Overview of Different Predictors among Patients with Cerebral Venous Thrombosis

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ABSTRACT

Cerebral venous thrombosis (CVT) is a rare type of stroke where the thrombosis occurs in the venous side of the brain circulation, leading to occlusion of one or more cerebral veins and dural venous sinus. There are many risk factors for CVT such as pregnancy, puerperium, oral contraceptive pills use, infections, inflammatory diseases, and thrombophilia. CVT is more common in women than in men.The widespread use of neuroimaging now allows for early diagnosis and has completely modified our knowledge on this disorder. CVT is more common than previously thought and it is recognised as a non-septic disorder with a wide spectrum of clinical presentations, numerous causes, and usually a favourable outcome with a low mortality rate. Prognosis of CVT is usually good in more than 80% of patients. However, identification of CVT patients with a possible unfavorable outcome can be challenging. The aim of the present study was to review the possible predictors among CVT patients.

Keywords: Cerebral Venous Thrombosis; Predictors; Neurological Scales

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INTRODUCTION

The World Health Organization (WHO) defines stroke as “rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting one day or longer or leading to death, with no apparent cause other than of vascular origin”. Irrespective of the logic differences of the definitions, it is generally believed that stroke is a syndrome caused by different disease processes, not a single homogenous disease. The WHO estimates that 15 million patients worldwide suffer from stroke every year. Nearly one third of these cases die, one third are left disabled and one third have a good outcome **(1,2)**,

Cerebral venous thrombosis (CVT) is less frequent than ischemic stroke or intracerebral haemorrhage . CVT is type of stroke, accounting for 0.5%–1% of all strokes **(3)**.

In the past, CVT had been associated with a dismal prognosis and high mortality rate, reaching 30–50% **(4)**. Recent studies and especially the CVT study, performed in the era of modern neuroimaging, LMWH administration, and

endovascular intervention, reported much lower mortality rates (3–10%) and significantly better outcome **(5-7)**.

1. Clinical Predictors:

a. Clinical presentation

Principal predictors of death in patients affected by cerebral venous thrombosis were: seizures, mental status disturbances, coma (Glasgow Coma Scale <9), deep cerebral venous thrombosis, right-sided hemorrhage and posterior fossa lesions **(8)**.

In the acute phase of CVT, the case-fatality is around 4%. Predictors of mortality at 30 days are depressed consciousness, mental status disorder, thrombosis of the deep venous system, right hemispheric hemorrhage, and posterior fossa lesions. The main cause of acute death is transtentorial herniation, secondary to a large hemorrhagic lesion, multiple lesions, or diffuse brain edema. Other causes of acute death include status epilepticus, medical complications, and pulmonary embolism. Deterioration after admission occurs in about 23% of patients, with worsening of mental status, headache, or focal deficits, or with new symptoms such as seizures. A new parenchymal lesion is present in one-third of patients who deteriorate. Fatalities after the acute phase are predominantly associated with the underlying disorder, in particular malignancies **(9,10)**.

Seizures are about equally divided between focal and generalized types; the association of both types is very common. Seizures are usually generalized in patients with isolated intracranial hypertension; by contrast, they are common and often partial in patients who have focal deficit. At present, there is no evidence for a prophylactic use of antiepileptic drugs in patients with cerebral venous thrombosis. The antiepileptic treatment should be started when the seizures occurs. The optimal duration of treatment for patients with seizures is a subject of debate. Prolonged treatment with antiepileptic drugs for 1 year could be reasonable for patients with early seizures and hemorrhagic lesions on CT scan **(11)**.

Increasing age is usually associated with other comorbidities, which leads to unfavorable outcome. Decreased consciousness and focal neurologic deficit were other predictors of poor outcome. These symptoms indicate the severity of CVST and might be related to the presence of parenchymal lesions **(12)**

Long-term prognostic factors were analyzed by multivariate methods in 3 previous studies **(13,14)**. CVT confirmed coma, cerebral hemorrhage, and malignancy as important prognostic factors for death or dependence. In addition, male sex, age >37 years, mental status disorder, thrombosis of the deep cerebral venous system, and CNS infection as variables that increase the risk of death or dependence. Seizures (10%) and new thrombotic events (4%) were the most frequent complications during follow-up. Recurrence of CVT and severe visual loss were exceptional but severe and potentially preventable occurrences **(4)**. On the other hand, the presence of isolated intracranial hypertension was a predictor of favorable outcome **(15).**

Severe visual loss due to CVT rarely occurs (2% to 4%). Papilledema can cause transient visual impairment, and if prolonged, optic atrophy and blindness may ensue. Visual loss is often insidious, with progressive constriction of the visual fields and relative sparing of central visual acuity. Visual deficits are more common in patients with papilledema and those who present with increased intracranial pressure. Delayed diagnosis is associated with an increased risk of later visual deficit. Patients with papilledema or visual complaints should have a complete neuro-ophthalmological study, including visual acuity and formal visual field testing **(12,14)**.

Male sex, superior sagittal sinus thrombosis or deep cerebral veins thrombosis, one or more lesion >5 cm, Glasgow Coma Scale <9, monoparesis or hemiparesis, puerperium as predisposing factor, to have neurological worsening, and delayedICH were predictors of poor outcome **(16)**.

A recent study on 70 CVT patients had categorized them into three groups: Group I with isolated intracranial hypertension; Group II—focal syndrome of neurological deficit; Group III subacute encephalopathy, found that headache was a significant predictor of good outcome, while hemiparesis was significant predictor of poor outcome. In addition, patients of group II and III, requiring longer duration of stay (>10 days) or need for mechanical ventilation, were the predictors of dependency and poor outcome (mRS> 2) **(7)**.

Although most CVT survivors will retain functional independence, retrospective surveys of CVT survivors report high rates of sequelae impacting quality of life, including pain, mood, fatigue and cognitive residua, even several years following their events. Retrospective series in CVT survivors have found that over half do not return to work, or have difficulty after returning to work, following their event **(8,17)**.

b. Neurological scales

Different neurological scales for consciousness assessment could be used as reliable methods for consciousness level.

- **The Glasgow Coma Scale (GCS):**

The Glasgow Coma Scale (GCS) is a neurological scale which aims to give a reliable and objective way of recording the conscious state of a patient for initial as well as follow-up assessment **(18)**.

GCS score on admission is an indicator of severity and in-hospital mortality after CVT. Singh et al reported the higher GCS score at admission and discharge and the longer pre-hospitalization period was significantly related to good outcome **(5)**. Similar results were obtained in Nizam's study and higher GCS was found to be associated with good outcome and low GCS was a predicting factor of poor outcome **(13)**.

- **National Institute of Health Stroke Scale (NIHSS)**

The original National Institute of Health Stroke Scale (NIHSS) was developed at the University of Cincinnati and subsequently modified for the national institute of

neurological disorders and stroke (NINDS) rtPA trial. The current version was first published in 1994. It has since become an integral part of stroke clinical trials and practice. Recently in (2015), Hussein and his colleagues were able to validate Arabic version of NIHSS **(19)**.

Currently, the NIHSS is generally acknowledged as the most validated and the most widely used clinical rating instrument with scores ranging from 0 to 42. A baseline NIHSS score greater than 16 indicates a strong probability of patient death, while a baseline NIHSS score less than 6 indicates a strong probability of a good recovery in about 60% of patients. On average, an increase of 1 point in a patient NIHSS score decreases the likelihood of an excellent outcome at 7 days by 24% and at 3 months by 17% **(20)**.

Increase of NIHSS $\geq$ 3 points and decline of GCS $\geq$ 3 points were found to be associated with poor outcome after sever CVT. Predictors of poor outcome may help guide treatment decisions such as need for mechanical thrombectomy (MT) or decompressive surgery **(21)**.

Even though the survival rate is good and most patients with CVT have no or only minor dependency when assessed with the mRS, there seems to be a considerable proportion of patients with cognitive impairment following CVT. In a more detailed examination of cognitive function after CVT, de Bruijn et al reported that 35% of their patients had cognitive impairment and that 40% had symptoms leading to restrictions in lifestyle when assessed after a mean time of 18.5 months after inclusion in their study. Deficits in working memory and depression may also occur after CVT **(22)**.

The 'hidden' complication of cognitive impairment is probably at risk of being greatly underestimated with the mRS examination. Therefore, cognitive function has to be specifically assessed in all patients after a CVT **(23)**.

- **Cerebral venous thrombosis -grading scale (CVT-GS)**

A cerebral venous thrombosis -grading scale (CVT-GS) (0–13 points; more points predicting poorer outcomes) which have an accuracy of 91.6% for the prediction of 30-day mortality and 85.3% for mRS >2. CVT-GS was composed of parenchymal lesion size > 6 cm (3 points), bilateral Babinski signs (3 points), male sex (2 points), parenchymal hemorrhage (2 points), and level of consciousness (coma: 3 points, stupor: 2, somnolence: 1, and alert: 0). CVT was categorized as mild (0–2 points, 0.4% fatality rate), moderate (3–7 points, 9.9% fatality rate), or severe (8–13 points, 61.4% fatality rate) **(24)**.

The CVT-GS is a simple and reliable score for predicting outcome that may help in decision-making in the acute clinical practice, which is the most important stage that determines the fate of patients suffering CVT **(24)**.

2. Laboratory Predictors

Inflammation plays an important role in the risk of CVT and the inflammation response activated by the brain lesion is regarded as a fatal response that provokes secondary brain injury. Systemic immune–inflammation index (SII) is a novel inflammatory index to comprehensively reflect the balance of host immune and inflammatory status. It was defined as follows: platelets ×neutrophils /lymphocytes. Increased SII at admission independently and strongly related to the poor prognosis of acute/subacute CVT Patients with CVT, especially in male and pregnancy/puerperium female. Recently, it has emerged as a powerful prognostic index in various malignant diseases, including renal cell cancer, gastric cancer and prostate cancer **(25)**.

- **The neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) :**

The neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR)**,** monocyte/high-density lipoprotein (HDL) ratio (MHR) and systemic immune-inflammation index (SII=platelets × neutrophils/lymphocytes) are novel inflammatory biomarkers investigated as prognostic markers in several thromboembolic pathologies such as stroke, coronary artery diseases, pulmonary embolism, and deep venous thrombosis and malignancies. These indicators are more stable than individual blood parameters, which may be altered by several variables (e.g., dehydration, overhydration, and blood specimen handling) **(26)**.

NLR , PLR and SII could help clinicians to suspect CVT, especially among the patients with unexplained headache and a normal plain CT, then decide which patients require MRI/MRV immediately for confirmation of the diagnosis. These would help to shorten the time from the onset of symptoms to diagnosis and reduce misdiagnosis **(27)**.

Virchow's triad (venous stasis, vessel wall injury, and hypercoagulable state) is the main pathophysiological mechanism leading to thrombus formation, and increasing evidence suggests that inflammation is involved in the pathophysiology of numerous thromboembolic diseases (cerebrovascular and cardiovascular diseases, venous thromboembolism, and pulmonary embolism). Although the role of inflammation in the development and prognosis of ischemic stroke is already well established **(28)**. The relationship between CVT and inflammation is still unclear.

The great majority of studies evaluating the relationship between CVT and inflammation have observed higher baseline PLR, NLR, and SII values on first admission **(25-28)**. Some of these studies also showed a correlation between disease severity, poor prognosis, and elevated inflammatory markers on admission.

In one retrospective study, the higher baseline NLR in CVT patients and serum NLR levels were positively correlated with the baseline degree of disability and poor outcome at discharge **(29)**.

A retrospective study on the usefulness of NLR in predicting the presence of cerebral venous sinus thrombosis (CVST) found that higher NLR was significantly and independently related to the presence of CVST, showing that inflammation may play an important role in CVST **(30)**. Therefore, it is suggested that anti-inflammation probably improves the outcome of CVT in patients without definite inflammatory

diseases. Although the use of steroids in CVT is not recommended in the current guideline, it does not mean the denial of the effect of immunoregulation in CVT **(27)**.

Higher PLR and NLR values were independently associated with the presence of CVT on admission and that clinical characteristics such as seizures, diplopia, blurred vision, and papilledema, regarded as clinical indicators for poor prognosis, were more common in patients with higher PLR and NLR values **(31)**.

PLR is simply calculated biomarker from the lymphocyte and platelet counts in the venous blood samples. High platelet counts were associated with an increased risk of venous thrombosis because of the location of platelet aggregates in the core of the thrombus. The platelet aggregates generate circulating microparticles in response to prohemostatic stimuli that are independent risk factors for venous thrombosis. In patients with a thrombosis of two or more sinuses, PLR values were significantly higher than thrombosis of one sinus group **(29)**.

Proposed mechanisms linking systemic inflammation with poor outcome include increased neutrophil infiltration of cerebral cortex, disruption of the blood brain barrier (BBB) and impaired tissue reperfusion. These processes lead to maladaptive secondary injury reactions, have been also implicated in animal models of CVT **(32)**. Additionally, experimental and clinical data from studies on deep venous thrombosis support a role for inflammation in the pathophysiology of thrombosis, particularly in initiation and amplification of coagulation **(28,30)**.

- **Lymphocyte to monocyte ratio (LMR):**

Lymphocytes, subtypes of leucocytes, play an important role in the post-ischaemic inflammation. Monocytes also have a pivotal role in the systemic inflammatory response. Lymphocyte to monocyte ratio (LMR) is a new thromboinflammatory marker, it may be more valuable than lymphocyte or monocyte counts alone in the prediction of various diseases including cardiovascular and cerebrovascular diseases and malignancy **(33)**. Therefore, we have reason to believe that LMR of peripheral blood and CVT are somehow linked.

LMR was significantly lower in the poor function outcome group. And Lower LMR value may be significantly related to the poor outcome of patients with CVT **(34)**.

- **Cardiac troponin (cTn):**

There is increasing recognition and research regarding the importance of the heart-brain axis in stroke prognosis. Cardiac troponin (cTn) is a cardiac-specific protein. It is elevated in acute ischemic stroke and intracranial hemorrhage and can suggest a poor prognosis. CVT may lead to venous stasis, which result in cardiac stress and elevated cTn. Patients with arterial ischemic stroke with elevated plasma cardiac troponin (cTn), compared with those without elevated cTn, have increased mortality **(35)**.

- **Other laboratory factors:**

Several studies have focused on determining the appropriate inflammatory factors to predict the outcome of patients with various thromboembolic diseases **(28,29,33)**.

As clinically easily available inflammatory factors, the increased hypersensitive C-reactive protein (Hs-CRP), interleukin-6 (IL-6) levels, and neutrophil-to-lymphocyte ratio (NLR) in the peripheral blood have been confirmed to be correlated with poor outcome in deep vein thrombosis (DVT), and pulmonary embolism (PE) **(36)**.

C-reactive protein (CRP) is a blood biomarker produced by the liver representing acute-phase systemic inflammation. CRP can accurately detect low-grade inflammation and is widely used in clinical practice particularly in cerebrovascular and cardiovascular diseases **(37)**. Elevated plasma CRP level should be considered as a prognostic factor of poor outcome in CVT **(29)**.

Albumin is a negative acute phase reactant that is down-regulated in the circulation in response to systemic inflammation **(38)**. Having long half-lives and being easy to measure in blood, CRP and albumin have been frequently used in daily practice for evaluating for systemic inflammation. High C-reactive protein (CRP)/albumin ratio (CAR), an inflammation marker, may be associated with an increased risk of CVT in pregnant women **(39).**

IL-6 is a significant inflammatory factor produced by various cells including endothelial cells. Previous animal and clinical experiments have revealed that IL-6 participates in inflammation during coagulation partly through provoking stimulation of acute-phase reactants or chemoattractants **(40)**.

Interleukin-6 level increase in patients with CVT. IL-6 levels was not related with brain lesion outcomes or early recanalization but had a significant association with unfavourable functional outcome in patients with CVT at 90 days **(26)**.

D-dimer units are generated by action of factor XIIIa on fibrin monomers and polymers and when the endogenous fibrinolytic system degrades cross-linked fibrin present in the organism. D-dimer is the final fragment of the plasmin-mediated degradation of cross-linked fibrin. D-dimer is a marker of endogenous fibrinolysis and should therefore be detectable in patients with deep vein thrombosis, pulmonary embolism and thromboembolic diseases **(41)**.

It was also reported that plasma D-dimer may help to predict the occurrence of acute or subacute CVT and is an important screening tool to determine the urgency of obtaining magnetic resonance imaging/magnetic resonance venography or digital subtraction angiography in patients presenting with clinical symptoms that are suspected of cerebral venous sinus thrombosis **(42)**.

D-dimer in CVT might be a reliable diagnostic tool in patients with an acute onset of symptoms. They presented a case-control study with 233 patients, in which 94.1% of the cases had an elevated D-dimer, with high sensitivity, specificity, positive predictive value and negative predictive value in the acute phase (within the first seven days) **(43)**.

Positive D-dimer did not correlate with the extent of venous sinus thrombosis or outcome but inversely correlated with duration of illness. The patients with positive

D-dimer results had a shorter duration of illness compared with those with negative D-dimer result. D-dimer levels tend to decrease progressively during the first week after a thromboembolic event and normalized within 3 months after deep vein thrombosis **(44)**.

Recent research indicated that D-dimer at admission was independent predictor of large vessel occlusion in stroke, and higher D-dimer was significantly associated with a stroke severity scale **(45)**.

The relation between D-dimer and CVT might be based on two features: composition and quantity of thrombus. Higher increase in D-dimer levels means fibrin-rich and larger thrombus, which predicts poor outcome for patients with thrombosis **(46)**. However, investigations on the correlation of D-dimer at different stage and the functional outcome of patients with CVST were limited.

A recent study by Sun et al found that elevated D-dimer level on admission were predictive of unfavorable recovery, while D-dimer level at discharge didn't affect the outcome after CVT **(28)**.

Normal D-dimers does not confidently rule out CVT, particularly in the setting of recent isolated headache **(47)**. Two conditions are more likely to produce false-negative D-Dimer results 1- presentation as isolated headache and a longer interval between the onset of symptoms and the evaluation of the patient, since D-dimer values normalize over 1–3 weeks 2-subacute or chronic onset of symptoms occurs in over 50% of CVT patients **(48)**.

3. Radiological predictors

Diagnostic imaging has a critical role in the diagnosis and management of CVT. The most widely used imaging modalities to diagnose CVT include CT of the brain, CT venography (CTV), MRI of the brain, MRV, and catheter-based cerebral angiography. CT may exhibit findings characteristic of CVT. For example, the presence of multiple hemorrhagic infarcts that are not confined to a specific arterial territory should raise suspicion for CVT. Non-contrasted CT scans also may reveal a phenomenon known as the "dense cord sign," a homogeneous hyperdensity that fills the vein or sinus (reflecting a thrombosed cortical vein). The dense cord sign may be seen in approximately 33% of cases of CVT **(49)**.

Singh et al in his study of 40 CVT patients found Superior sagittal sinus with or without inferior sagittal sinus thrombosis was the most common in 67.5% patients followed by right transverse sinus, left transverse sinus thrombosis **(50)**. This was similar to results of previous studies where Superior sagittal sinus was involved in 68% of cases **(52,53)**. In a recent study, transverse sinus was the most frequently involved sinus in 67% of patients **(54)**.

Intracerebral hemorrhages (ICH) are frequent in patients with cerebral venous thrombosis, and lead to worse outcome, Intracerebral hemorrhages occur in approximately one-third of patients with CVT, and are usually associated with a more severe clinical presentation at onset and a worse outcome. Hemorrhagic CVT is categorized into early hemorrhages, delayed hemorrhages, and expanded

hemorrhages. Early ICH (E-ICH) is any ICH present on CT or MRI scan at time of diagnosis of CVT and delayed ICH (D-ICH) is any ICH that was not present on CT or MRI scan at time of diagnosis but occurred later, with or without clinical worsening. Among CVT patients, those with E-ICH were older, and more likely to have a severe clinical presentation and a worse 6-month outcome that CVT patients without ICH **(55)**.

Venous infarction on MRI was a significant predictor of clinical deterioration in patients with CVT. Venous infarction is common in CVT, When CVT occurs, there is an increase in venous pressure, which results in disruption of the blood–brain barrier, vasogenic oedema and haemorrhage, and a decrease in capillary perfusion pressure leading to cytotoxic oedema. As venous pressure continues to increase, this leads to more severe cerebral edema and venous ischaemia, all of which contribute to the development of venous infarction **(56)**. This was supported by Stolz et al. who found venous infarct to be a predictor of poor outcome at six months after CVT. Thus, patients with CVT with venous infarcts should be identified as high-risk, and close observation is warranted **(57)**.

Diffusion-weighted imaging (DWI) hyperintensity indicating diffusion restriction was also predictive of clinical deterioration in patients with CVT. Mullins et al. suggested that DW MR imaging in combination with clinical history of seizure identified three parenchymal lesion types in patients with CVT: lesions with elevated diffusion, most consistent with vasogenic edema, that resolved; lesions with low diffusion, most consistent with cytotoxic edema in patients without seizure activity, that persisted; and lesions with low diffusion in patients with seizure activity, that resolved. This information may be important in prospectively determining the severity of irreversible injury, in the evaluation of new therapeutic agents, in the determination of prognosis, and in patient management **(58)**.

The presentation of CVT is not stereotyped and there has been ambiguity about clinical and radiological predictors of poor outcome. As some of the studies have found the importance of low GCS at presentation, presence of focal neurological deficits, and deep venous system, as the predictors of poor outcome **(50,52)** and few studies have focused on radiological factors like number of sinuses involved, site of venous infarct and presence of parenchymal lesions to predict poor outcome **(26,32)**.

Kalita et al by using cerebral venous sinus thrombosis score (CVST score) which was computed giving 1 point for each thrombosed sinus and 3 points to superior sagittal sinus (SSS), found that the extent of CVST does not determine clinical severity, MRI lesion, and outcome, however The location of parenchymal lesion is related to thrombosis of draining sinus (**59)**.

One of the studies by Singh et al correlated parenchymal lesion with clinical outcome, found that the presentation of CVT as parenchymal lesion with mass effect is a predictor of dependant/death/poor clinical outcome at discharge and after one year (late outcome). While patients without parenchymal lesions and those with parenchymal lesion without mass effect have prediction for Independent/good clinical outcome at discharge and after 1 year. Unilateral large parenchymal lesions (> 30 ml) were found to be associated with poor outcome and the association was found to be

statistically very significant. The most common site of parenchymal lesion was parietal lobe, followed by temporal lobe, frontal lobe, thalamus, and occipital lobe. **(26)**.

CONCLUSION:

Predictors of CVT outcome is one of the greatest advances in the field of CVT is the change in outcome and prognosis of the disease throughout the years.

Predictors of CVT outcome could be classified into clinical, laboratory and radiological predictors.

Age, decreased consciousness and focal neurological deficit on admission, and expanded intracranial hemorrhage are predictors of poor outcome.

The patients who are at higher risk of unfavorable outcome should be recognized and closely monitored.

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References:

1- **Louzada, M. L., Carrier, M., Lazo-Langner, A., Dao, V., Kovacs, M. J., Ramsay, T. O., ... & Wells, P. S. (2012).** Development of a clinical prediction rule for risk stratification of recurrent venous thromboembolism in patients with cancer-associated venous thromboembolism. *Circulation*, *126*(4), 448-454.

2- **Al-Ani, F., Wang, Y. P., & Lazo-Langner, A. (2020).** Development of a clinical prediction rule for venous thromboembolism in patients with acute leukemia. *Thrombosis and Haemostasis*, *120*(02), 322-328.

3- **Girot, M., Ferro, J. M., Canhão, P., Stam, J., Bousser, M. G., Barinagarrementeria, F., & Leys, D. (2007).** Predictors of outcome in patients with cerebral venous thrombosis and intracerebral hemorrhage. *Stroke*, *38*(2), 337-342.

4- **Korathanakhun, P., Sathirapanya, P., Geater, S. L., & Petpichetchian, W. (2014).** Predictors of hospital outcome in patients with cerebral venous thrombosis. *Journal of Stroke and Cerebrovascular Diseases*, *23*(10), 2725-2729.

5- **Ay, C., Dunkler, D., Marosi, C., Chiriac, A. L., Vormittag, R., Simanek, R., ... & Pabinger, I. (2010).** Prediction of venous thromboembolism in cancer patients. *Blood, The Journal of the American Society of Hematology*, *116*(24), 5377-5382.

6- **Canhão, P., Ferro, J. M., Lindgren, A. G., Bousser, M. G., Stam, J., & Barinagarrementeria, F. (2005).** Causes and predictors of death in cerebral venous thrombosis. *Stroke*, *36*(8), 1720-1725.

7- **Li, S., Liu, K., Zhang, R., Gao, Y., Fang, H., Liu, X., ... & Xu, Y. (2019).** Lower lymphocyte to monocyte ratio is a potential predictor of poor outcome in patients with cerebral venous sinus thrombosis. *Stroke and Vascular Neurology*, *4*(3).

8- **Heit, J. A. (2015).** Epidemiology of venous thromboembolism. *Nature Reviews Cardiology*, *12*(8), 464-474.

9- **Davoudi, V., & Saadatnia, M. (2014).** Risk factors for remote seizure development in patients with cerebral vein and dural sinus thrombosis. *Seizure*, *23*(2), 135-139.

10- **Tøndel, B. G., Morelli, V. M., Hansen, J. B., & Brækkan, S. K. (2022).** Risk factors and predictors for venous thromboembolism in people with ischemic stroke: A systematic review. *Journal of Thrombosis and Haemostasis*, *20*(10), 2173-2186.

11- **De Bruijn, S. F. T. M., De Haan, R. J., & Stam, J. (2001).** Clinical features and prognostic factors of cerebral venous sinus thrombosis in a prospective series of 59 patients. *Journal of Neurology, Neurosurgery & Psychiatry*, *70*(1), 105-108.

12- **Goyal, G., Charan, A., & Singh, R. (2018).** Clinical presentation, neuroimaging findings, and predictors of brain parenchymal lesions in cerebral vein and dural sinus thrombosis: a retrospective study. *Annals of Indian Academy of Neurology*, *21*(3), 203.

13- **Leys, D., & Cordonnier, C. (2008).** Cerebral venous thrombosis: Update on clinical manifestations, diagnosis and management. *Annals of Indian Academy of Neurology*, *11*(Suppl 1), S79.

14- **Shakibajahromi, B., Haghighi, A. B., Salehi, A., Vardanjani, H. M., Ghaedian, M., Safari, A., & Mowla, A. (2020).** Clinical and radiological characteristics and predictors of outcome of cerebral venous sinus thrombosis, a hospital-based study. *Acta Neurologica Belgica*, *120*, 845-852.

15- **Masuhr, F., Mehraein, S., & Einhäupl, K. (2004).** Cerebral venous and sinus thrombosis. *Journal of neurology*, *251*, 11-23.

16- **Idiculla, P. S., Gurala, D., Palanisamy, M., Vijayakumar, R., Dhandapani, S., & Nagarajan, E. (2020).** Cerebral venous thrombosis: a comprehensive review. *European neurology*, *83*(4), 369-379.

17- **Amer, M. H. (2013).** Cancer-associated thrombosis: clinical presentation and survival. *Cancer management and research*, 165-178.

18- **Misra, U. K., Kalita, J., Chandra, S., Kumar, B., & Bansal, V. (2012).** Low molecular weight heparin versus unfractionated heparin in cerebral venous sinus thrombosis: a randomized controlled trial. *European journal of neurology*, *19*(7), 1030-1036.

19- **Aguiar de Sousa, D., Lucas Neto, L., Arauz, A., Sousa, A. L., Gabriel, D., Correia, M., ... & Ferro, J. M. (2020).** Early recanalization in patients with cerebral venous thrombosis treated with anticoagulation. *Stroke*, *51*(4), 1174-1181.

20- **Breteau, G., Mounier-Vehier, F., Godefroy, O., Gauvrit, J. Y., Mackowiak-Cordoliani, M. A., Girot, M., ... & Leys, D. (2003).** Cerebral venous thrombosis: 3-year clinical outcome in 55 consecutive patients. *Journal of neurology*, *250*, 29-35.

21- **Einhäupl, K., Stam, J., Bousser, M. G., De Bruijn, S. F. T. M., Ferro, J. M., Martinelli, I., & Masuhr, F. (2010)**. EFNS guideline on the treatment of cerebral venous and sinus thrombosis in adult patients. *European journal of neurology*, *17*(10), 1229-1235.

22- **Einhäupl, K., Bousser, M. G., De Bruijn, S. F. T. M., Ferro, J. M., Martinelli, I., Masuhr, F., & Stam, J. (2006).** EFNS guideline on the treatment of cerebral venous and sinus thrombosis. *European journal of neurology*, *13*(6), 553-559.

23- **Dinc, Y., Özpar, R., Hakyemez, B., & Bakar, M. (2021).** The relationship between early neurological deterioration, poor clinical outcome, and venous collateral score in cerebral venous sinus thrombosis. *Neurological Sciences and Neurophysiology*, *38*(3), 158.

24- **Ferro, J. M., Coutinho, J. M., Dentali, F., Kobayashi, A., Alasheev, A., Canhão, P., ... & RE-SPECT CVT Study Group. (2019).** Safety and efficacy of dabigatran etexilate vs dose-adjusted warfarin in patients with cerebral venous thrombosis: a randomized clinical trial. *JAMA neurology*, *76*(12), 1457-1465.

25- **Khorana, A. A., Kuderer, N. M., Culakova, E., Lyman, G. H., & Francis, C. W. (2008).** Development and validation of a predictive model for chemotherapy-associated thrombosis. *Blood, The Journal of the American Society of Hematology*, *111*(10), 4902-4907..

26- **Northup, P. G., McMahon, M. M., Ruhl, A. P., Altschuler, S. E., Volk-Bednarz, A., Caldwell, S. H., & Berg, C. L. (2006)**. Coagulopathy does not fully protect hospitalized cirrhosis patients from peripheral venous thromboembolism. *Official journal of the American College of Gastroenterology| ACG*, *101*(7), 1524-1528.

27- **Khorana, A. A., & Connolly, G. C. (2009).** Assessing risk of venous thromboembolism in the patient with cancer. *Journal of Clinical Oncology*, *27*(29), 4839.

28- **Huang, Y., Ding, H., Luo, M., Li, S., Xie, C., Zhong, Y., & Li, Z. (2022).** Combined analysis of clinical and laboratory markers to predict the risk of venous thromboembolism in patients with IDH1 wild-type glioblastoma. *Supportive Care in Cancer*, *30*(7), 6063-6069.

29- **Reed, R. C., & Rutledge, J. C. (2010).** Laboratory and clinical predictors of thrombosis and hemorrhage in 29 pediatric extracorporeal membrane oxygenation nonsurvivors. *Pediatric and Developmental Pathology*, *13*(5), 385-392.

30- **Potaczek, D. P., Jankowska, E. A., Wypasek, E., & Undas, A. (2016).** Iron deficiency: a novel risk factor of recurrence in patients after unprovoked venous thromboembolism. *Polskie Archiwum Medycyny Wewnętrznej= Polish Archives of Internal Medicine*, *126*(3).

31- **Caprini, J. A., Glase, C. J., Anderson, C. B., & Hathaway, K. (2004).** Laboratory markers in the diagnosis of venous thromboembolism. *Circulation*, *109*(12_suppl_1), I-4.

32- **Mu, S., Li, J., Lin, K., Fang, Y., Lin, F., Li, Z., ... & Wang, S. (2022).** Predictive factors for early-onset seizures in patients with cerebral venous sinus thrombosis. *Frontiers in Neurology*, *13*, 842807.

33- **Akboga, Y. E., Bektas, H., & Anlar, O. (2017).** Usefulness of platelet to lymphocyte and neutrophil to lymphocyte ratios in predicting the presence of cerebral venous sinus thrombosis and in-hospital major adverse cerebral events. *Journal of the neurological sciences*, *380*, 226-229.

34- **Nieto, J. A., Solano, R., Ruiz-Ribo, M. D., Ruiz-Gimenez, N., Prandoni, P., Kearon, C., ... & Riete Investigators. (2010).** Fatal bleeding in patients receiving anticoagulant therapy for venous thromboembolism: findings from the RIETE registry. *Journal of thrombosis and haemostasis*, *8*(6), 1216-1222.

35- **Pabinger, I., Thaler, J., & Ay, C. (2013).** Biomarkers for prediction of venous thromboembolism in cancer. *Blood, The Journal of the American Society of Hematology*, *122*(12), 2011-2018.

36- **Mehvari Habibabadi, J., Saadatnia, M., & Tabrizi, N. (2018).** Seizure in cerebral venous and sinus thrombosis. *Epilepsia Open*, *3*(3), 316-322.

37- **Simanek, R., Vormittag, R. C. A. Y., Ay, C., Alguel, G., Dunkler, D., Schwarzinger, I., ... & Pabinger, I. (2009).** High platelet count associated with venous thromboembolism in cancer patients: results from the Vienna Cancer and Thrombosis Study (CATS). *Journal of Thrombosis and Haemostasis*, *8*(1), 114-120.

38- **Ruíz-Giménez, N., Suárez, C., González, R., Nieto, J. A., Todolí, J. A., Samperiz, Á. L., ... & Riete Investigators. (2008).** Predictive variables for major bleeding events in patients presenting with documented acute venous thromboembolism. Findings from the RIETE Registry. *Thrombosis and haemostasis*, *100*(07), 26-31.

39- **Davoudi, V., & Saadatnia, M. (2014).** Risk factors for remote seizure development in patients with cerebral vein and dural sinus thrombosis. *Seizure*, *23*(2), 135-139.

40- **Ay, C., Vormittag, R., Dunkler, D., Simanek, R., Chiriac, A. L., Drach, J., ... & Pabinger, I. (2009).** D-dimer and prothrombin fragment 1+ 2 predict venous

thromboembolism in patients with cancer: results from the Vienna Cancer and Thrombosis Study. *Journal of Clinical Oncology*, *27*(25), 4124-4129.

41- **Pan, X., Wang, Z., Chen, Q., Xu, L., & Fang, Q. (2021).** Development and validation of a nomogram for lower extremity deep venous thrombosis in patients after acute stroke. *Journal of Stroke and Cerebrovascular Diseases*, *30*(5), 105683.

42- **Abdalkader, M., Shaikh, S. P., Siegler, J. E., Cervantes-Arslanian, A. M., Tiu, C., Radu, R. A., ... & Jovin, T. G. (2021).** Cerebral venous sinus thrombosis in COVID-19 patients: a multicenter study and review of literature. *Journal of Stroke and Cerebrovascular Diseases*, *30*(6), 105733.

43- **Pan, L., Ding, J., Ya, J., Zhou, D., Hu, Y., Fan, C., ... & Meng, R. (2019).** Risk factors and predictors of outcomes in 243 Chinese patients with cerebral venous sinus thrombosis: A retrospective analysis. *Clinical Neurology and Neurosurgery*, *183*, 105384.

44- **Khan, M., Arauz, A., Uluduz, D., Barboza, M. A., Duman, T., Cano-Nigenda, V., ... & Venost Study Group. (2022).** Predictors of mortality and functional outcome in pregnancy and puerperium-related cerebral venous thrombosis. *Cerebrovascular Diseases*, 1-8.

45- **Fei, Y., Hu, J., Li, W. Q., Wang, W., & Zong, G. Q. (2017).** Artificial neural networks predict the incidence of portosplenomesenteric venous thrombosis in patients with acute pancreatitis. *Journal of Thrombosis and Haemostasis*, *15*(3), 439-445.

46- **Tufano, A., Guida, A., Coppola, A., Nardo, A., Di Capua, M., Quintavalle, G., ... & Di Minno, G. (2014).** Risk factors and recurrent thrombotic episodes in patients with cerebral venous thrombosis. *Blood Transfusion*, *12*(Suppl 1), s337.

47- **Zakai, N. A., Wright, J., & Cushman, M. (2004).** Risk factors for venous thrombosis in medical inpatients: validation of a thrombosis risk score. *Journal of Thrombosis and Haemostasis*, *2*(12), 2156-2161.

48- **Liang, Z. W., Gao, W. L., & Feng, L. M. (2017).** Clinical characteristics and prognosis of cerebral venous thrombosis in Chinese women during pregnancy and puerperium. *Scientific reports*, *7*(1), 43866.

49- **Yii, I. Y., Mitchell, P. J., Dowling, R. J., & Yan, B. (2012).** Imaging predictors of clinical deterioration in cerebral venous thrombosis. *Journal of Clinical Neuroscience*, *19*(11), 1525-1529.

50- **Dentali, F., Gianni, M., Crowther, M. A., & Ageno, W. (2006).** Natural history of cerebral vein thrombosis: a systematic review. *Blood*, *108*(4), 1129-1134.

51- **Worsley, D. F., Alavi, A., Aronchick, J. M., Chen, J. T., Greenspan, R. H., & Ravin, C. E. (1993).** Chest radiographic findings in patients with acute pulmonary embolism: observations from the PIOPED Study. *Radiology*, *189*(1), 133-136.

52- **Vanukuri, N. K., Pedapati, R., Shanmugam, S., Hazeena, P., Rangasami, R., & Venkatasubramanian, S. (2022)**. Effect of recanalization on clinical outcomes in patients with cerebral venous thrombosis–an ambispective study. *European Journal of Radiology*, *153*, 110385.

53- **Kumral, E., Polat, F., Uzunköprü, C., Callı, C., & Kitiş, Ö. (2012).** The clinical spectrum of intracerebral hematoma, hemorrhagic infarct, non-hemorrhagic infarct, and non-lesional venous stroke in patients with cerebral sinus–venous thrombosis. *European Journal of Neurology*, *19*(4), 537-543.

54- **Wasay, M., Bakshi, R., Bobustuc, G., Kojan, S., Sheikh, Z., Dai, A., & Cheema, Z. (2008).** Cerebral venous thrombosis: analysis of a multicenter cohort from the United States. *Journal of stroke and cerebrovascular diseases*, *17*(2), 49-54.

55- **Kucinski, T., Koch, C., Eckert, B., Becker, V., Krömer, H., Heesen, C., ... & Zeumer, H. (2003).** Collateral circulation is an independent radiological predictor of outcome after thrombolysis in acute ischaemic stroke. *Neuroradiology*, *45*, 11-18.

56- **Abdalkader, M., Shaikh, S. P., Siegler, J. E., Cervantes-Arslanian, A. M., Tiu, C., Radu, R. A., ... & Jovin, T. G. (2021).** Cerebral venous sinus thrombosis in COVID-19 patients: a multicenter study and review of literature. *Journal of Stroke and Cerebrovascular Diseases*, *30*(6), 105733.

57- **Arauz, A., Vargas-González, J. C., Arguelles-Morales, N., Barboza, M. A., Calleja, J., Martínez-Jurado, E., ... & Merino, J. G. (2016).** Time to recanalisation in patients with cerebral venous thrombosis under anticoagulation therapy. *Journal of Neurology, Neurosurgery & Psychiatry*, *87*(3), 247-251.

58- **Wasay, M., Bakshi, R., Bobustuc, G., Kojan, S., Sheikh, Z., Dai, A., & Cheema, Z. (2008).** Cerebral venous thrombosis: analysis of a multicenter cohort from the United States. *Journal of stroke and cerebrovascular diseases*, *17*(2), 49-54.

59- **Montalvan, V., Neves, G., Bueso, T., Ota, R., Bushnaq, S., Windisch, T., & Bushnaq, S. (2022).** Predicting poor response to anti-coagulation therapy in cerebral venous thrombosis using a simple clinical-radiological score. *Journal of Clinical Neuroscience*, *105*, 26-30.