated at $\leq$ - 20 ºC until analysis[180]. The concentration will be reported as a quantitative continuous variable (mmol/L)

- **CRP levels**: 3 - 5 mL of blood will be collected by venepuncture into a vacuum tube with anticoagulant (EDTA, heparin). The blood will be centrifugated to obtain 1 mL of serum or plasma (at least 0.3 mL). The serum will be immediately analysed with latex-enhanced nephelometry method or refrigerated at $\leq$ - 20 ºC until analysis[181]. The concentration will be reported as a quantitative continuous variable (mg/dL)

- **IL-6 levels**: 3 - 5 mL of blood will be collected by venepuncture into a vacuum tube with heparin. The blood will be centrifugated at 2000 g for 10 min. The obtained plasma will be immediately analysed with electrochemiluminescent

immunoassay (ECLIA) or refrigerated at - 20 ºC until analysis[182]. The concentration will be reported as a quantitative continuous variable (pg/mL)

STATISTICAL ANALYSIS

1. Variables analysis

A bivariant analysis will be done to determine the association of the independent variables with the dependent variable (clinical evolution), a qualitative nominal variable. A normality test will be performed for the quantitative variables.

- **Quantitative variables with normal distribution**: T-student test will be performed, since the qualitative variable has 2 levels
- **Quantitative variables without normal distribution**: Mann-Whitney U test will be performed
- **Qualitative variables**: The $\chi 2$ test (r x s tables) will be used. Tables 2x2 will also be done with the calculation of relative risk, attributable risk and odds ratio

2. Model derivation

A random sample of 70% of the cohort will be used for the derivation procedure, and the remaining 30% for the validation procedure.

A multivariant analysis will be performed with a logistic regression. Cumulative hazard functions will be obtained from monthly Kaplan-Meier estimates. Hazard ratios will be obtained from binomial hazards regression models. The logarithm transformation will be applied to some variables to improve their normality when required.

Binomial hazards regression will be used to derive the prediction model. Binomial regression coefficients will be estimated with variables that show univariate significant differences ($p < 0.05$). The Bayesian information criterion (BIC) will be used to select the best prediction model. A simplified dichotomic version of the quantitative continuous variables will also be tested to check the BIC, and used in the final score if there is not a significant difference in order to achieve a simpler score easier to apply.

Binomial regression coefficients will also be calculated to the new-born and pregnant women subgroups.

3. Model validation

- **Reliability assessment**: The best binomial regression model in the validation dataset (the remaining 30%) will be compared with a function originally derived by a z-score test

- **Accuracy test**: A calibration test will be performed comparing the estimated clinical evolution using the prediction model with the observed clinical evolution. The Hosmer-Lemeshow goodness-of-fit test will calculate a $\chi 2$ value; $\chi 2$ values < 12.59 will be considered substantial fit for the 2 groups (corresponding to a p-value > 0.05)

The C-index and the Brier score will evaluate the discrimination and calibration capacity of the prediction score in the validation dataset.

A sensibility analysis will be performed through a competitive risk analysis to consider deaths unrelated to CVT.

All statistical analysis will be performed using R software (version 4.0.3).

ETHICS AND LEGALITY

The study will be performed following the principles of the Helsinki Declaration of Ethical Principles for Medical Research Involving Human Subjects by the World Medical Association signed in 1964 and amended in 2013, and according to the four Beauchamp and Childress ethical principles of non-maleficence, beneficence, autonomy and justice.

Participants will receive an information sheet (*Annex 11*) and will be asked to sign an informed consent (*Annex 12*) as a requirement for the inclusion, according to the "*Ley 41/2002, de 14 de noviembre, básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica*". There are two types of information sheets, one for adults and one for children. There are two types of informed consents, one for adults and one for parents, and an informed assent document (*Annex 13*) for children. The information sheet and assent document will only be given to the child they are emotionally and intellectually capable of understanding the intervention effects. In comatose patients, the information sheet and informed consent will be given to the closest family member, and will have to be confirmed once the patient is able to.

There will be an adequate management of the personal data from the patients according to the "*Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales*" and the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016. Patients personal data and clinical history information will remain anonymous and handled only according to the laws and for the development of the study. The data access will only be available for the research team.

The study protocol will be submitted to the Clinical Research Ethics Committee or *Comitè d'Ètica d'investigació clínica* (CEIC) of each participating health centre, and all the given recommendations will be considered.

QUALITY CONTROL MECHANISMS. STUDY LIMITATIONS

1. Strengths

- A sufficient sample size, obtained with a sample size calculator, reduces the chance of aleatory error
- The participant loss should not be an important issue since the following period is relatively short and the actions required for the study will be performed within the normal management of the disease. Also, death is considered as a variable, so it will not represent a participant loss
- The multicentric design diminishes the chance of selection bias, increasing the external validation of the study
- The study has a complex design to represent all kinds of patients with CVT from several health centres, aiming for a strong external validity
- There is a clear definition of all the variables and all the collection methods and protocols to follow to ensure the minimization of systematic error and the reproducibility of the study

2. Limitations

- The consecutive non-probabilistic sampling method could cause a selection bias, which is tried to be reduced by establishing wide enough inclusion criteria and a sufficient sample size
- The period of recruitment and data collection is relatively high due to the low incidence of CVT, increasing the risk of difference amongst patients because of the evolving improvements in hospitals on diagnosis, monitoring and treatment

- It is possible that one or more of the requested participating health centres reject to take part in the study

- The protocol for the imaging techniques is well established in the methodology; however, not all participating centres will have the exact same machines and conditions, or may have different internal protocols

- One imaging variable can only be obtained through MR imaging, and it is possible that MR cannot be evaluated in some patients (acute severe patients or with contraindications for MR). In these cases, the variable will be omitted, since it's preferable not to obtain a complete representation from one variable than excluding all the patients without a MR

- The analysis of the new-born and pregnant women subgroups will be limited because of the subgroups size. However, the objective is to investigate major differences between these groups and the general population in relation with prognostic factors

- The validation of the poor outcome prediction might be difficult, since the statistical power will be predictably limited due to the low proportion of subjects with poor outcome

- The objective of this study is to achieve a useful and simple score, so the score items (variables) must be as simple as possible. If the variables obtained with the statistical analysis are not as simple as expected, the external validation and clinical practice use might be difficult

- The notable cost of the study could be a limitation in obtaining the required funds. It is essential to highlight the potential benefit this could generate in the society, helping in the management of this disease that often cause huge occupational difficulties of young individuals with long expected working lives

- The coordination of many national centres is an important logistic challenge. Hiring personnel to ensure a good coordination and execution of the working plan,

securing an appropriate protocol development, is the main factor that increases the budget, but it is indispensable to guarantee a strong evidence in the results

WORK PLAN

1. Research team

The research team conducting the study will be comprised by:

- **General coordinator**: Responsible for the bibliographic research and development of the protocol, formation and coordination of the research team, supervision of the study progress, interpretation of the results and elaboration of the conclusions and result publication and diffusion

- **Project managers**: Responsible for the supervision and coordination of the recruitment supervisors from different health centres. There will be 3 project managers

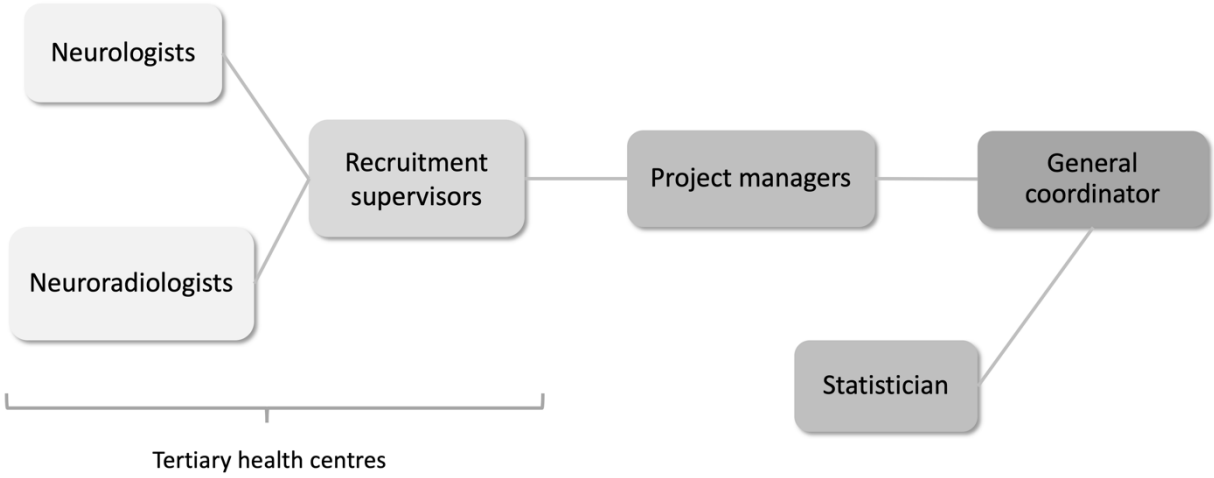
- **Recruitment supervisors**: Responsible for the supervision of the recruitment and review of the procedures and data collection of all the cases in one specific health centre (one from each participating centre)

- **Neurologists**: Responsible for the evaluation of the clinical and laboratory variables through the medical activity (one from each participating centre)

- **Neuroradiologists**: Responsible for the evaluation of the imaging variables through evaluation of the imaging techniques (one from each participating centre)

- **Statistician**: Responsible for the statistical analysis of the data (independently hired)

Figure 15. Research team organisation structure.



2. Work stages

- **Stage 1**: Preparation (2 months). Carried out by the general coordinator
    - Activity 1: Protocol elaboration through bibliographic research and study plan design. Developed by the general coordinator (1 month and 1 week)
    - Activity 2: Participation request on the selected health centres and submitting of the protocol to the corresponding *Comitè d'ètica d'investigació clínica (CEIC)*. Developed by the general coordinator (3 weeks)
- **Stage 2**: Coordination (2 months)
    - Activity 3: Hiring of the independent project managers. A meeting will be performed about the study protocol, and training on the study supervision and incorporation of the recruitment supervisors, neurologists and neuroradiologists. Developed by the general coordinator and project managers (1 month)
    - Activity 4: Recruitment of the research team. A recruitment supervisor, a neurologist and a neuroradiologist will be incorporated from each participating health centre by the project manager. The chosen members of

the team will be discussed and approved with the general coordinator. An independent statistician will also be hired. Developed by the project managers and the general coordinator (3 weeks)

- Activity 5: When the team is completed, an informative meeting will be made in each participating centre. The project managers will explain the study protocol and work plan to the recruitment supervisor, neurologist and neuroradiologist of each centre. Developed by the project managers, recruitment supervisors, neurologists and neuroradiologists (1 week)

- **Stage 3**: Recruitment and data collection (3 years)

  - Activity 6: The consecutive non-probabilistic recruitment will be started. Patients fulfilling the inclusion criteria and without exclusion criteria (*Section 3 from Methodology*) will be offered to participate in the study with the information sheet (*Annex 11*), and asked to sign the informed consent (*Annex 12 and 13*) if they accept. Developed by the recruitment supervisors and neurologists

  - Activity 7: The data collection will be performed following the procedure described for each variable (*Section 5 from Methodology*). Developed by the neurologists and neuroradiologists

  - Activity 8: The recruitment supervisors will review and send the data from each case of the corresponding centre to the project managers. The project managers will review all the cases from the different recruitment supervisors and send them to the general coordinator. Developed by the recruitment supervisors and the project managers

- **Stage 4**: Data analysis and interpretation (2 months)

  - Activity 9: The collected data will be organized and sent to the independent statistician, who will perform the statistical analysis and present it to the general coordinator. Developed by the statistician (1 month)

- Activity 10: The obtained data will be assessed and discussed by the research team and the general coordinator will elaborate the study results, discussion and conclusion. Developed by the complete research team (1 month)

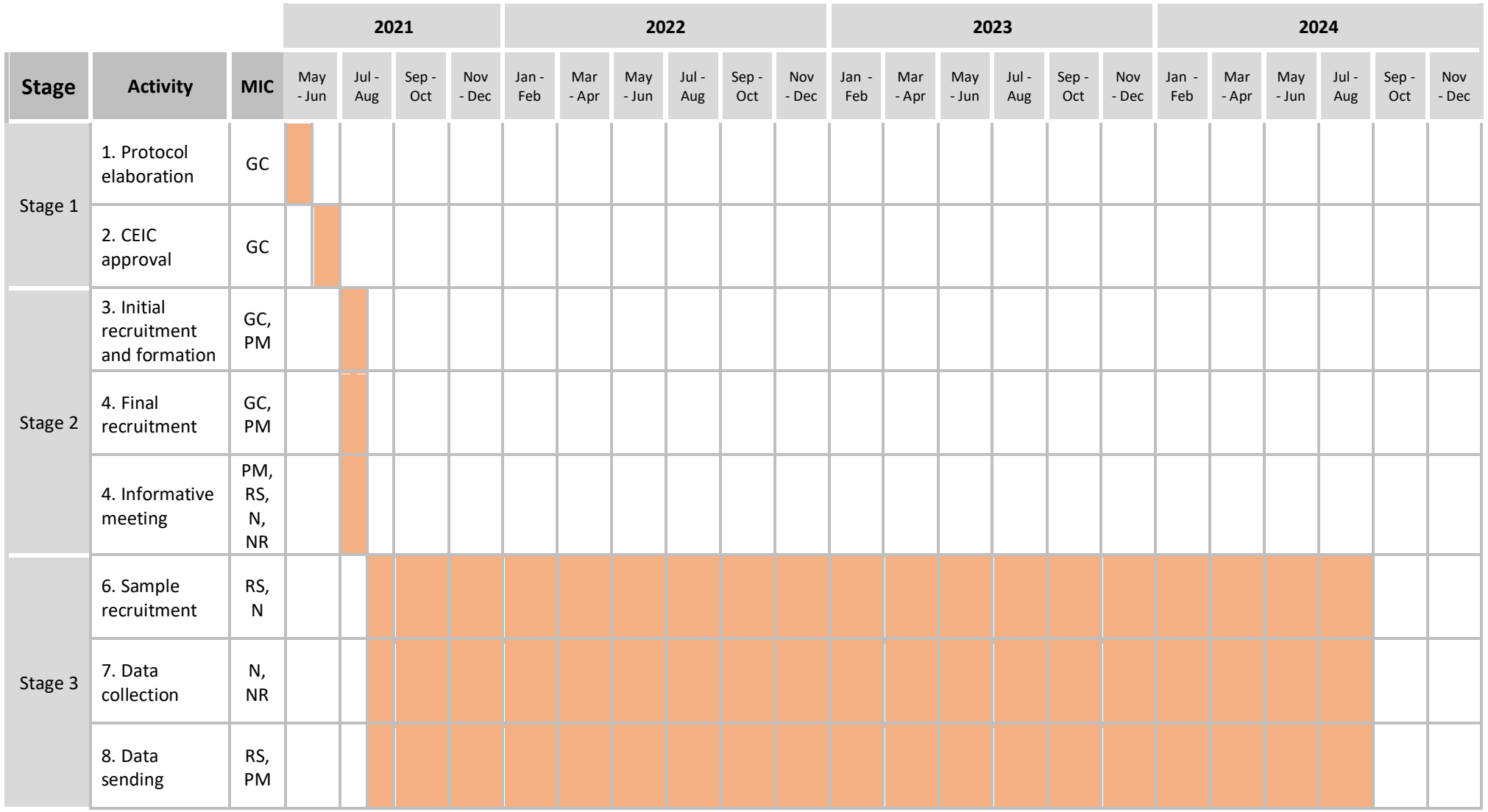
- **Stage 5**: Study publication and diffusion (2 months)

  - Activity 11: An appropriate structure will be assessed and applied to the final article. Developed by the general coordinator (2 weeks)

  - Activity 12: Consideration and selection of medical and scientific journals will be performed for the article publication. The article will be submitted to the selected journals. Developed by the general coordinator (1 month and 2 weeks)

  - Activity 13: If the article is accepted, diffusion of the findings will be carried out. Developed by the general coordinator

CHRONOGRAM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May - Jun
Jul - Aug
Sep - Oct
Nov - Dec
Stage 1
1. Protocol elaboration
GC
2. CEIC approval
GC
Stage 2
3. Initial recruitment and formation
GC, PM
4. Final recruitment
GC, PM
4. Informative meeting
PM, RS, N, NR
Stage 3
6. Sample recruitment
RS, N
7. Data collection
N, NR
8. Data sending
RS, PM

Stage 4	9. Statistical analysis	S																							
	10. Results development	CRT																							
Stage 5	11. Article structuration	GC																							
	12. Article publication	GC																							
	13. Article diffusion	GC																							

MIC: Member in charge; GC: General coordinator; CRT: Complete research team; PM: Project manager; RS: Recruitment supervisor; N: Neurologist; NR: Neuroradiologist; S: Statistician

BUDGET

The imaging techniques and blood laboratory tests are performed in patients with CVT whether they are included in the study or not. Therefore, these costs are not included in the study.

The neurologists and neuroradiologists will not be extra rewarded to participate in the study, to avoid a main economic incentive. The participating members will get scientific recognition and prestige on the medical community.

The included costs in the study are:

	Amount	Price per unit	Total
Materials			
Printing: Information sheets, informed consent, scales	12 pages/patient (1650 patients)	0.05 €/page	990 €
Staff			
Statistician	120 hours	35 €/hour	4200 €
Project managers	3 project managers x 3 years	25000 €/year	225000 €
Recruitment supervisors	1650 cases	50 €/case	82500 €
Allowances			
Travels (formation meeting)	3 project managers x 1 meeting	200 €/person	600 €
Publication			
Article publication	1	2000 €/publication	2000 €
TOTAL COST			**315290 €**

FEASABILITY

The medical team of the study will be composed by recruitment supervisors, neurologists and neuroradiologists of each participating health centre. Recruitment supervisors will get remunerated for every submitted case. Independent project managers and a statistician will be hired to help develop the study.

The resources needed are included in the normal management of a patient with CVT, and will be provided by the Spanish National Health System. The only exception to these is the printing of information sheets, informed consents and scales for evaluation of each patient.

The study population includes 983 men and 667 women. Considering the approximate incidence is 1.64 cases and 1.87/100.000 inhabitants/year for men and women, respectively, and the Spanish total population of 47.329.981 inhabitants, there are about 388 men and 443 women with CVT every year in Spain.

The requested participating centres are 75 tertiary health centres, which represent approximately a 90% of the medical assistance of patients with CVT. Therefore, we will have approximately 349 men and 399 women cases every year. Rejections to participate in the study should not be significant since the clinical, laboratory and imaging procedures to obtain the variables are included in the normal management of the disease. To achieve the sample size, approximately a 3-year period of recruitment will be required.

This is an important logistic challenge that will be coordinated with the support of the *Sociedad Española de Radiología Médica (SERAM)*.

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FIGURE INDEX

TABLE INDEX

ANNEXES

1. Annex 1. Imaging techniques comparison table

		DIAGNOSTIC PERFORMANCE[76,82]	BENEFITS [73,75,76,81]	DRAWBACKS[73,75,76,81]
CT	NCCT	• In isolated cortical thrombosis, the sensibility and specificity is 25% and 100%, respectively, due to the limitation in the distinction of dense cord sign to the location adjacent to the skull • In other CVT, sensibility is 41-100% and specificity 77-100%, with a large variability probably due to the data obtained from observational retrospective studies that use different standards to compare the technique	• Availability • Fast acquisition time • Low cost	• Related to blood attenuation, high haematocrit levels can induce false positive results, and anaemia can induce false negative results • Can have false negatives in subacute thrombosis due to reduction of the attenuation • Ionizing radiation • Use of iodine contrast (allergies, kidney diseases) • Limitation in the view of the skull base duo to bone artefacts
	CECT	• Even with the administration of intravenous contrast, there can be absence of direct and indirect signs up to a 30% of cases • A meta-analysis determined that the combined NCCT + CECT achieve a sensibility of 79% and a specificity of 90%		
CTV		• In comparative studies with multiple imaging techniques, CTV proved a sensitivity and specificity of 100%, but the evidence is limited • The performance diminish in cortical thrombosis (sensitivity of 6-75%) because of the limitation in distinguishing a venous filling defect from an anatomical variation	• Good performance and anatomic detail • Fast acquisition time • Useful it patients with deterioration or MR contraindication • Not influenced by flow artefacts	• Ionizing radiation • Use of iodine contrast • Metal artefacts • Limitation in the view of the skull base duo to bone artefacts
MR	SE GRE SW	• The combination of all sequences achieve a sensibility of 84-97% and specificity of 28-96% • For the diagnosis of cortical thrombosis, GRE has a sensitivity and specificity of 97-98% and 100%, respectively	• Better assessment of indirect signs • It can detect etiologic factors	• Low availability • High cost • Unsuited for patients with ferromagnetic devices
MRV	PC-MRV	• It has a sensitivity of 89% and specificity of 88%	• Fast acquisition time	• Vulnerable to flow artefacts • Limited performance in cortical thrombosis • Skill-based • High acquisition time
	TOF-MRV	• It has a sensitivity of 85% and specificity of 88%	• Good for slow flows	
	3D-CE	• It has a sensitivity of 85% and specificity of 98%	• Great anatomic detail • Good in sinus and cortical thrombosis • Not affected by flow artefacts • Can distinguish venous hypoplasia from thrombosis	• Low availability • High cost

2. Annex 2. Modified Rankin Scale (mRS)

Measures the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability.

- No symptoms at all 0
- No significant disability despite symptoms; able to carry out all usual duties and activities +1
- Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance +2
- Moderate disability; requiring some help, but able to walk without assistance +3
- Moderately severe disability; unable to walk and attend to bodily needs without assistance +4
- Severe disability; bedridden, incontinent and requiring constant nursing care and attention +5
- Dead +6

3. Annex 3. Glasgow Coma Scale (GCS)

- Eye Opening Response
    - Spontaneous--open with blinking at baseline 4 points
    - To verbal stimuli, command, speech 3 points
    - To pain only (not applied to face) 2 points
    - No response 1 point
- Verbal Response
    - Oriented 5 points
    - Confused conversation, but able to answer questions 4 points
    - Inappropriate words 3 points

- Incomprehensible speech 2 points
- No response 1 point

- Motor Response
  - Obeys commands for movement 6 points
  - Purposeful movement to painful stimulus 5 points
  - Withdraws in response to pain 4 points
  - Flexion in response to pain (decorticate posturing) 3 points
  - Extension response in response to pain (decerebrate posturing) 2 points
  - No response 1 point

4. Annex 4. The International Classification of Headache Disorders (3rd edition). Section 6.6.1 Headache attributed to cerebral venous thrombosis (CVT)

Headache caused by cerebral venous thrombosis (CVT). It has no specific characteristics: it is most often diffuse, progressive and severe, but can be unilateral and sudden (even thunderclap), or mild, and sometimes is migraine-like.

Diagnostic criteria

A. Any new headache, fulfilling criterion C

B. Cerebral venous thrombosis (CVT) has been diagnosed

C. Evidence of causation demonstrated by both of the following:

   1. headache has developed in close temporal relation to other symptoms and/or clinical signs of CVT, or has led to the discovery of CVT

   2. either or both of the following:

      a) headache has significantly worsened in parallel with clinical or radiological signs of extension of the CVT

b) headache has significantly improved or resolved after improvement of the CVT

D. Not better accounted for by another ICHD-3 diagnosis.

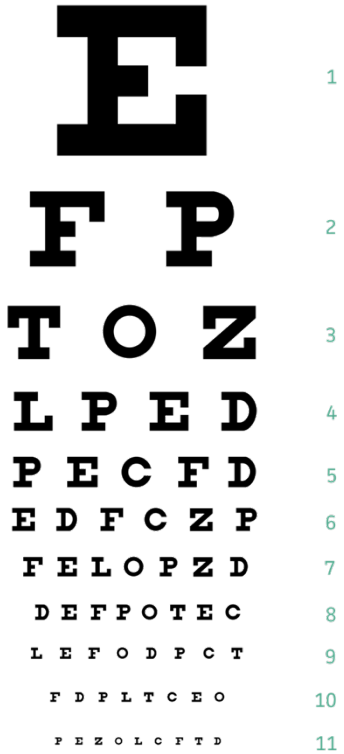
5. Annex 5. The International Classification of Diseases (ICD) 11. Classification of vision impairment and Snellen vision chart

A. Distance vision impairment

1. Mild: Presenting visual acuity worse than 6/12
2. Moderate: Presenting visual acuity worse than 6/18
3. Severe: Presenting visual acuity worse than 6/60
4. Blindness: Presenting visual acuity worse than 3/60

B. Near vision impairment: Presenting visual acuity worse than N6 or M.08 with existing correction

The distance vision impairment categories are based on the results from the Snellen chart test:



6. Annex 6. Frisen grades

- Grade 0. Notice there is no halo of obscuration of the peripapillary nerve fiber layer.
- Grade 1. There is a C-shaped halo of retinal nerve fiber layer edema obscuring the peripapillary retina.
- Grade 2. The halo is now circumferential; there is no temporal gap and no vessel obscuration.
- Grade 3. Major vessels are obscured by edema as they leave the disc (arrow).
- Grade 4. Major vessels are now obscured by edema on the optic disc.
- Grade 5. All vessels are at least partially obscured by edema.

7. Annex 7. National Institutes of Health Stroke Scale (NIHSS)

N I H
STROKE
SCALE

Patient Identification. ___ ___-___ ___ ___-___ ___ ___

Pt. Date of Birth ___ ___/___ ___/___ ___

Hospital _____(___ ___-___ ___)

Date of Exam ___ ___/___ ___/___ ___

Interval: [ ] Baseline [ ] 2 hours post treatment [ ] 24 hours post onset of symptoms ±20 minutes [ ] 7-10 days
[ ] 3 months [ ] Other _____(___ ___)

Time: ___ ___:___ ___ [ ]am [ ]pm

Person Administering Scale _____

Administer stroke scale items in the order listed. Record performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, not what the clinician thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the patient should not be coached (i.e., repeated requests to patient to make a special effort).

Instructions	Scale Definition	Score
1a. Level of Consciousness: The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.	0 = **Alert;** keenly responsive. 1 = **Not alert**; but arousable by minor stimulation to obey, answer, or respond. 2 = **Not alert**; requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic.	_____
1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues.	0 = **Answers** both questions correctly. 1 = **Answers** one question correctly. 2 = **Answers** neither question correctly.	_____
1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to him or her (pantomime), and the result scored (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.	0 = **Performs** both tasks correctly. 1 = **Performs** one task correctly. 2 = **Performs** neither task correctly.	_____
2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI), score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness, or other disorder of visual acuity or fields should be tested with reflexive movements, and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.	0 = **Normal.** 1 = **Partial gaze palsy;** gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present. 2 = **Forced deviation,** or total gaze paresis not overcome by the oculocephalic maneuver.	_____

Rev 10/1/2003

NIH STROKE SCALE

Patient Identification. ___ ___-___ ___ ___-___ ___ ___

Pt. Date of Birth ___ ___/___ ___/___ ___

Hospital _____(___ ___-___ ___)

Date of Exam ___ ___/___ ___/___ ___

Interval: [ ] Baseline [ ] 2 hours post treatment [ ] 24 hours post onset of symptoms ±20 minutes [ ] 7-10 days
[ ] 3 months [ ] Other _____(___ ___)

3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia, is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patient receives a 1, and the results are used to respond to item 11.	0 = **No visual loss.** 1 = **Partial hemianopia.** 2 = **Complete hemianopia.** 3 = **Bilateral hemianopia** (blind including cortical blindness).	_____
4. Facial Palsy: Ask – or use pantomime to encourage – the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barriers obscure the face, these should be removed to the extent possible.	0 = **Normal** symmetrical movements. 1 = **Minor paralysis** (flattened nasolabial fold, asymmetry on smiling). 2 = **Partial paralysis** (total or near-total paralysis of lower face). 3 = **Complete paralysis** of one or both sides (absence of facial movement in the upper and lower face).	_____
5. Motor Arm: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = **No drift;** limb holds 90 (or 45) degrees for full 10 seconds. 1 = **Drift;** limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = **Some effort against gravity;** limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = **No effort against gravity;** limb falls. 4 = **No movement.** UN = **Amputation** or joint fusion, explain: _____ **5a. Left Arm** **5b. Right Arm**	_____ _____
6. Motor Leg: The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = **No drift;** leg holds 30-degree position for full 5 seconds. 1 = **Drift;** leg falls by the end of the 5-second period but does not hit bed. 2 = **Some effort against gravity;** leg falls to bed by 5 seconds, but has some effort against gravity. 3 = **No effort against gravity;** leg falls to bed immediately. 4 = **No movement.** UN = **Amputation** or joint fusion, explain: _____ **6a. Left Leg** **6b. Right Leg**	_____

Rev 10/1/2003

NIH STROKE SCALE

Patient Identification. ___ ___-___ ___ ___-___ ___ ___

Pt. Date of Birth ___ ___/___ ___/___ ___

Hospital _____(___ ___-___ ___)

Date of Exam ___ ___/___ ___/___ ___

Interval: [ ] Baseline [ ] 2 hours post treatment [ ] 24 hours post onset of symptoms ±20 minutes [ ] 7-10 days
[ ] 3 months [ ] Other _____(___ ___)

7. Limb Ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.	0 = **Absent.** 1 = **Present in one limb.** 2 = **Present in two limbs.** UN = **Amputation** or joint fusion, explain: _____	_____
8. Sensory: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas (arms [not hands], legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, "severe or total sensory loss," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a=3) are automatically given a 2 on this item.	0 = **Normal;** no sensory loss. 1 = **Mild-to-moderate sensory loss;** patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched. 2 = **Severe to total sensory loss;** patient is not aware of being touched in the face, arm, and leg.	_____
9. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet and to read from the attached list of sentences. Comprehension is judged from responses here, as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in a coma (item 1a=3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.	0 = **No aphasia;** normal. 1 = **Mild-to-moderate aphasia;** some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response. 2 = **Severe aphasia;** all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = **Mute, global aphasia;** no usable speech or auditory comprehension.	_____
10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untestable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.	0 = **Normal.** 1 = **Mild-to-moderate dysarthria;** patient slurs at least some words and, at worst, can be understood with some difficulty. 2 = **Severe dysarthria;** patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. UN = **Intubated** or other physical barrier, explain:_____	_____

Rev 10/1/2003

NIH STROKE SCALE

Patient Identification. ___ ___-___ ___ ___-___ ___ ___

Pt. Date of Birth ___ ___/___ ___/___ ___

Hospital _____(___ ___-___ ___)

Date of Exam ___ ___/___ ___/___ ___

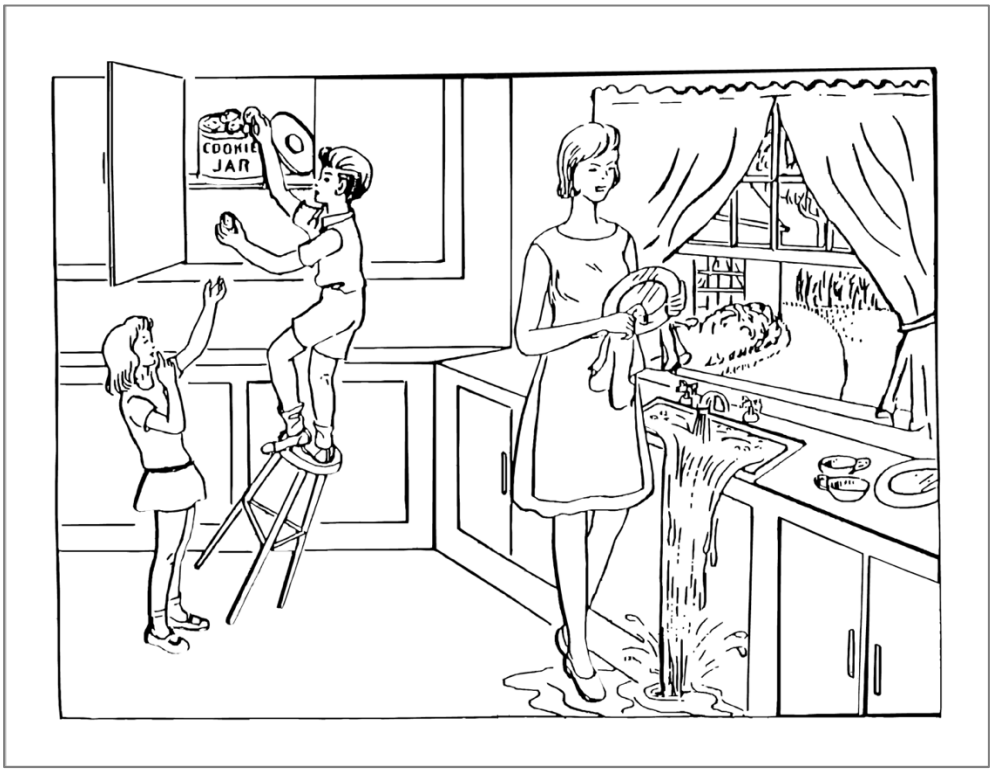
Interval: [ ] Baseline [ ] 2 hours post treatment [ ] 24 hours post onset of symptoms ±20 minutes [ ] 7-10 days
[ ] 3 months [ ] Other _____(___ ___)

11. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.	0 = **No abnormality.** 1 = **Visual, tactile, auditory, spatial, or personal inattention** or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = **Profound hemi-inattention or extinction to more than one modality;** does not recognize own hand or orients to only one side of space.	_____

_____

_____

Rev 10/1/2003



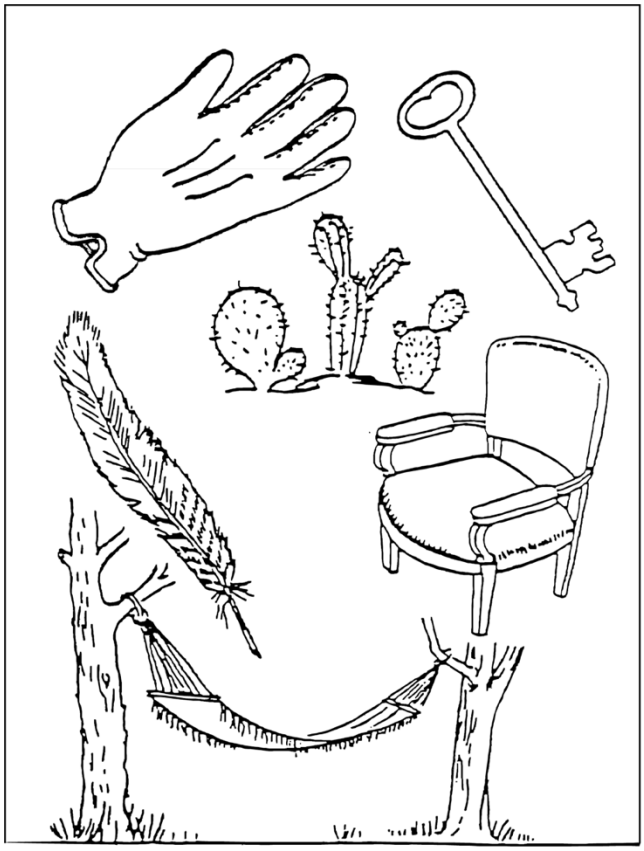
You know how.

Down to earth.

I got home from work.

Near the table in the dining room.

They heard him speak on the radio last night.



MAMA

TIP – TOP

FIFTY – FIFTY

THANKS

HUCKLEBERRY

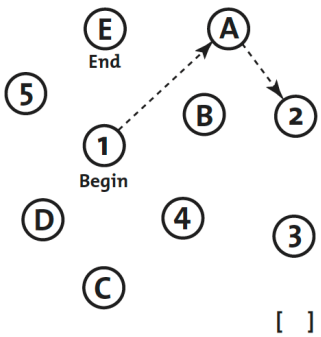
BASEBALL PLAYER

8. Annex 8. Montreal Cognitive Assessment (MoCA)

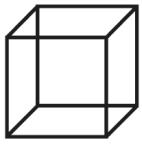
MONTREAL COGNITIVE ASSESSMENT (MOCA)

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE — POINTS



Copy cube



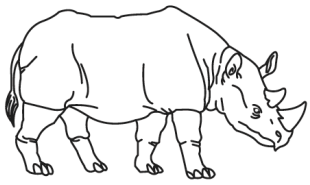
[ ] [ ]

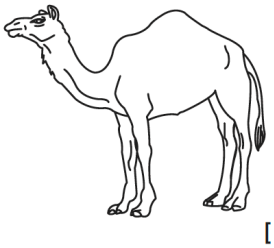
Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands

__/5

NAMING





[ ] [ ] [ ]

__/3

MEMORY — Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION — Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2

__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

__/3

LANGUAGE — Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ]

__/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words)

__/1

ABSTRACTION — Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler

__/2

DELAYED RECALL

	FACE	VELVET	CHURCH	DAISY	RED	Points for UNCUED recall only
Has to recall words WITH NO CUE	[ ]	[ ]	[ ]	[ ]	[ ]	
Optional — Category cue						
Optional — Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

__/6

 Version November 7, 2004

www.mocatest.org

Normal ≥ 26 / 30

TOTAL __/30

Add 1 point if ≤ 12 yr edu

9. Annex 9. Ischemic stroke imaging signs (Radiopaedia)

	CT	MR
Early hyperacute (0 - 6 hours)	Loss of grey-white matter differentiation Cortical hypodensity with associated parenchymal swelling with gyral effacement	High DWI signal and reduced ADC values The affected parenchyma appears normal in other sequences
Late hyperacute (6 - 24 hours)		Hyperintensity on T2 (more easily seen in FLAIR) Hypointensity on T1 (from 16 hours)
Acute (24 hours - 1 week)	Increase of the hypoattenuation and swelling. Mass effect signs can be present	High DWI signal and reduced ADC values Hyperintensity on T2 and FLAIR with progressive signal increasing Hypointensity on T1
Subacute (1 - 3 weeks)	Elevation of the cortical attenuation (CT fogging phenomenon) because of cortical petechial haemorrhages	ADC pseudonormalization at 10 - 15 days, DWI persists elevated Hyperintensity in T2 and FLAIR (unless haemorrhage or cystic encephalomalacia). T2 fogging can appear Hypointensity on T1, but there may be cortical intrinsic hyperintensity due to cortical laminar necrosis or pseudolaminar necrosis
Chronic (> 3 weeks)	Gliosis as low-density region with negative mass effect	High ADC values, DWI with variable signal Hyperintensity in T2 Hypointensity in T1 with/without cortical hyperintensity (persists 2 - 4 months)

10. Annex 10. Haemoglobin levels to diagnose anaemia at sea level (g/L) (WHO)

	Non-anaemia	Anaemia		
		Mild	Moderate	Severe
Children 6 - 59 months of age	110 or higher	100 - 109	70 - 99	lower than 70
Children 5 - 11 years of age	115 or higher	110 - 114	80 - 109	lower than 80
Children 12 - 14 years of age	120 or higher	110 - 119	80 - 109	lower than 80
Non-pregnant women (15 years of age and above)	120 or higher	110 - 119	80 - 109	lower than 80
Pregnant women	110 or higher	100 - 109	70 - 99	lower than 70
Men (15 years of age and above)	130 or higher	110 - 129	80 - 109	lower than 80

11. Annex 11. Information sheet

Hoja de información para el/la paciente adulto

Estimado/a paciente,

Esta hoja contiene información sobre el estudio que se está llevando a cabo y del cual se le pide su participación. El estudio ha sido revisado y aprobado por el Comité Ético de Investigación Clínica de su centro de salud.

Título del estudio

Evaluación de un modelo pronóstico para la identificación de pacientes con trombosis venosa cerebral de mal pronóstico.

Participación voluntaria

La participación en este estudio es voluntaria y puede decidir no participar o cancelar su participación en cualquier momento una vez empezado el estudio. Ninguna decisión supondrá un perjuicio para usted ni su atención sanitaria.

Objetivos del estudio

El objetivo principal del estudio es obtener una herramienta que permita prever qué pacientes con trombosis venosa cerebral van a tener una mala evolución para poder ofrecer un seguimiento o tratamiento más adecuado y conseguir reducir la mortalidad y secuelas que esta enfermedad puede ocasionar.

Descripción del estudio

El estudio se llevará a cabo en su centro de salud durante un período de 6 meses. Es un estudio observacional, por lo que no se realizará ninguna intervención adicional, y el manejo hospitalario no será muy distinto de un/a paciente que no participe en el estudio.

Durante el ingreso hospitalario se realizarán pruebas específicas clínicas en forma de preguntas o tests neurológicos mediante entrevista para comprobar la repercusión de la enfermedad. También se llevará a cabo una prueba de imagen con resonancia magnética al menos en el

momento del ingreso y antes del alta. Otras pruebas a realizar serán análisis de sangre cada día durante el ingreso.

Posteriormente, se realizará una visita de seguimiento a los 6 meses para evaluar las posibles secuelas del proceso.

Con los datos recogidos de su caso y de todos los demás, el equipo de investigadores realizará cálculos para elaborar una herramienta útil para predecir pacientes con un probable mal resultado funcional y poder plantear actuaciones adaptadas.

Beneficios y riesgos de la participación

El estudio está enfocado a proporcionar un beneficio general a los pacientes con trombosis venosa cerebral, y no se obtendrá un beneficio directo personal por su participación.

Al ser un estudio observacional, los procedimientos realizados son los mismos que se utilizan habitualmente, y por lo tanto su participación no conlleva un riesgo añadido.

Confidencialidad y protección de datos

Los datos obtenidos con el estudio estarán anonimizados y sólo serán accesibles por parte de los miembros del equipo de investigación y con el único objetivo del desarrollo del estudio, de acuerdo con lo establecido en la Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales. Si usted decide cancelar su participación en el estudio, los datos serán borrados.

No dude en realizar cualquier pregunta que le surja, en este momento o durante el estudio. Si está de acuerdo con su participación, se le entregará este documento y deberá firmar un consentimiento informado.

Muchas gracias por su atención y colaboración

Hoja de información para el/la paciente menor de edad

Estimado/a paciente,

Esta hoja tiene información sobre el estudio que se está haciendo y para el que se pide su participación. El estudio ha sido revisado y aprobado por el Comité Ético de Investigación Clínica de su centro de salud.

Título del estudio

Evaluación de un modelo pronóstico para la identificación de pacientes con trombosis venosa cerebral de mal pronóstico.

Participación voluntaria

La participación en este estudio es voluntaria y puede decidir no participar o cancelar su participación en cualquier momento una vez empezado el estudio. Ninguna decisión supondrá un perjuicio para usted ni su atención sanitaria.

Objetivos del estudio

El objetivo principal del estudio es obtener una herramienta que permita prever qué pacientes con trombosis venosa cerebral van a tener una mala evolución para poder ofrecer un seguimiento o tratamiento más adecuado y conseguir reducir la mortalidad y secuelas que esta enfermedad puede provocar.

Descripción del estudio

El estudio se llevará a cabo en el hospital durante un período de 6 meses. El manejo hospitalario no será muy diferente de un/a paciente que no participe en el estudio.

Durante el ingreso hospitalario se realizarán pruebas en forma de preguntas o tests mediante entrevista. También se llevará a cabo una prueba de imagen con resonancia magnética. Otras pruebas a realizar serán análisis de sangre cada día.

Posteriormente, se realizará una visita a los 6 meses para ver las posibles secuelas.

Beneficios y riesgos de la participación

El estudio está enfocado a proporcionar un beneficio general a los pacientes con trombosis venosa cerebral, y no se obtendrá un beneficio directo personal por su participación.

La participación en el estudio no conlleva más riesgo.

Confidencialidad y protección de datos

Los datos obtenidos con el estudio serán anónimos y nadie que no sea del estudio podrá consultarlos ni utilizarlos. Si quiere cancelar su participación en el estudio, se borrarán los datos.

No dude en realizar cualquier pregunta que le surja, en este momento o durante el estudio. Si está de acuerdo con su participación, se le entregará este documento y deberá firmar un consentimiento informado.

Muchas gracias por su atención y colaboración

12. Annex 12. Informed consent document

Consentimiento informado (paciente adulto)

Título del estudio

Evaluación de un modelo pronóstico para la identificación de pacientes con trombosis venosa cerebral de mal pronóstico.

Yo, _____ , con DNI/NIE _____ , declaro que:

- He leído la hoja de información del estudio
- He podido realizar preguntas acerca del estudio, que han sido correctamente resueltas
- He recibido suficiente información acerca de las características del estudio, así como los posibles riesgos y beneficios del mismo para mí y para el avance de la ciencia
- He sido informado/a por parte del/de la investigador/a _____ de las implicaciones y objetivos del estudio
- Comprendo que la participación en el estudio es voluntaria y que podré cancelarla comunicándolo a mi médico cuando yo decida, sin necesidad de dar una explicación y sin que afecte a mi atención sanitaria
- Doy libremente mi conformidad para participar en el estudio
- Entiendo y acepto la recogida y tratamiento de mis datos personales y médicos por parte del equipo de investigación, que deberán mantenerse confidenciales y anonimizados

Firma del/de la paciente	*Firma del/de la investigador/a*

Lugar y fecha: _____ , _____ de _____ del _____

Consentimiento informado por representación (padre / madre / tutor/a)

Título del estudio

Evaluación de un modelo pronóstico para la identificación de pacientes con trombosis venosa cerebral de mal pronóstico.

Yo, _____ , con DNI/NIE _____ , padre/madre/tutor/a de _____ , declaro que:

- He leído la hoja de información del estudio
- He podido realizar preguntas acerca del estudio, que han sido correctamente resueltas
- He recibido suficiente información acerca de las características del estudio, así como los posibles riesgos y beneficios del mismo para mi hijo/hija/tutorado/a y para el avance de la ciencia
- He sido informado/a por parte del/de la investigador/a _____ de las implicaciones y objetivos del estudio
- Comprendo que la participación en el estudio es voluntaria y que podré cancelarla comunicándolo a mi médico cuando yo decida, sin necesidad de dar una explicación y sin que afecte a mi atención sanitaria
- Doy libremente mi conformidad para que mi hijo/hija/tutorado/a participe en el estudio
- Entiendo y acepto la recogida y tratamiento de los datos personales y médicos de mi hijo/hija/tutorado/a por parte del equipo de investigación, que deberán mantenerse confidenciales y anonimizados

Firma del/de la padre/madre/tutor/a	*Firma del/de la investigador/a*

Lugar y fecha: _____ , _____ de _____ del _____

13. Annex 13. Informed assent document

Asentimiento informado (paciente menor de edad)

Título del estudio

Evaluación de un modelo pronóstico para la identificación de pacientes con trombosis venosa cerebral de mal pronóstico.

Yo, _____ , con DNI/NIE _____ , declaro que:

- He leído la hoja de información del estudio
- He podido realizar preguntas acerca del estudio, que han sido correctamente resueltas
- He recibido suficiente información acerca de las características del estudio, así como los posibles riesgos y beneficios del mismo para mí y para el avance de la ciencia
- He sido informado/a por parte del/de la investigador/a _____ de las implicaciones y objetivos del estudio
- Comprendo que la participación en el estudio es voluntaria y que podré cancelarla comunicándolo a mi médico cuando yo decida, sin necesidad de dar una explicación y sin que afecte a mi atención sanitaria
- Doy libremente mi asentimiento para participar en el estudio
- Entiendo y acepto la recogida y tratamiento de mis datos personales y médicos por parte del equipo de investigación, que deberán mantenerse confidenciales y anonimizados

Firma del/de la paciente	*Firma del/de la investigador/a*

Lugar y fecha: _____ , _____ de _____ del _____

14. Annex 14. Sample calculation tables

Variable	Obtained from
Male sex	A Multicenter Study of 1144 Patients with Cerebral Venous Thrombosis: The VENOST Study
Pregnancy / puerperium	Risk factors, clinical profile, and longterm outcome of 428 patients of cerebral sinus venous thrombosis
Oral contraceptives	Association of admission clinical predictors and functional outcome in patients with Cerebral Venous and Dural Sinus Thrombosis
Malignancy	Association of admission clinical predictors and functional outcome in patients with Cerebral Venous and Dural Sinus Thrombosis
Trauma	Association of admission clinical predictors and functional outcome in patients with Cerebral Venous and Dural Sinus Thrombosis
Glasgow Coma Scale score less than 8	High-Risk Features of Delayed Clinical Progression in Cerebral Venous Thrombosis: A Proposed Prediction Score for Early Intervention
Headache	Risk factors, clinical profile, and longterm outcome of 428 patients of cerebral sinus venous thrombosis
Visual impairment	Association of admission clinical predictors and functional outcome in patients with Cerebral Venous and Dural Sinus Thrombosis
Papilledema	Risk factors, clinical profile, and longterm outcome of 428 patients of cerebral sinus venous thrombosis
Altered mental status	Association of admission clinical predictors and functional outcome in patients with Cerebral Venous and Dural Sinus Thrombosis
Seizures	Risk factors, clinical profile, and longterm outcome of 428 patients of cerebral sinus venous thrombosis
Any edema	Severe Cerebral Venous and Sinus Thrombosis: Clinical Course, Imaging Correlates, and Prognosis
Any infarction	Severe Cerebral Venous and Sinus Thrombosis: Clinical Course, Imaging Correlates, and Prognosis
Any haemorrhage	Severe Cerebral Venous and Sinus Thrombosis: Clinical Course, Imaging Correlates, and Prognosis
Any midline shift	Severe Cerebral Venous and Sinus Thrombosis: Clinical Course, Imaging Correlates, and Prognosis
Thalamic / basal ganglia edema	Severe Cerebral Venous and Sinus Thrombosis: Clinical Course, Imaging Correlates, and Prognosis
Any sulcal effacement	Severe Cerebral Venous and Sinus Thrombosis: Clinical Course, Imaging Correlates, and Prognosis
Any herniation sign	Severe Cerebral Venous and Sinus Thrombosis: Clinical Course, Imaging Correlates, and Prognosis
Hydrocephalus	Severe Cerebral Venous and Sinus Thrombosis: Clinical Course, Imaging Correlates, and Prognosis
Anemia	Long-Term Outcomes in Patients with Anemia And Cerebral Venous Thrombosis
Hyperglycemia	Elevated fasting blood glucose is predictive of the severity and poor outcome in nondiabetic patients with cerebral venous thrombosis

		Alpha risk	0.05
		Beta risk	0.20
Minimum expected relative risk	2.0	Dropout rate	0.1

Variable	Event rate in Non-exposed	Non-Exposed / Exposed ratio	Proportion (E / NE)
Male sex	0.035	0.679	983 / 667
Pregnancy / puerperium	0.39	10.26	16 / 164
Oral contraceptives	0.47	2.52	13 / 32
Malignancy	0.45	6.33	11 / 96
Trauma	0.38	21.0	16 / 336
Glasgow Coma Scale score less than 8	0.23	9.85	47 / 462
Headache	0.16	0.97	139 / 134
Visual impairment	0.46	4.33	11 / 47
Papilledema	0.22	1.47	75 / 110
Altered mental status	0.34	3.76	27 / 101
Seizures	0.12	1.97	152 / 299
Any edema	0.20	0.07	705 / 49
Any infarction	0.34	0.62	56 / 34
Any haemorrhage	0.27	0.25	155 / 38
Any midline shift	0.29	1.23	52 / 63
Thalamic / basal ganglia edema	0.55	3.22	5 / 16
Any sulcal effacement	0.08	0.21	832 / 174
Any herniation sign	0.30	1.92	41 / 78
Hydrocephalus	0.39	1.53	27 / 41
Anemia	0.12	2.26	146 / 329
Hyperglycemia	0.08	3.44	213 / 732