A dissertation on

"NEUTROPHIL TO LYPMHOCYTE RATIO AND PLATELT TO LYMPHOCYTE RATIO AS PREDICTIVE MARKERS OF CLINICAL SEVERITY IN CEREBRAL VENOUS AND SINUS THROMBOSIS"

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CERTIFICATE

This is to certify that the dissertation entitled **"NEUTROPHIL TO LYPMHOCYTE RATIO AND PLATELT TO LYMPHOCYTE RATIO AS PREDICTIVE MARKERS OF CLINICAL SEVERITY IN CEREBRAL VENOUS AND SINUS THROMBOSIS"** is a bonafide original work done by **Dr. KISHWANTH R**, in partial fulfillment of the requirements for M.D GENERAL MEDICINE BRANCH- I Examination of the Tamil Nadu Dr. MGR Medical University to be held in MAY 2020, under my guidance and supervision in 2019.

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DECLARATION

I, **Dr. KISHWANTH R,** registration number : **201711008** solemnly declare that the dissertation entitled **"NEUTROPHIL TO LYPMHOCYTE RATIO AND PLATELT TO LYMPHOCYTE RATIO AS PREDICTIVE MARKERS OF CLINICAL SEVERITY IN CEREBRAL VENOUS AND SINUS THROMBOSIS"** is done by me at Madras Medical College & Rajiv Gandhi Govt. General Hospital, Chennai during 2018 under the guidance and supervision of **Prof. Dr. S. USHALAKSHMI., M.D., FMMC**. The dissertation is submitted to The Tamilnadu Dr. M. G. R. Medical University towards the partial fulfillment of requirements for the award of M.D. Degree (Branch I) in General Medicine.

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ABBREVIATIONS

CVST	Cerebral Venous and Sinus Thrombosis
NLR	Neutrophil to Lymphocyte Ratio
PLR	Platelet to Lymphocyte Ratio
UFH	Unfractionated Heparin
LMWH	Low Molecular Weight Heparin
hs- CRP	highly sensitive C reactive Protein
RDW	Red Cell Distribution Width
PDW	Platelet Distribution Width
ISCVT	International Study of Cerebral Vein and Dural Sinus Thrombosis
SLE	Systemic Lupus Erythematosis
IBD	Inflammatory Bowel Disease
INR	International Normalized Ratio
CT	Computed Tomogram
MRI	Magnetic Resonance Imaging
ICP	Intracranial Pressure
CrCl	Creatinine Clearance

CONTENTS

INTRODUCTION

Cerebral venous and sinus thrombosis (CVST), one of the uncommon varieties of cerebrovascular events mainly affects young and middle-aged adults, and is three times more common among women than men due to the increased risk associated with pregnancy and puerperium and with oral contraceptives [1-3]. The annual incidence ranges from 0.22 to 1.57 per 100,000 with a median age of 37 years [4-6]. CVST is now known to have a more varied clinical spectrum than previously realized because of its myriad causes and presentations, leading to severe morbidity and mortality. It can be diagnosed and confirmed only by radiological imaging techniques as patients present with vague clinical symptoms which overlap with other cerebrovascular events ranging from headache to coma. For physicians working at hospitals where scope for imaging techniques are remote, a common, easily available surrogate markers would help them diagnose CVST and would help in prompt referral to a higher center for definitive treatment. Rather than discrete values like platelet count, leucocyte count, platelet and red cell distribution width and hs-crp, which can get influenced by a number of parameters, ratios like neutrophil to lymphocyte ratio and platelet to lymphocyte ratio give a more reliable prediction. As CVST is both an inflammatory and a thrombotic event, NLR and PLR has been found to be better predictors than hs-CRP or

RDW/PDW in the recent studies. According to ongoing researches, NLR is found to have higher negative predictive value and PLR to have a higher positive predictive value. This study aims to assess the usefulness of NLR and PLR as predictive markers of CVST, and correlate them with clinical severity scales.

AIMS AND OBJECTIVES

1. To assess the neutrophil to lymphocyte ratio and platelet to lymphocyte ratio in cerebral venous thrombosis
2. To assess the association between the ratios and cerebral venous thrombosis
3. To correlate the ratios with mRS and ISCVT scores.
4. To assess if the ratios can be used as predictive markers.

REVIEW OF LITERATURE

Cerebral venous and sinus thrombosis (CVST), one of the uncommon varieties of cerebro vascular events mainly affects young and middle-aged adults, and is three times more common among women than men due to the increased risk associated with pregnancy and puerperium and with oral contraceptives [1-3]. The annual incidence ranges from 0.22 to 1.57 per 100,000 with a median age of 37 years [4-6]. CVST is now known to have a more varied clinical spectrum than previously realized because of its myriad causes and presentations, leading to severe morbidity and mortality. It can be diagnosed and confirmed only by radiological imaging techniques as patients present with vague clinical symptoms which overlap with other cerebrovascular events ranging from headache to coma.

Etiology:

The factors can be divided into acquired and gentetic thrombophilia and other casuses. Among the acquired thrombophilia, pregnancy and oral contraceptive pills predominate. Genetic throbophilia includes antithrombin deficiency, protein C/S deficiency, factor V leiden mutation, G20210A prothrombin mutation, hyperhomocystenemia among which Factor V Leiden mutation remains the highest risk factor for developing the event. Other causes

include SLE, Behcet disease, granulomatosis with polyangitis, thromboangitis obliterans, IBD, and sarcoidosis[1-7].

Symptomatology:

The symptoms can be classified into three clusters which represent a spectrum of neurological manifestations.

1. Isolated intracranial hypertension syndrome (headache with or without vomiting, papilledema, and visual problems)
2. Focal syndrome (focal deficits, seizures, or both)
3. Encephalopathy (multifocal signs, mental status changes, stupor, or coma)

Symptoms can also be pertaining to multiple cranial nerve palsies, cavernous sinus thrombosis and sub arachnoid hemorrhage. The clinical symptoms and signs depend on a variety of factors including age, sex, number of sinuses/ veins involved, site of occlusion and the interval between the onset of occlusion and presentation to the hospital**. (figure.1)**

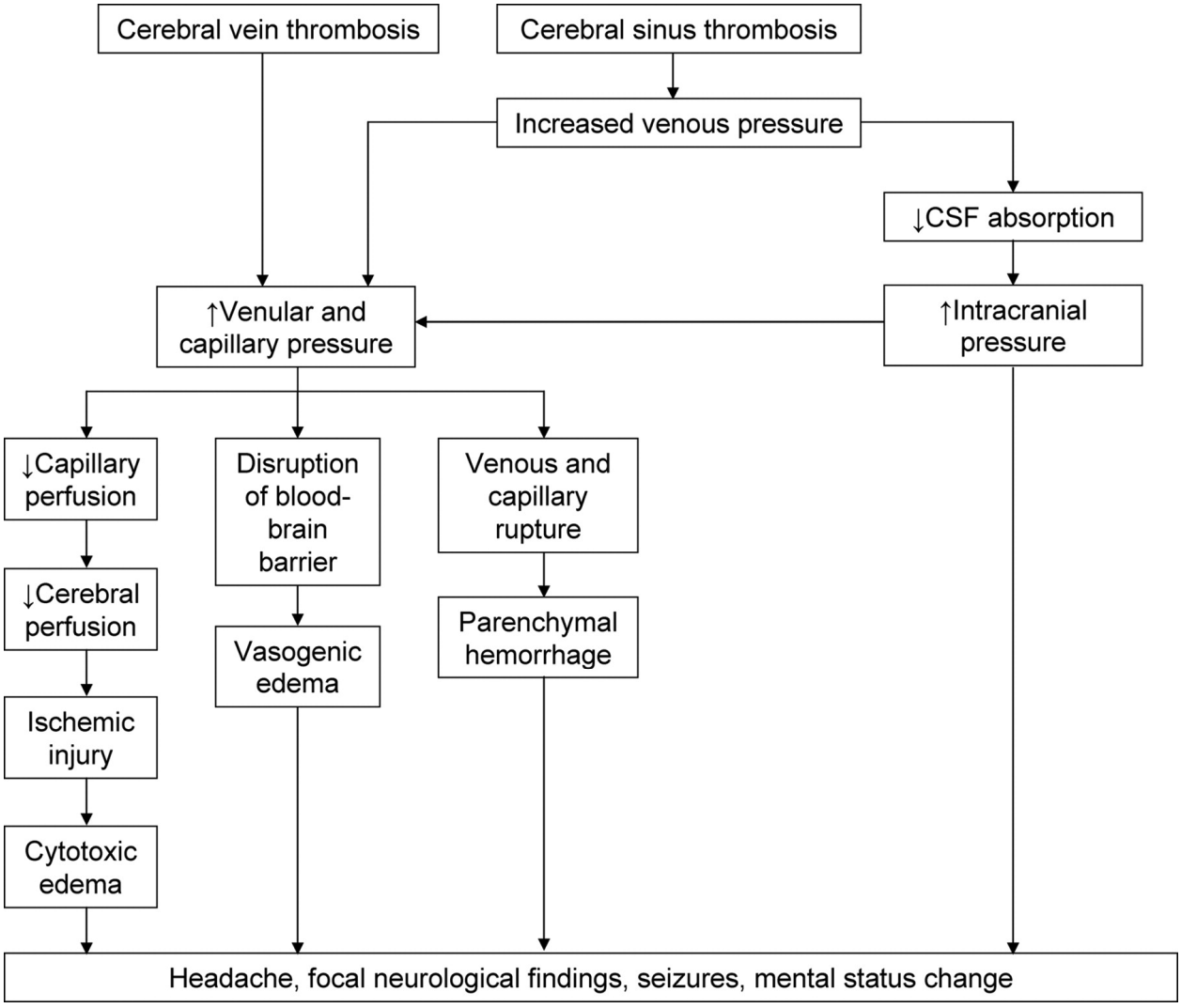

Figure 1: Pathophysiology of symptoms

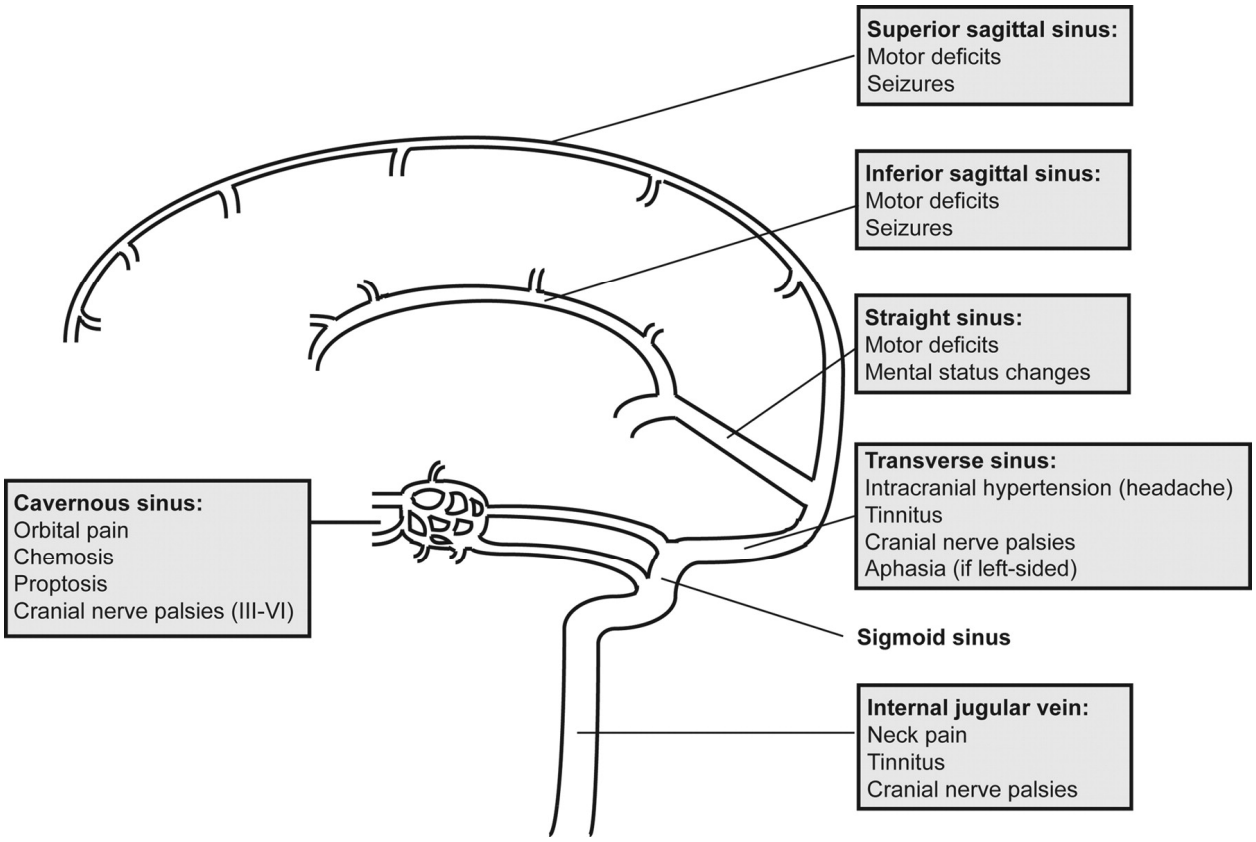

Figure 2: localization of symptoms

Headache:

Headache is the most common symptom and sometimes can be the only symptom of presentation with poor value of localization or can precede other symptoms. Headache can be acute (like thunderclap headache) , subacute, taking weeks to develop or chronic.

Isolated intracranial hypertension syndrome:

Patients can present with headache associated with visual disturbance and vomiting. The objective finding in the cases having a chronic course or who present late would be the presence of papilloedema.

Seizures:

Either focal or generalized seizures, even status epilepticus occurs more commonly in CVST when compared to other cerebro vascular events. Variables associated with seizures include supratentorial parenchymal brain lesions, sagittal sinus and cortical vein thrombosis, and motor deficits [8].

Encephalopathy

Patients can present with altered level of consciousness or loss of consciousness due to raised ICP.

Isolated sinus and vein thrombosis:

Clinical features can also vary according to the site of occlusion as follows

- Cavernous sinus – orbital pain, chemosis, protptosis and oculomotor nerve palsy
- Isolated cortical vein – sensory/motor deficits and seizures

- Sagittal sinus – motor/sensory deficits and seizures.
- Lateral sinus – pulsating tinnitus
- Lateral sinus or jugular/posterior fosssa veins – multiple cranial nerve palsies.
- Straight sinus – coma, seizures and motor deficits [9]

Severity scoring:

Though in depth clinical examination determines the clinical severity, various scoring systems are available to predict the outcome. Among which, mRS (modified Rankin Score) which describes the degree of disability/ dependence after a stroke and ISCVT (International Study on Cerebral Vein and Dural Sinus Thrombosis) that predicts the 6 months mortality rate are being used. A score > 3 represents poor prognosis in ISCVT.

Table 1: Modified Rankin Score

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

Table 2: ISCVT score

Prognostic factor	Score
Malignancy	2
Coma	2
Thrombosis of deep venous system	2
Mental disturbance	1
Male gender	1
Parenchymal hemorrhage	1

Diagnosis:

The diagnosis of CVST should be suspected in patients who present with one or more of the following:

1. New onset headache
2. Headache with features that differ from the usual pattern (eg, progression or change in attack frequency, severity, or clinical features) in patients with a previous primary headache
3. Symptoms or signs of intracranial hypertension
4. Encephalopathy
5. Focal neurologic symptoms and signs, especially those not fitting a specific vascular distribution or those involving multiple vascular territories

6. Seizures

High degree of suspicion is important in those with known prothrombotic states.

Neuroimgaing

Urgent imaging is recommended either by MRI venography or CT venography.

Non Contrast CT brain shows both direct and indirect signs of CVST. Direct signs include

- The **cord sign**, **(figure. 3a)** seen on a contrast CT or linear hyperdensity over the cerebral cortex caused by a thrombosed cortical vein

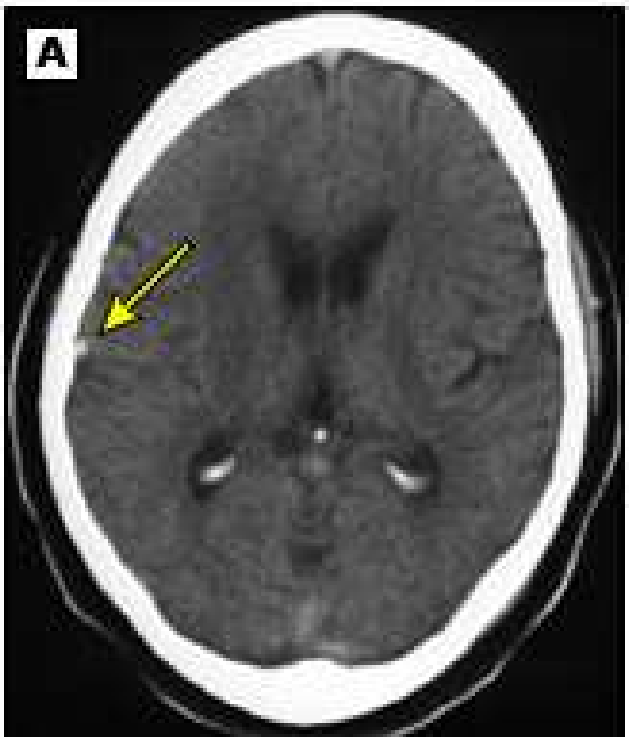

Figure.3a

- **Dense triangle sign (figure. 3a),** a triangle shaped hypredensity on the posterior part of superior sagittal sinus.

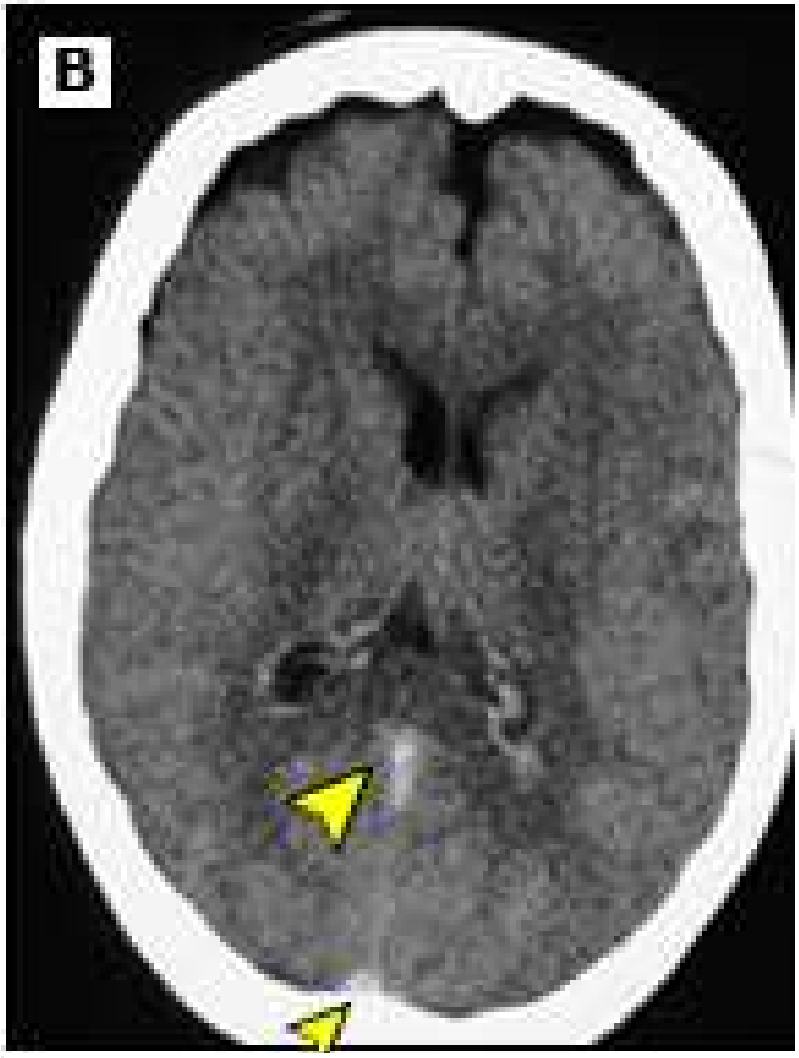

Figure.3b: Dense Triangle sign

- The **empty delta sign (figure. 3c)** (also called the empty triangle or negative delta sign), seen on contrast CT as a triangular pattern of enhancement surrounding a central region lacking contrast enhancement in the posterior part of the superior sagittal sinus.

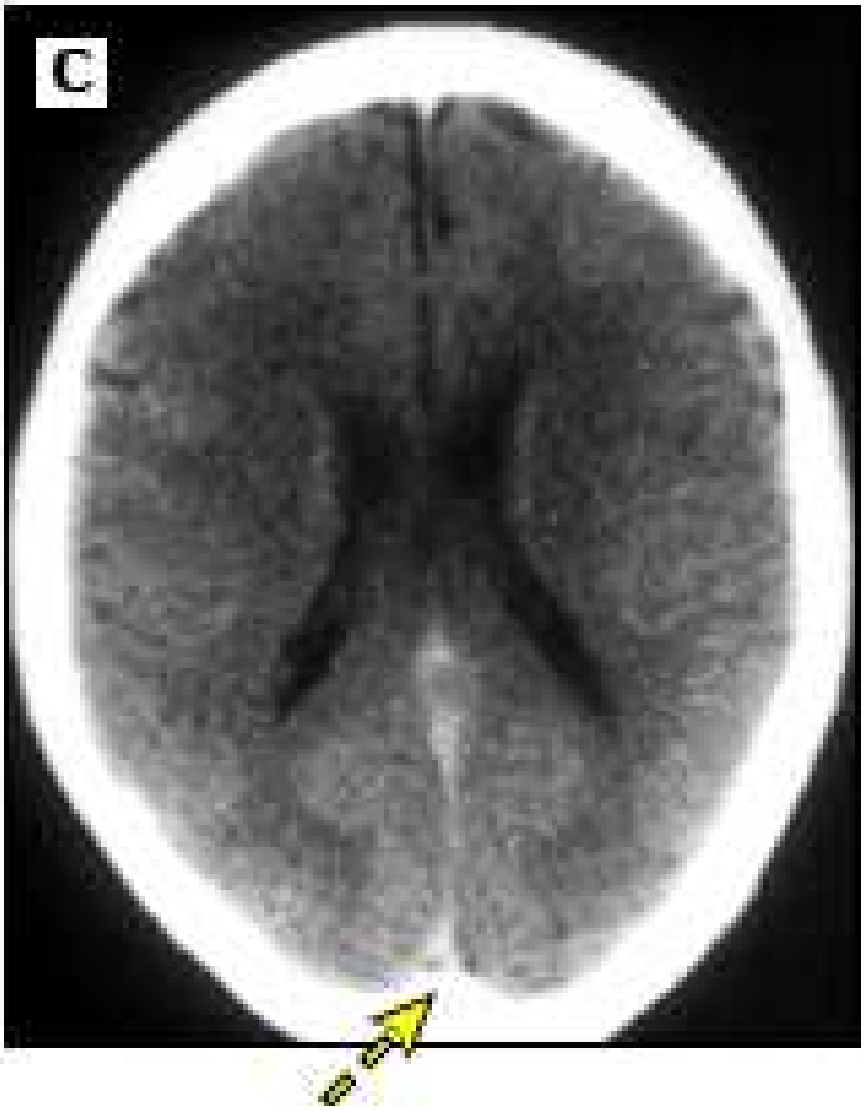

Figure.3c: Empty Delta sign

There are other indirect signs to suggest the presence of CVST, like cerebral hemorrhage, hemorrhagic infarcts or rarely sub arachnoid hemorrhage confined to the convexity. Non hemorrhagic infarcts can also be seen which don't correspond to the arterial territory [10].

CT Venography:

The centres where MRI cannot be readily availed, CT venography is a useful alternative which can demonstrate venous filling defects, sinus wall enhancement or increased collateral venous drainage [11,12]. When combined with a non contrast CT brain, the overall accuracy becomes 90 to 100 percent, depending on the occlusion site [13]. Though CT venography gives good visualization of the cerebral venous system in a short time, it has got its own disadvantages of patients developing reactions against the contrast material and that it cannot be used in pregnancy [11-13].

MRI:

T2 susceptibility- weighted sequences along with venography is the most sensitive method for demonstrating thrombus and the image depends on the age of the thrombus **(figure. 4a and 4b)**[14,15].

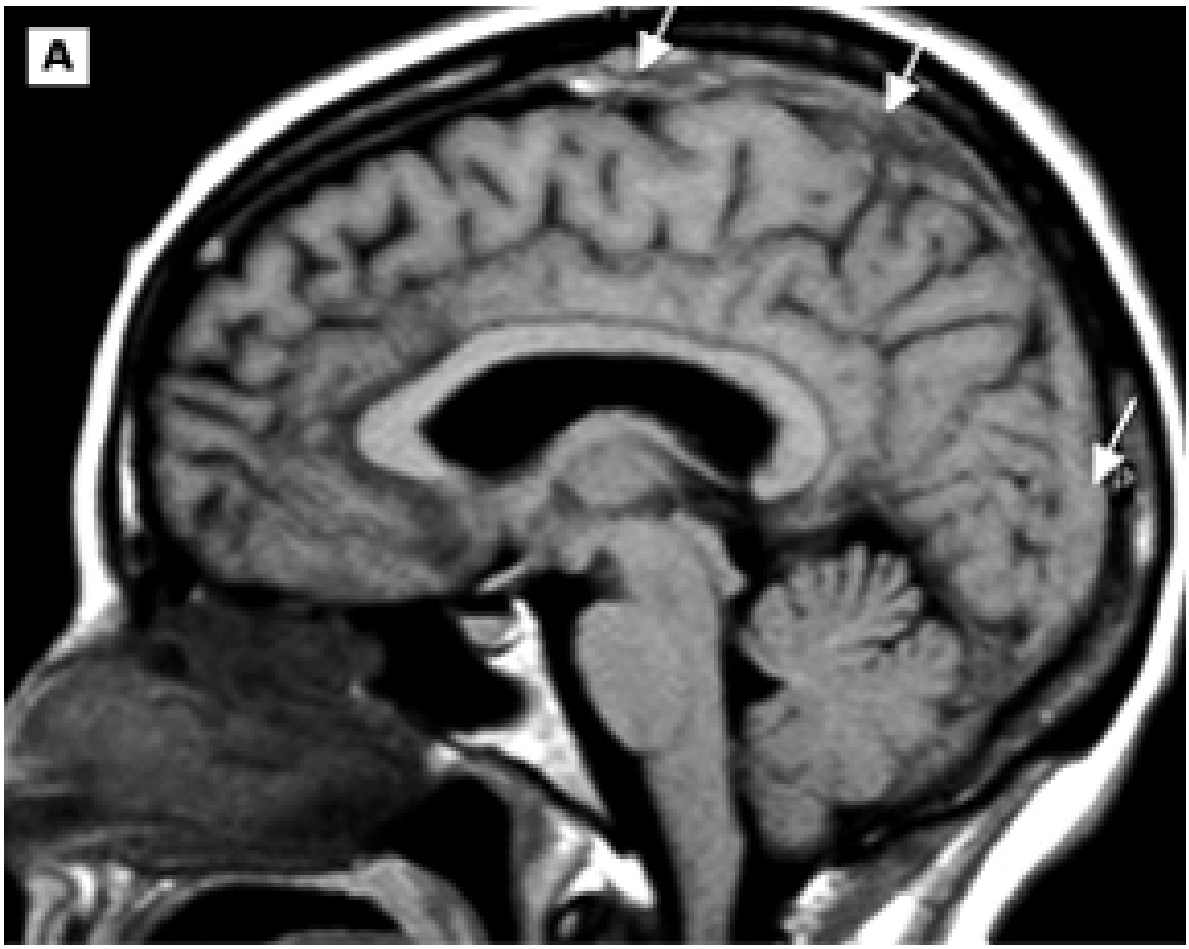

Figure 4a:
T1-weighted magnetic resonance imaging discloses an isointense signal in the superior sagittal sinus (arrows), corresponding to a thrombus (A), the corresponding

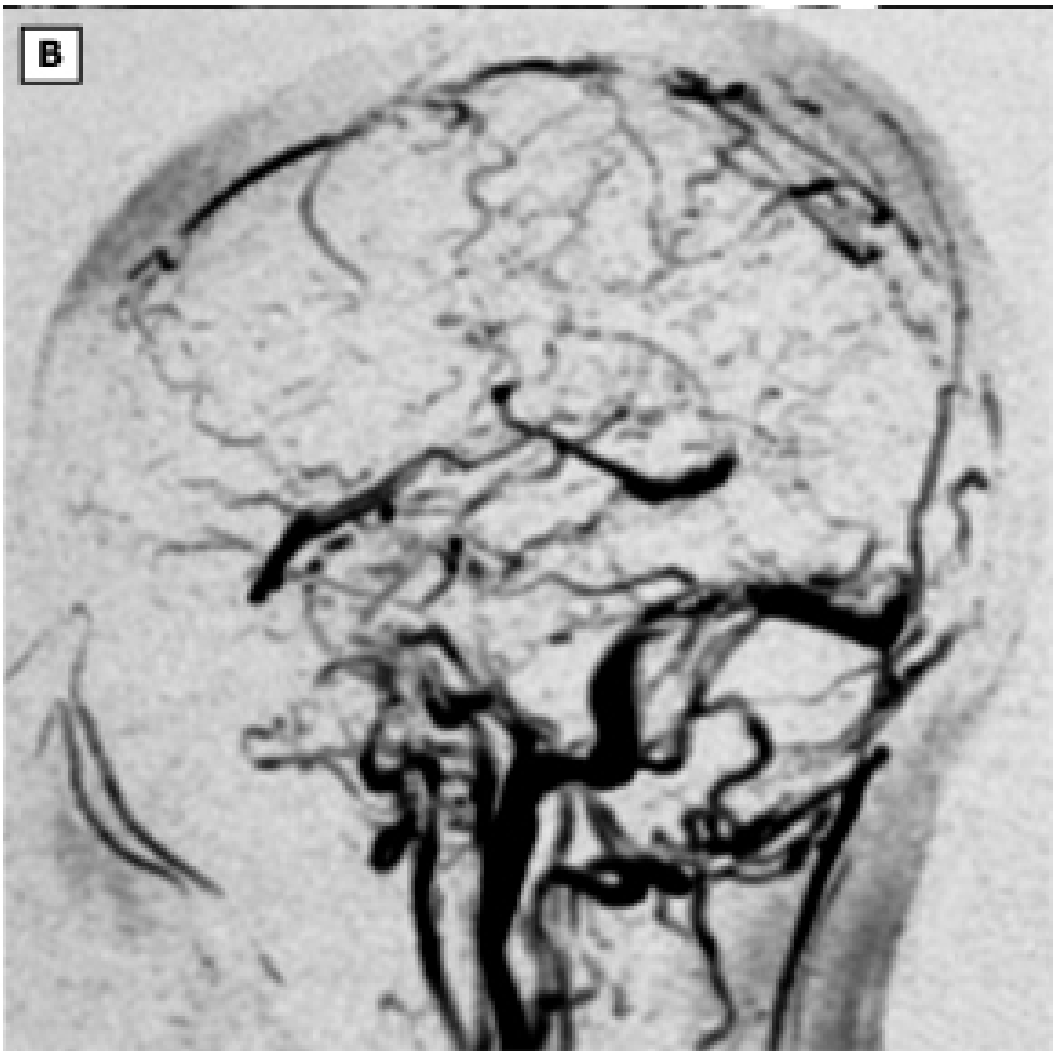

Figure.4b: Absence of flow on magnetic resonance venography

- In the first five days, the thrombosed sinuses appear isointense on T1-weighted images and hypointense on T2-weighted images
- Beyond five days, venous thrombus becomes more apparent because signal is increased on both T1- and T2-weighted images
- After the first month, thrombosed sinuses exhibit a variable pattern of signal, which may appear isointense.

Parenchymal brain lesions secondary to venous occlusion, including cerebral edema or venous infarcts appear as hypointense or isointense on T1-weighted MRI, and hyperintense on T2-weighted MRI **(figure. 5a and 5b)** while hemorrhagic infarcts appear as hyperintense lesions on both T1 and T2 MRI sequences **(fig. 6)**

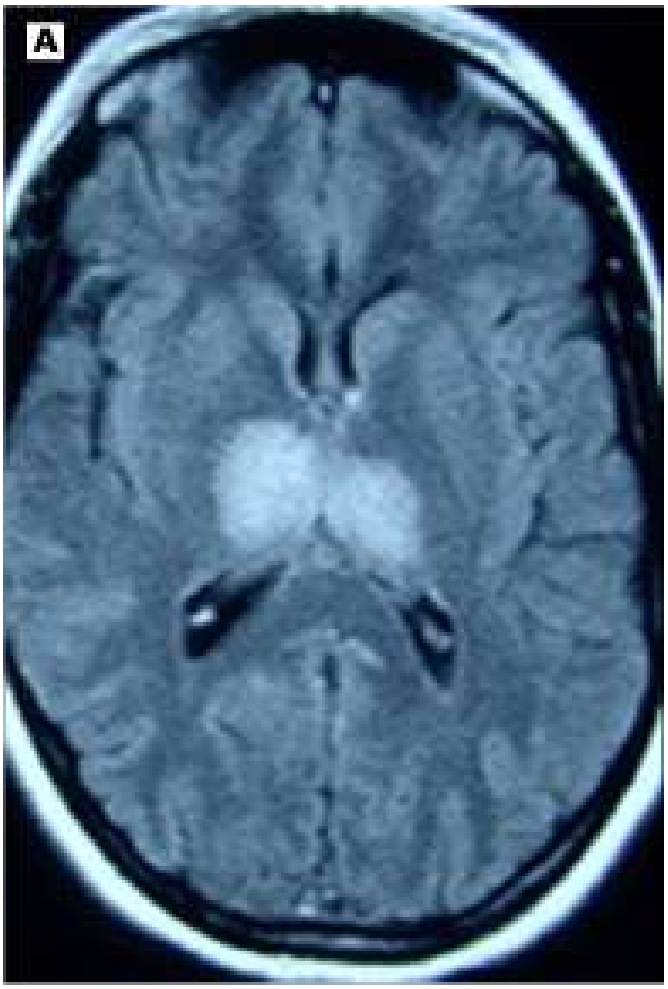

Figure 5a: Bilateral thalamic edema in a case of deep cerebral venous system thrombosis, identified in a T2-weighted FLAIR MRI.

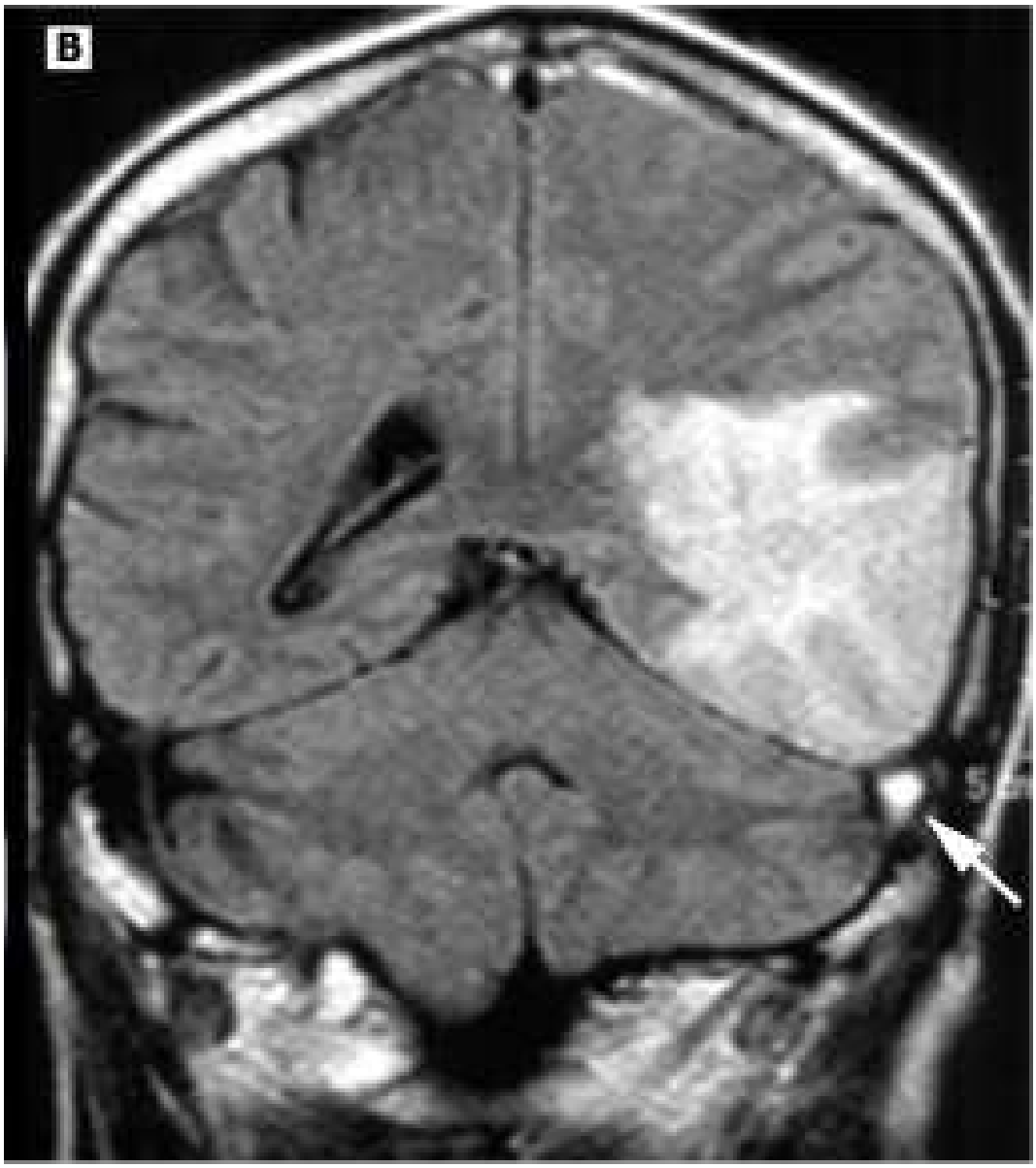

Figure.5

A) T2-weighted FLAIR MRI (coronal view) showing left temporal hemorrhagic infarct due to a thrombosis of left lateral sinus (arrow).

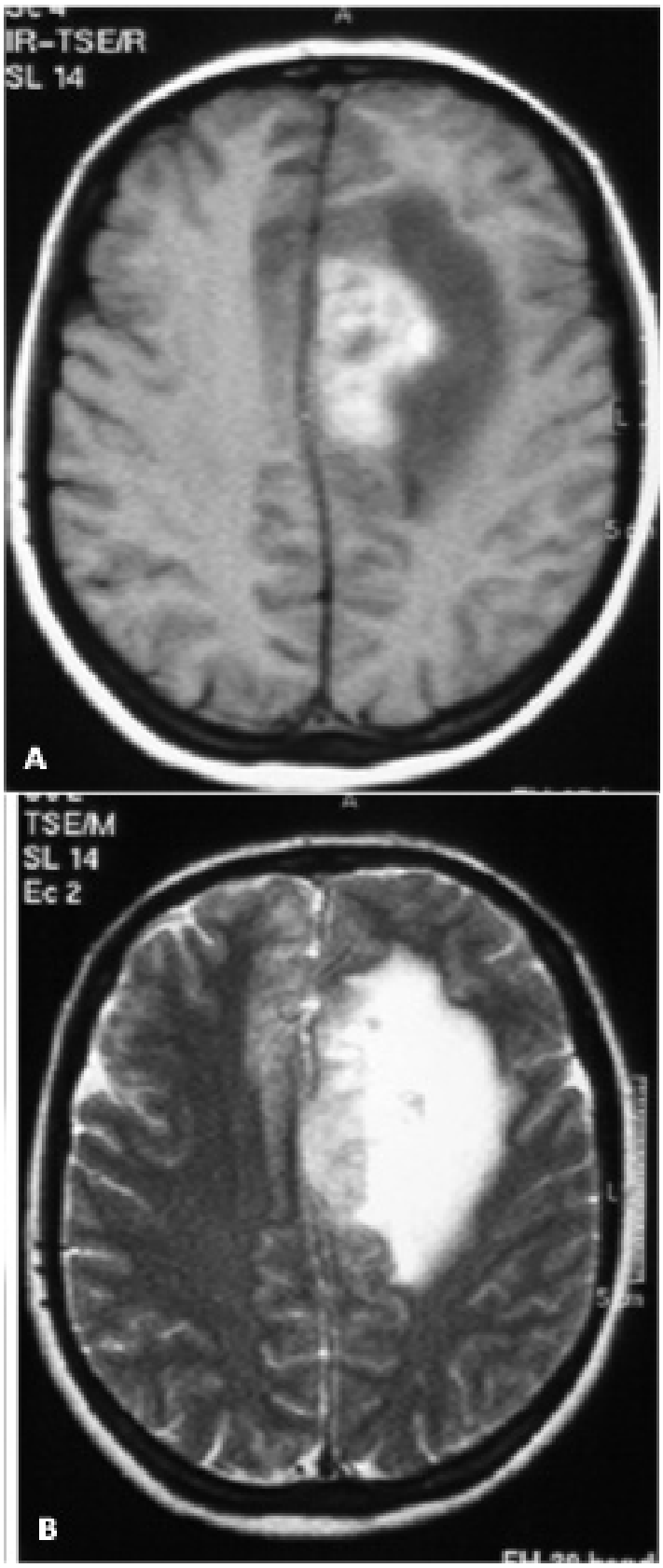

Figure 6. Brain MRI showing hemorrhagic venous infarction as hyperintense on T1- and T2-weighted sequences.

Laboratory investigations:

There is no single lab investigation which could confirm the presence of CVST in the early phases of the disease. The investigations are available only to suggest the possible conditions that contribute to the development of CVST like hypercoagulable states, infections or any other inflammatory processes. The investigations include, D- dimer, CSF analysis and hypercoagulable states evaluation.

D-dimer:

Though the values can be elevated in a case of CVST, a normal value doesn't rule it out. Thus it can be used to predict only the possibility of CVST.

Lumbar puncture:

Lumbar puncture can be useful exclude meningitis in a patient with CVST. It can also be therapeutic in reducing the CSF pressure when vision is threatened. Performing a lumbar puncture in a patient with CVST is not harmful as a study conducted by Canhao et al [16].

Evaluation of hypercoagulable states:

When appropriate, screening should include:

- Antithrombin
- Protein C
- Protein S
- Factor V Leiden
- Prothrombin G20210A mutation
- Lupus anticoagulant, anticardiolipin, and anti-beta2 glycoprotein-I antibodies

Though no underlying etiology or risk factor for CVT can be found in approximately 13 percent of adult patient, it is important to continue searching for a cause even after the acute phase of CVT, as some patients may have a condition such as the antiphospholipid syndrome, polycythemia, thrombocythemia, malignancy, or inflammatory bowel disease that can be discovered weeks or months after the acute phase. If blood picture shows abnormal anemia or hemolysis a search of paroxysmal nocturnal hemoglobinuria (PNH) should be ensued.

Differential Diagnosis:

- **Idiopathic intracranial hypertension**: This condition has to be considered when patients present with signs of raised ICT like, headache with or without vomiting, papilledema and visual problems.
- **Vascular (arterial) events/ infections**: suspected in patient presenting with focal neurological deficits.
- **Demyelination/ inflammations**: suspected in patients with multifocal deficits, mental changes, stupor or coma.
- **Pre-eclampsia or eclampsia:** suspected in pregnant women.

Treatment:

Treatmen need to be started as soon as the diagnosis is confirmed, consisting of reversing the underlying cause when known, control of seizures and intracranial hypertension, and antithrombotic therapy. Anticoagulation is the mainstay of acute and subacute treatment for CVST.

Management after acute phase:

Acute antithrombotic therapy:

The main aim of treatment in CVST includes:

- To recanalize the occluded sinus/vein

- To prevent the propagation of the thrombus, namely to the bridging cerebral veins
- To treat the underlying prothrombotic state, in order to prevent venous thrombosis in other parts of the body, particularly pulmonary embolism, and to prevent the recurrence.

Early anticoagulation:

Heparin, either unfractionated (UFH) or LMWH (Low Molecular Weight Heparin) is drug of choice for treatment, even if the patient presents with hemorrhagic infarcts. LMWH has proven to be superior to UFH, unless there are contraindications like renal failure [17, 18]. There appears to be a very minimal risk of intracerebral bleed, heparin is still used as researches prove that the mechanism of intracerebral bleeding in CVST is due to increased venous pressure and blockade resulting in rupture of venules [19]. European Stroke Organization guidelines for the diagnosis and treatment of cerebral venous thrombosis, American Academy of Chest Physicians (ACCP), American Heart Association/American Stroke Association (AHA/ASA) recommend acute initiation of heparin followed by a switch to oral anticoagulants for 3-6 months, irrespective of the presentation (hemorrhagic/non hemorrhagic) based on whether the thrombosis was due to a provoked or an unprovoked cause [20-22].

Thrombolysis and endovascular procedures:

Such procedures are not recommended especially in patient with low risk factors for poor outcome like altered GCS.

Elevated ICP:

ICP can be elevated by a number of causes including multiple large hemorrhagic lesions, infarcts or edema. Routine management include head end elevation, osmotic agent infusion, mild sedation if indicated, ICU admission, hyperventilation to target PaCO2 between 30-35 mmhg and ICP monitoring. Highly invasive procedures like hemicraniectomy are reserved for those with impending herniation due to unilateral lesion [23]. Other methods like therapeutic LP, steroid administration, ventricular shunting have not been proven to be beneficial.

Seizures:

Patients presenting with seizures or those with supratentorial lesions like edema, infarcts or hemorrhage on imaging need seizure prophylaxis. There are high chances of seizures in those with risk factors and not on prophylaxis in the early phases of illness (within two weeks of presentation)[24].

Antibiotics:

Patients with associated meningitis or otitis media should be started on antibiotics to prevent further episodes of thrombosis.

Long term anticoagulation and choice of anticoagulants:

Long term anticoagulation is needed to prevent future episodes of CVST and other forms of extracerebral thrombosis including DVT and PTE [25]. The most preferred anticoagulant is warfarin, a vitamin k antagonist to maintain an INR between 2 and 3 [20]. For patients with malignancy who do not have severe renal insufficiency (CrCl < 30 ml/min), LMWH is preferred than oral vitamin K antagonists. The efficacy of direct thrombin inhibitors and factor Xa inhibitors in preventing future CVST episodes are still under research.

There is no definitive evidence for the exact duration of anticoagulant therapy. Recommendations based on clinical trials are as follows [20-22].

- For patients with a provoked CVT associated with a transient risk factor, anticoagulation is continued for three to six months.
- For patients with an unprovoked CVT, anticoagulation is continued for 6 to 12 months.

- For patients with recurrent CVT, venous thromboembolism after CVST, or a first CVT with a severe, anticoagulation may be continued indefinitely.

Aspirin: Aspirin is recommended in patients who cannot tolerate oral anticoagulation though the efficacy has not been tested in multi centric trials.

Seizures: AED should be continued until seizure-free for atleast one year [26].

Headache: Azetazolamide or furosemide can be added.

Visual impairment: Long standing raised ICP causes papilledema and visual impairment though absolute visual loss is a rare event. Serial monitoring of visual acuity and fundus helps in management.

Pregnancy: A history of CVST, including pregnancy or peurperium induced event is not a contra indication for future pregnancies. Patient with such history should be administered LMWH during subsequent pregnancy and peurperium and must avoid pregnancy while on warfarin therapy [20, 27, 28]. Women with prior thrombotic events should also be advised to avoid OCP.

Prognsois:

Predictors of mortality at 30 days in the ISCVT were as follows [29]:

- Depressed consciousness
- Altered mental status
- Thrombosis of the deep venous system
- Right hemisphere hemorrhage
- Posterior fossa lesions

The main cause of acute death with CVT is transtentorial herniation secondary to a large hemorrhagic lesion [29]. Other causes of early death include herniation due to multiple lesions or to diffuse brain edema, status epilepticus, medical complications, and pulmonary embolism.

Predictors of poor long-term prognosis in the ISCVT were as follows [30]:

- Central nervous system infection
- Any malignancy
- Thrombosis of the deep venous system
- Hemorrhage on head CT or MRI
- Glasgow coma scale score <9 on admission
- Mental status abnormality

- Age >37 years
- Male gender

The risk of recurrent CVT is approximately 2 to 4 percent, while the risk of recurrent venous thromboembolism in other locations after CVT ranges from 4 to 7 percent [33, 34].

Good outcomes are associated CVST presenting as just a raised ICP [20, 31] and poor outcomes are associated with longer diagnostic delay [32]. Since the prognosis of CVST depends the time at which treatment is initiated, it becomes crucial to diagnose the condition as early as possible. The health care centers in remote areas where the access to the imaging techniques is limited or even impossible, diagnosis of such a condition becomes challenging as it presents with a wide range of symptoms. So a simple clinical or laboratory marker helps in triaging the patients and in prompt referral to higher centers where imaging facilities are available and for expert management. In search of such a common, easy-to-do marker, keeping in mind that CVST involves both thrombotic and inflammatory processes, the neutrophil count and platelet counts were chosen to predict the possibility of the disease. But as an increased count is not specific for any disease, ratios were evolved and studied in various clinical conditions.

Neutrophil to lymphocyte ratio and platelet to lymphocyte ratio were the first ratios to be studied in various clinical events like stroke and Myocardial Infarction [35-37].

Markers:

Any threat to the internal milieu will evoke a protective response called inflammation where in the various lineages of blood cells come into play to restore the normal homeostasis. Inflammation recruits cells of all blood lineages including granulocytes and non granulocytes. An important supporting branch of inflammation is an event called thrombosis. Inflammation and thrombosis are so intertwined with each other that both the processes cannot be delineated separately in an acute event. The two most constant cells to take part are neutrophils and platelets.

Neutrophils:

Neutrophils, the most abundant circulating phagocytes, are the first cells recruited into sites of infection and inflammation. They are attracted by a variety of chemotactic factors generated at these sites. These factors are recognized by the N-formylmethionine (N-fmet) PRR for N-formyl bacterial oligopeptide and by receptors for complement-derived C5a, leukotriene B4 (secreted by numerous immune cells), and the neutrophil chemokine interleukin-8 (IL-8), which is

secreted by activated innate immune cells and epithelial cells. These cells not only take part in immunity at the site of infection or inflammation but also help in tissue repair at injured sites [38].

Any tissue damage would result in release of damage associated molecular patterns (DAMPs) from necrotic cells and chemokines from the surrounding endothelial cells. These substances attract the neutrophils to the damaged site, a process called chemotaxis. All of these chemoattractants diffuse from the site of infection or injury to provide a chemotactic gradient for neutrophil migration and to further activate neutrophils as they transmigrate. The neutrophils promote tissue repair by scavenging cellular debris, stimulating angiogenesis and activating macrophages towards reparative phase. Recent studies have proven that these cells are capable of *de novo* synthesis of proteins for cytokine production and membrane receptor expression, thus clustering into subpopulations. As a result, different subpopulations of neutrophils have now been identified under both physiological and disease states. Steady-state-associated neutrophils include cluster of differentiation (CD) 177+ cells, olfactomedin 4 (OLFM4)+ neutrophils, proangiogenic neutrophils (PAN), neutrophils undergoing reverse migration, and aged neutrophils [39,40]. Thus neutrophils get activated, get multiplied into subpopulation and cater all the events of any acute or chronic inflammatory process **(figure.7)**

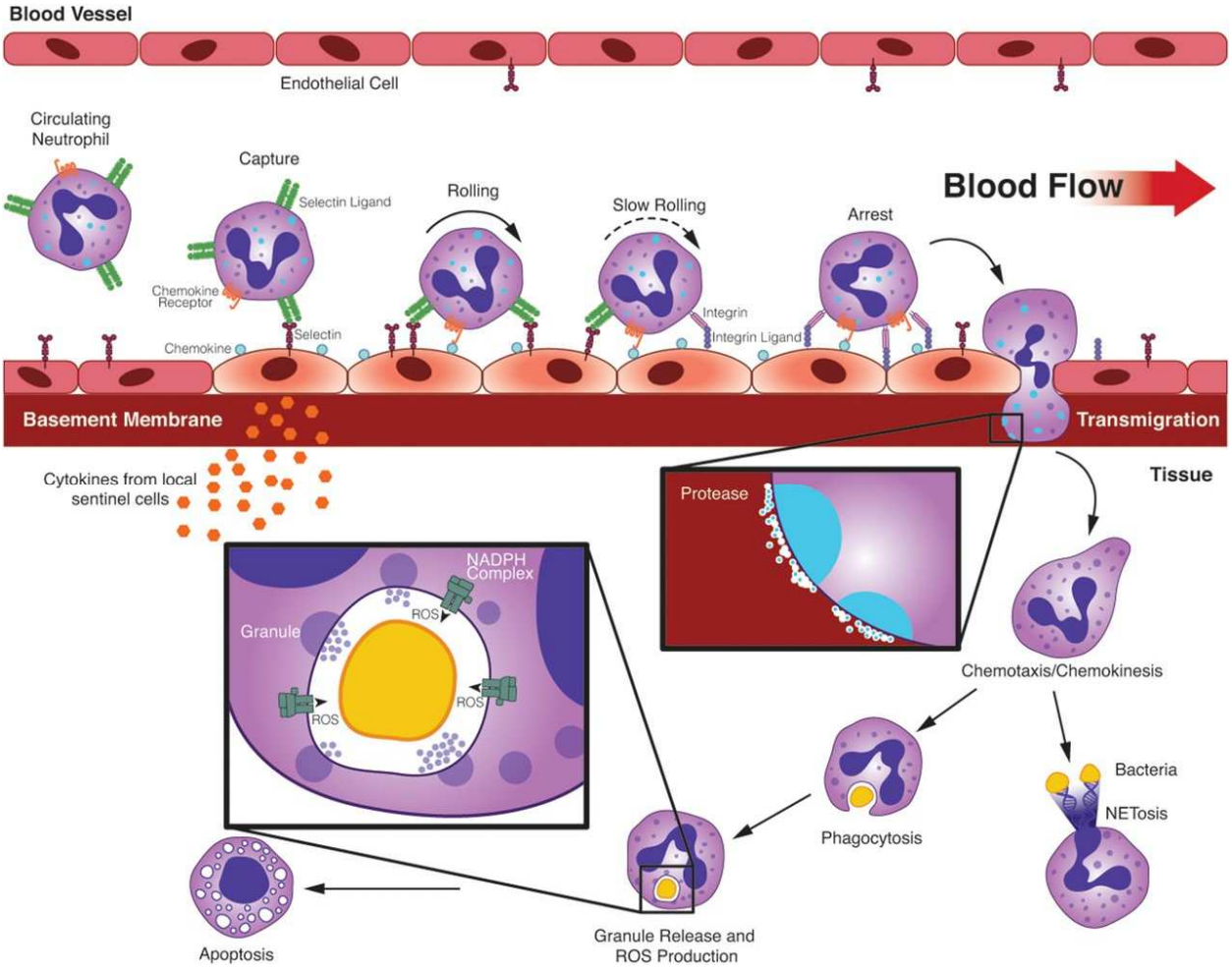

Figure.7: Neutrophil recruitment

Platelets [39]**:**

Platelets are a group of cell fragments formed from megakaryocytes which serve the process of hemostasis. The functions include adhesion to the site of endothelial injury, activation and secretion, aggregation, interaction with coagulation factors. Whenever there is a acute disease process causing endothelial damage, the endothelial components like collagen, ADP, epinephrine and thrombin among which collagen and thrombin are the most powerful activators of platelets. Following activation, the platelets undergo significant shape changes and adhere to the subendothelial vWF and this process is mediated by a cell surface protein, GPIb/IX/V complex.

Activated and adhered platelets undergo further conformational changes and another cell surface protein, GPIIb/IIIa gets activated resulting in large aggregates of platelets. Platelet aggregates secrete alpha granules containing fibrinogen, vWF, PDGF, platelet factor -4, p – selectin and dense granules containing ADP, ATP, histamine and serotonin. Each component takes part in the hemostatic process simultaneously along various pathways. This in turn initiates the coagulation cascade with a balance maintained between procoagulant and anticoagulant activities **(figure. 8)**.

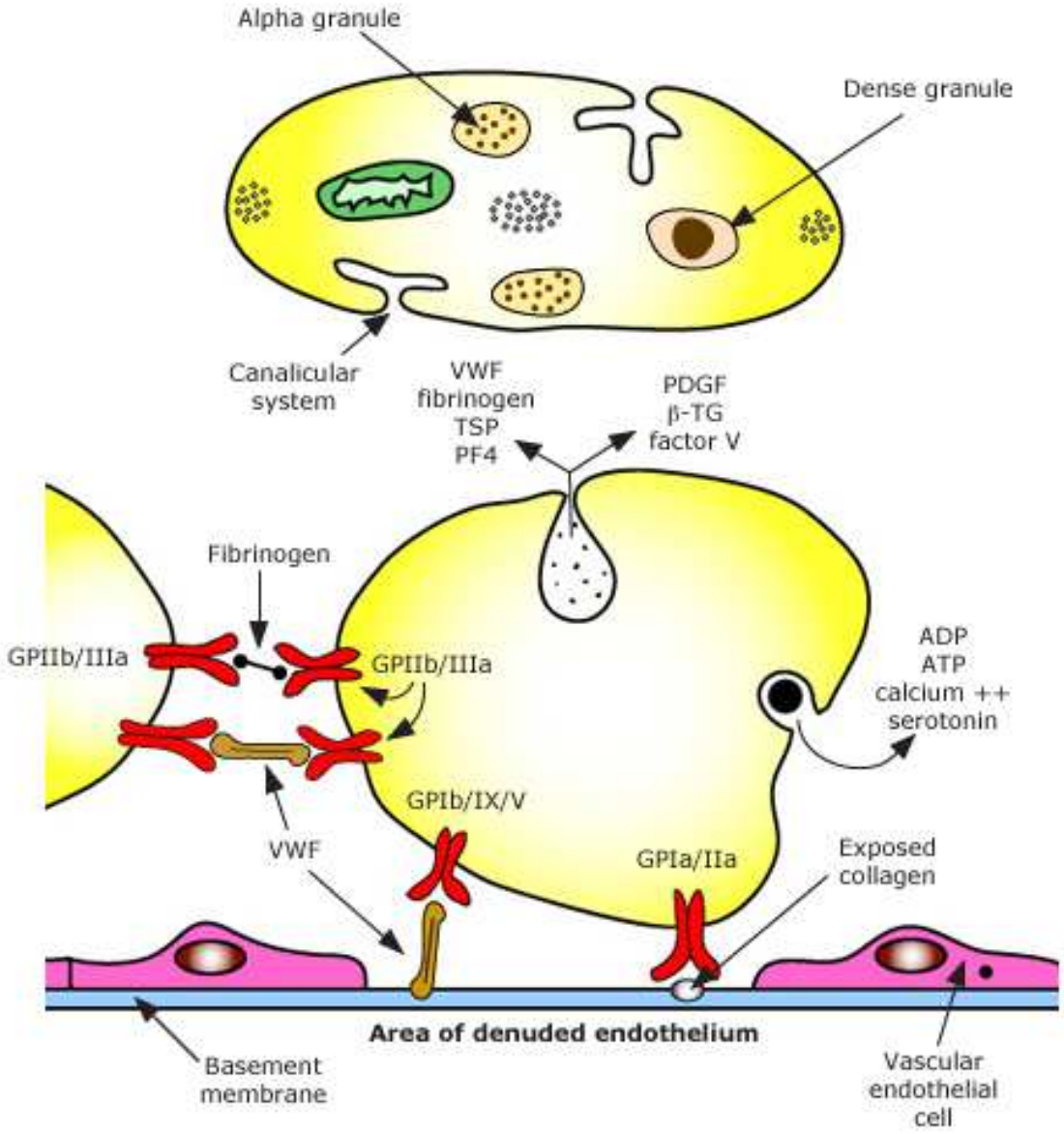

Figure.8: Platelet activation

Neutrophil – Platelet inteplay.

The role of platelets in inflammation have been studied extensively which led to the following conclusions.

- Platelet factor – 4 was capable of killing parasites like plasmodium
- Activated protein C (anticoagulant), binds to endothelial protein C receptor (EPCR) forming a complex that cleaves endothelial protease activated receptor (PAR-1) resulting in anti-inflammatory and anti-apoptotic processes.
- Carboxypeptidase B2 can inactivate C3a and C5a, the major anaphylotoxins.
- Neutrophils in response to damage associated molecular pattern (DAMPs) or pathogen associated molecular pattern (PAMPs), deliver tissue factor to the damaged site and can form neutrophil extracellular traps (NETs) **(figure.9)** that activate factor XII and vWF.
- Factor VIII and X have antimicrobial activities acting as opsonins.

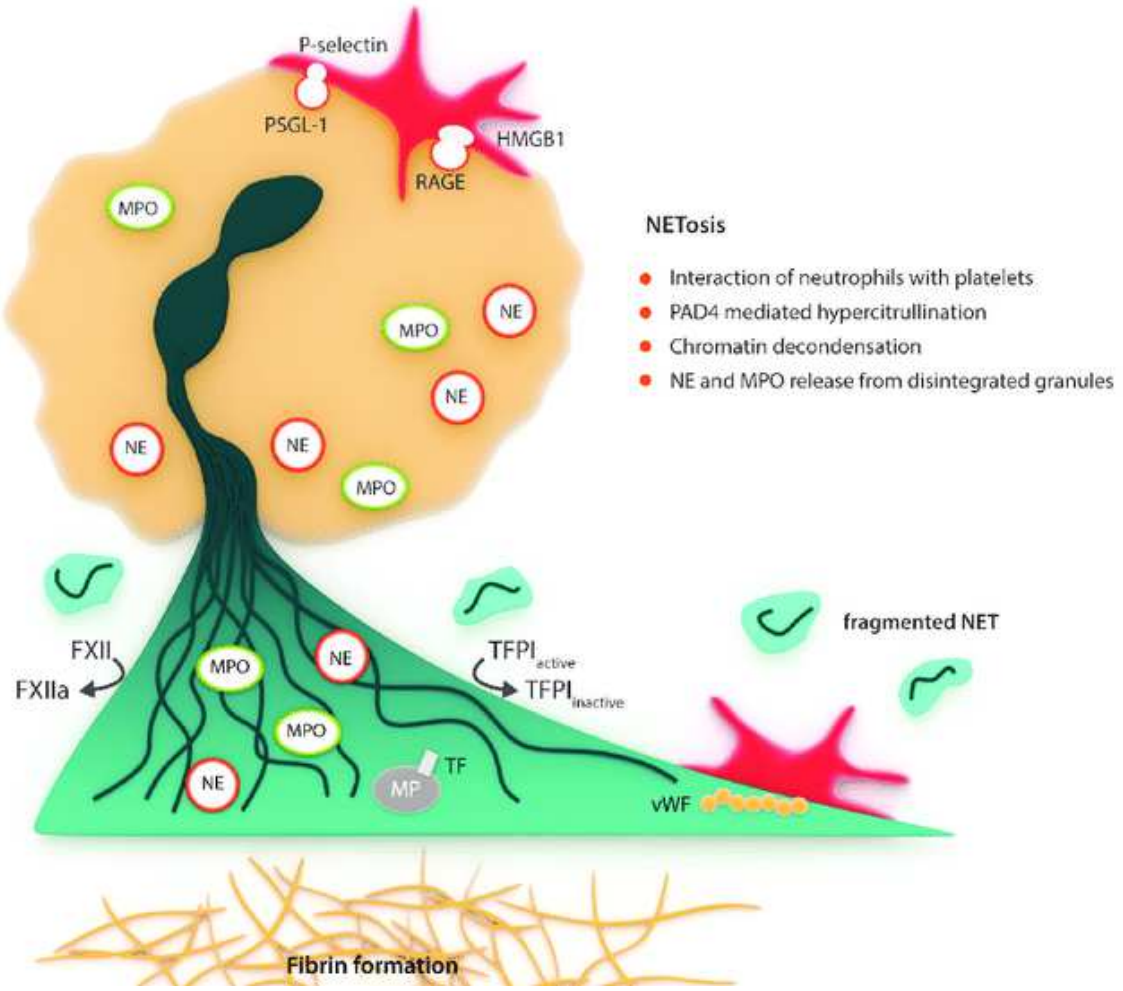

Figure.9: NETs

Lymphocytes [40]**:**

The primary tissues responsible for the initial generation of B and T lymphocytes are the bone marrow and thymus, respectively. Secondary lymphoid tissues include lymph nodes, spleen, tonsils, and lymphoid aggregations in the mucosa of the gastrointestinal and respiratory tracts. Within these secondary lymphoid tissues B and T cells are largely segregated, with B cells mainly

localized to follicles and T cells in the interfollicular areas. Lymphocytes generally constitute 8 to 33 percent of WBCs in peripheral blood.

ALC is calculated as follows:

ALC (cells/microL) = WBC (cells/microL) x percent lymphocytes ÷ 100

Lymphocyte subsets:

- T cells (CD3+)
- B cells (CD20+)
- NK cells (CD56+)

- **T lymphocyte subtypes**
  - Helper/inducer T cells (CD4+)
  - Suppressor/cytotoxic T cells (CD8+)

Lymphocyte differentiation and maturation are life-long processes that take place in the bone marrow and secondary lymphoid organs. Lymphocytosis may be caused by increased production, redistribution (from bone marrow and/or secondary lymphoid organs), and/or decreased cell death (eg, from impaired apoptosis in some lymphoproliferative disorders). Various causes of lymphocytosis differ in the contribution from each of these mechanisms. Increased lymphocyte production may be due to a malignant process or in response to an infectious or inflammatory stimulus. Reactive processes may lead to expansion of one or more subsets of lymphocytes.

The role of lymphocytes in thrombosis, though not direct, is facilitated by the presence of platelets. The role of lymphocyte involvement in thrombosis was studied in atheromatous plaques in vitro. When human blood was perfused through a collagen coated parallel plate flow chamber, platelets markedly enhanced the lymphocyte adhesion. This adhesion was inhibited by P-selectin, GPIIb/IIIa blocking agents, CD40L. This adhesion was more pronounced in the T cell type more than the B cells. Recruitment of lymphocytes to the site of tissue injury results in release of reparative cytokines thus helping in healing process [41].

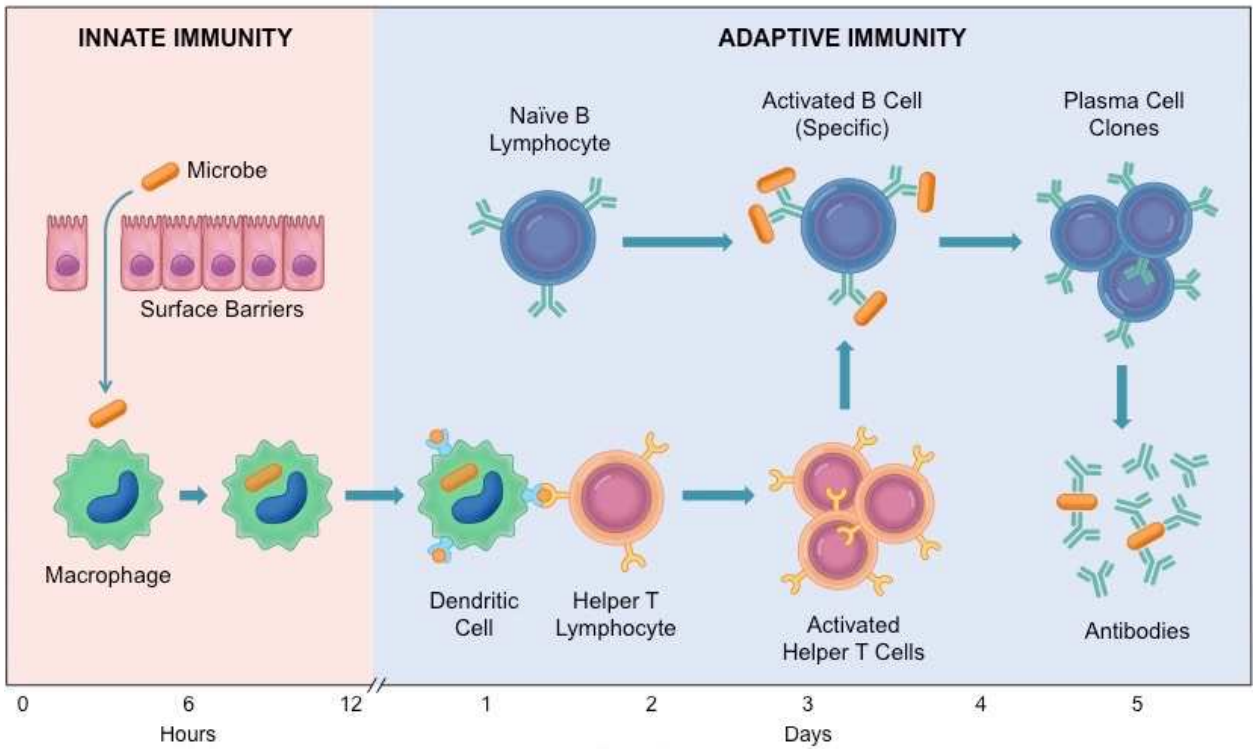

Figure.10: Lymphocytes

Neutrophil to lymphocyte ratio:

There is a close relationship between inflammation and thrombosis and growing evidence that neutrophils and platelets play a role in venous thromboembolism [42, 43]. Endogenous cortisol and catecholamines may be major drivers of the NLR. Increased levels of cortisol, catecholamines and various cytokines are known to increase the neutrophil count while simultaneously decreasing the lymphocyte count [44, 45]. NLR increases rapidly following acute stress (<6 hours) [46]. This prompt response time may make NLR a better reflection of acute stress than lab values which are more sluggish to respond, like shift to the left of Arneth index.

NLR may be calculated using either *absolute* cell counts or *percentages*, as shown:

$$\text{NLR} = \frac{\text{absolute neutrophil count (or) relative \% of neutrophils}}{\text{Absolute lymphocyte count (or) relative \% if lymphocytes}}$$

NLR has been described to predict the prognosis in acute MI and many different types of cancer. Generally, a higher NLR is correlated with high mortality and poor prognosis. The values are smaller in Asian population when compared to the rest of the world. According to recent studies, the mean NLR of all other races was around 2 except in non Hispanic blacks. NLR also changes according to age

and gender probably due to the effect of sex hormones on pre-menopausal females. NLR is comparatively higher in premenopausal females when compared males of the same age while it is the reverse in populations >50 years of age. According a large study conducted in South Korea between 2014-2016, the mean NLR for males and females across all ages were found to be 1.63 (+/- 0.76) and 1.66 (+/- 0.88) respectively [47]. Any value above 3 is considered abnormal or raised.

Clinical utility of NLR [48]:

- To differentiate patients having different illnesses but presenting with similar complaints.
- Prognostication for patients with a known disease
- Individual trajectory over time.
- Diagnosis of bacteremia or septic shock.

Limitations of NLR [49]:

The use of NLR as a disease marker has extended into a wide variety of diseases like, MI, carcinoma, rheumatological disorders and many others. Yet it suffers certain pitfalls which includes

- **Exogenous steroid administration:**

Steroid administration induces marrow towards leucocyte production. It also causes the marginated pool of neutrophils to enter the circulation.

- **Active hematological disorder:**

Any leukemia affects the neutrophil count either in positive or negative manner.

- **Chemotherapy and other drugs:**

Chemotherapy causes myelosuppression. The degree and pattern of suppression depends on the individual drugs. On the other hand, administration of colony stimulating factors increase the neutrophil counts disproportionately.

- **HIV:**

The utility of NLR in these patients is under study. Patients with HIV can have a high baseline NLR due to chronic lymphopenia.

- Pre analytical or sampling errors.

NLR in different studies:

- A recent meta-analysis of NLR for the diagnosis of appendicitis pooled 17 studies to reach the following conclusions NLR >4.7 were 89% sensitive and 90% specific for the diagnosis of appendicitis.NLR >8.8 is 77% sensitive and 100% specific for a diagnosis of complicated appendicitis [50]. The study proved that NLR was not only able to diagnose appendicitis but also differentiate between complicated and uncomplicated appendicitis. It seems clear that NLR is a considerable improvement upon the white blood cell count and should arguably *replace* the white blood count in any diagnostic consideration.
- Ljungstrom et al evaluated the performance of several markers among a population of 1,572 patients admitted to the emergency department with a clinical suspicion of sepsis. No single test was found significant. Only a battery of tests was able to measure the outcome of the patients in sepsis. Overall, NLR had similar performance compared to lactate or procalcitonin [51] .
- Several studies have evaluated the use of NLR to predict mortality in pulmonary embolism. Meta-analysis suggests that NLR may be more strongly predictive of mortality than troponin. Though 2D ECHO and CT Pulmonary Angiogram provides accurate diagnosis in this scenario, one potential role of NLR could be an early red

flag that the patient is high-risk, because the NLR will generally be obtained with the initial laboratory panel [52, 53].

- Wang 2018 reported NLR trends among patients with spontaneous intracranial hemorrhage. Non survivors experienced an increase in NLR over 24-48 hours, whereas survivors had a stable NLR. At baseline, all patients had fairly low NLR, suggesting that intracranial hemorrhage doesn't necessarily trigger a strong systemic stress response [54].

Platelet to lymphocyte ratio:

Platelets secrete and express a large number of substances that are important mediators of coagulation, thrombosis, and inflammation and their count and volume determined by hematopoiesis are affected by the systemic inflammatory state. Platelets act as acute phase reactants i.e., their values increase during inflammation due to an acute rise in serum cortisol levels. Thrombocytosis and the platelet interaction with T lymphocytes are accompanied by a shift from pro inflammatory to anti-inflammatory environment. Over the past decade, PLR has emerged as a predictive marker of neoplastic, prothrombotic and metabolic diseases.

PLR can be calculated as:

$$PLR = \frac{\text{Absolute platelet count}}{\text{Absolute lymphocyte count (or) relative \% if lymphocytes}}$$

PLR better predicts systemic inflammation when compared to either platelet or lymphocytes alone. There appears to be a strong correlation between PLR and venous thromboembolism [55, 56]. The mean reference value for PLR is 97.51 ± 31.67 [57].

Clinical utility of PLR [48]:

- More of a prognostic marker than a diagnostic marker.
- Studied in immune-inflammatory pathologies
- Serial values used to predict mortality rates pre and post-operative conditions
- Prognostication of patients with known malignancies.

Limitations of PLR [49]**:**

- **Exogenous steroid administration**:

Steroid administration induces marrow towards thrombopoisis. It also releases the sequestered pool of thrombocytes from the spleen to enter the circulation.

- **Active hematological disorder:**

Any leukemia affects the platelet count either in positive or negative manner.

- **Chemotherapy and other drugs:**

Chemotherapy causes myelosuppression. The degree and pattern of suppression depends on the individual drugs.

- **HIV:**

The utility of PLR in these patients is under study. Patients with HIV can have a high baseline PLR due to chronic lymphopenia.

- Pre analytical or sampling errors

PLR in various studies:

- PLR was also studied in sepsis for its prognostic value. Data from 5537 sepsis patients were analyzed retrospectively which showed higher values at admission were associated with an increased mortality and the values were of less significance in patients with SOFA >10, acute kidney injury and those on inotrope supports [58].

- The prognostic significance of PLR was studied in a cohart of Acute Heart Failure patients over 7 years and was found to be associated with higher mortality rates at the end of 6 months [59].

- A meta analysis done by Changai hospital, China based on data collected from 9 individual studies, revealed the prognostic value of PLR in different Barcelona Clinic Liver cancer stages in Hepatocellular carcinoma and concluded PLR to be a significant biomarker of prognosis [60].

- The recent researches focus on the use of PLR in rheumatological pathologies like Behcets disease and Familial Mediterranean Fever and have found the significance of PLR in proinflammatory and prothrombotic states [61].

Other novel ratios:

Monocyte to lymphocyte ratio has been studied in tuberculosis, and was found to be increased in pulmonary tuberculosis than TB lymphadenitis [62]. The ratio was also studied in NSTEMI and was concluded that MLR was an independent predictor of Major Adverse Cardiac Events (MACE) in NSTEMI [63]. Unlike NLR and PLR which lacked their utility in HIV population, MLR extended its significance in differentiating HIV-infected children with confirmed TB from those with unlikely TB and declined with TB treatment [64].

MATERIALS AND METHODS

SETTING

This study was conducted at the Institute of Internal Medicine, Rajiv Gandhi Government General Hospital (RGGGH), Madras Medical College, Chennai.

ETHICS COMMITTEE APPROVAL

Obtained.

STUDY DURATION

The study was conducted over a period of twelve months.

STUDY POPULATION

Patients with cerebral venous and sinus thrombosis between 18 – 60 years, admitted in RGGGH

SAMPLE SIZE

96 patients.

TYPE OF STUDY

Observational Prospective study.

INCLUSION CRITERIA

- Males and females aged between 18 – 60 years
- Patients with radiologicaly proven CVST.

EXCLUSION CRITERIA

- Patients with known thromboembolic disorders.
- Known chronic inflammatory conditions
- Exogenous steroid administration
- Known cases of CAD, previous stroke.

DATA COLLECTION AND METHODS

The study population includes those patients with radiologicaly proven CVST admitted in IIM, RGGGH. An elaborate history was elicited and a detailed clinical examination was performed in the study population. Based on the criteria patients were included in the study after getting informed consent. The GCS, the mRS (Modified Rankin Score) and ISCVT risk scores during the presentation were derived on the bedside for those included in the study. A complete hemogram at the first presentation was done and NLR and PLR were calculated. All the obtained data was entered in the proforma. The data were entered in micrsoft excel sheet. The calculated ratios were then correlated with mRS and ISCVT score.

OBSERVATION AND RESULTS

In our study, 96 radiological diagnosed CVST patients with various manifestations were included after applying preliminary exclusion criteria based on history. Out of 96 patients, 2 were excluded who satisfied the exclusion criteria only after investigations. One was a 56 year old female apparently diagnosed to have a haematological malignancy with a total count of 34000. Another patient was a 45 year old male who showed ischemic changes in ECG and diagnosed to have STEMI of anteroinferior wall. The statistical data was applied to the remaining 94 patients and the results are projected. The data obtained as are as follows.

AGE DISTRIBUTION:

The largest representative age group was those between 18 and 28 years measuring a 35.1% and the least representative group was between 48 and 58 years accounting for a mere 2% **(table.3 and figure.11a and 11b)**

Table 3: Age distribution of CVST

Age_group	Frequency	Percent
18-28 Years	33	35.1
29-38 Years	29	30.9
39-48 Years	30	31.9
49-58 Years	2	2.1
Total	94	100.0

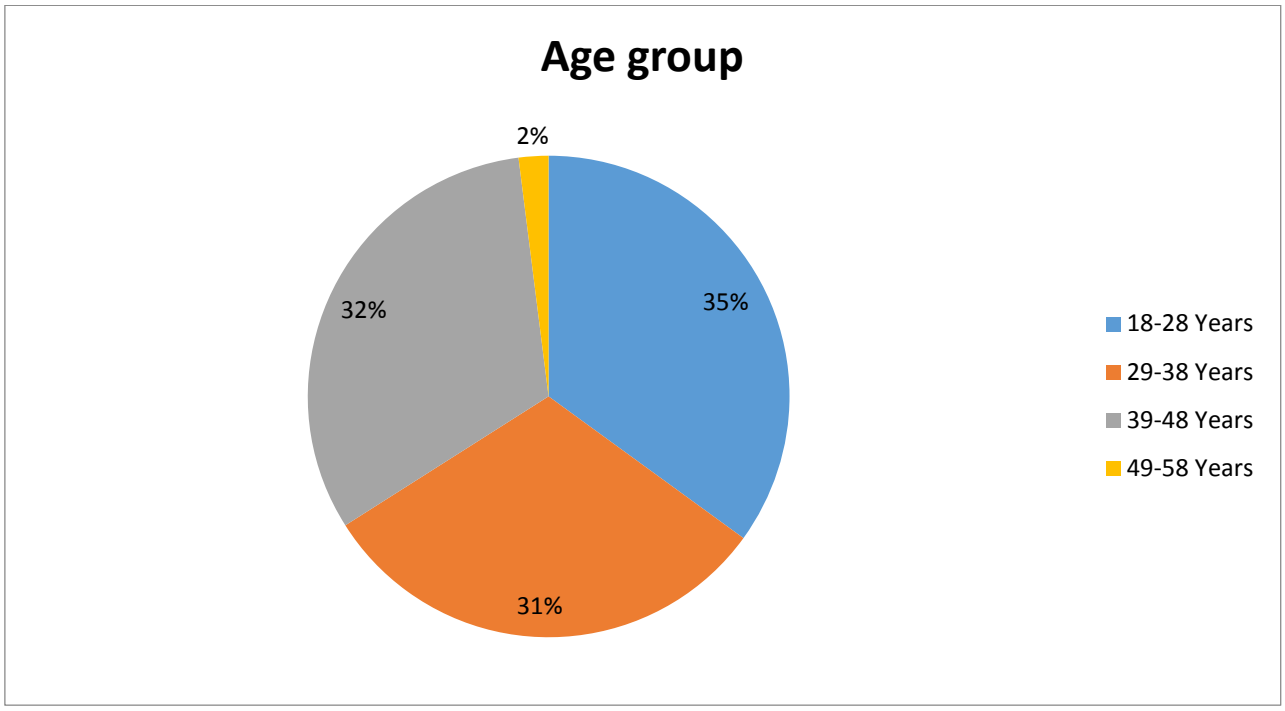

Figure.11a: Age distribution.

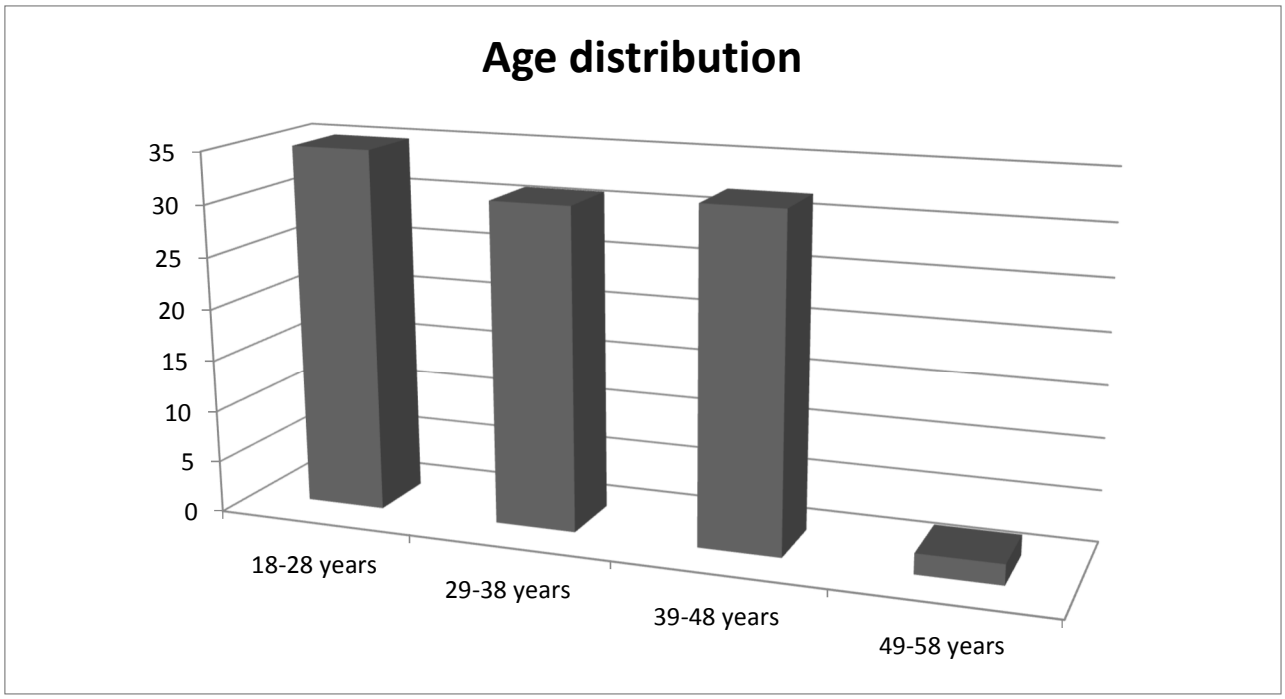

Figure.11b: Age distribution.

GENDER DISTRIBUTION:

There was more number of males about 61.7% than females 38.3% **(table.4 and figure.12a and 12b).**

Table.4: Gender distribution

gender	Frequency	Percent
Male	58	61.7
Female	36	38.3
Total	94	100.0

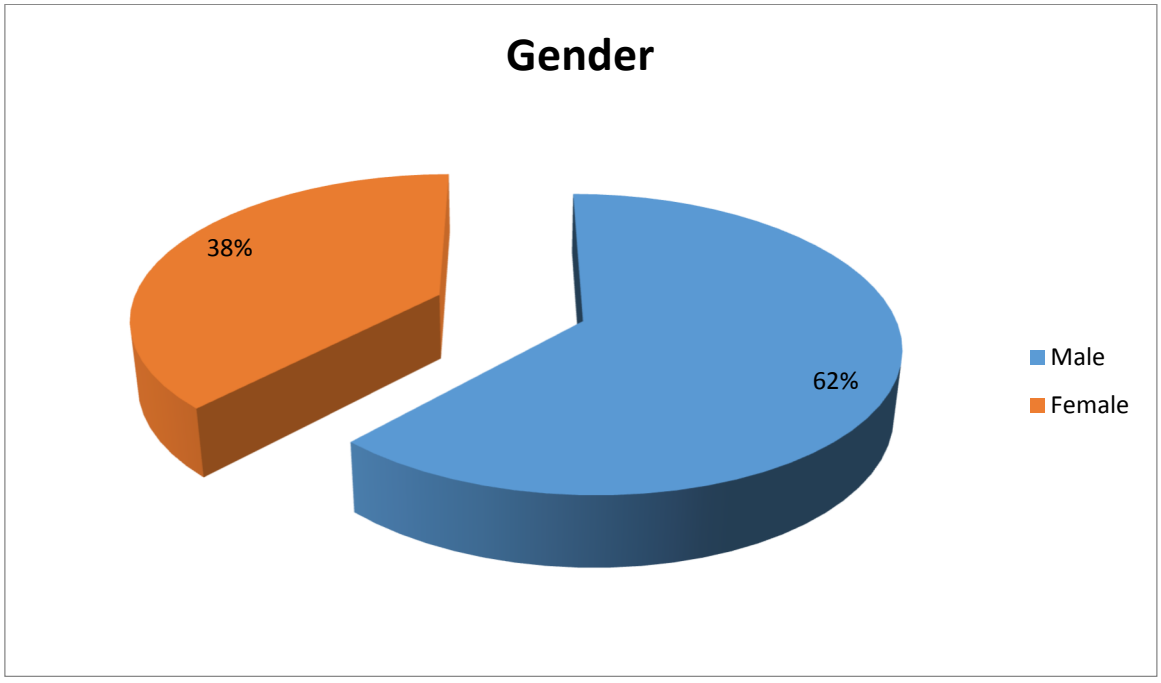

Figure.12a: Gender distribution

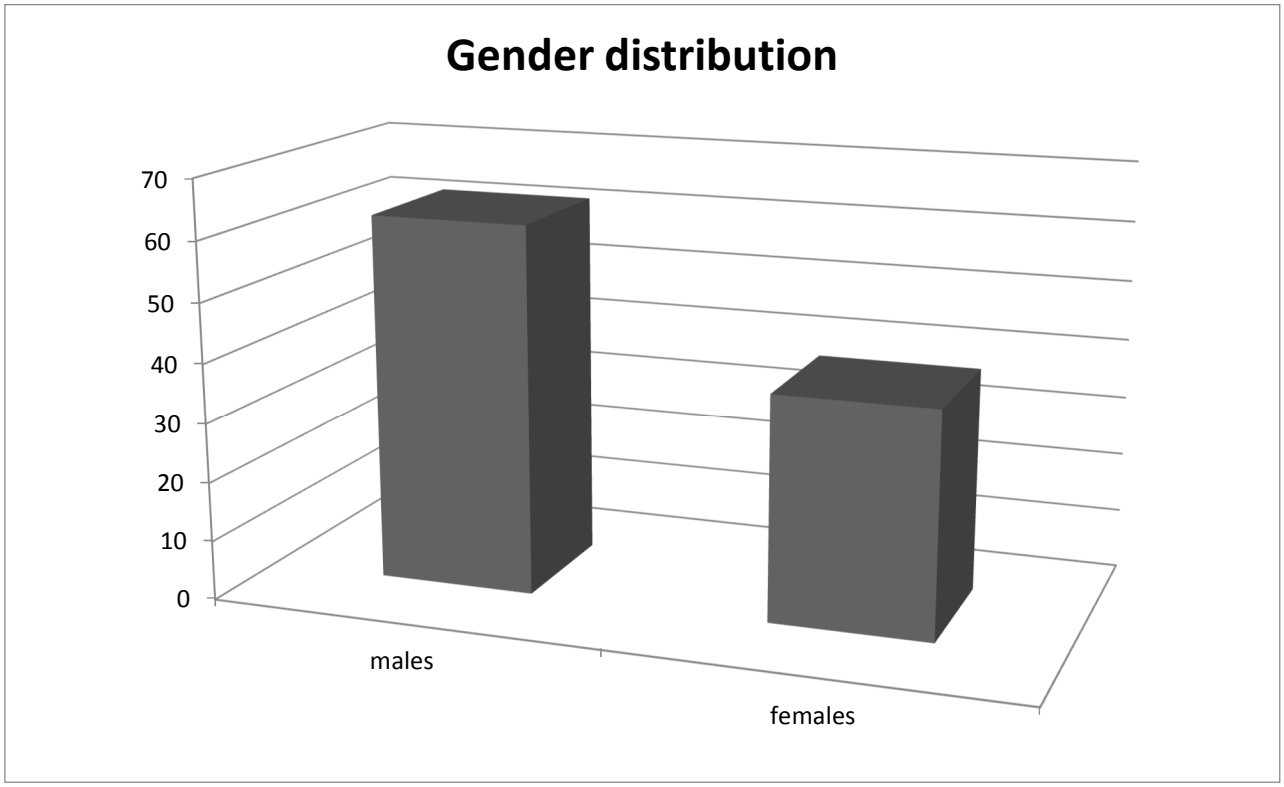

Figure.12b: Gender distribution

Etiological distribution in females:

Out of 36 females, 24 of them were post partum (within 7 days post delivery), 2 were diagnosed with SLE and 10 with conditions like protein c deficiency, Oral contraceptive pills intake and others **(figure.13).**

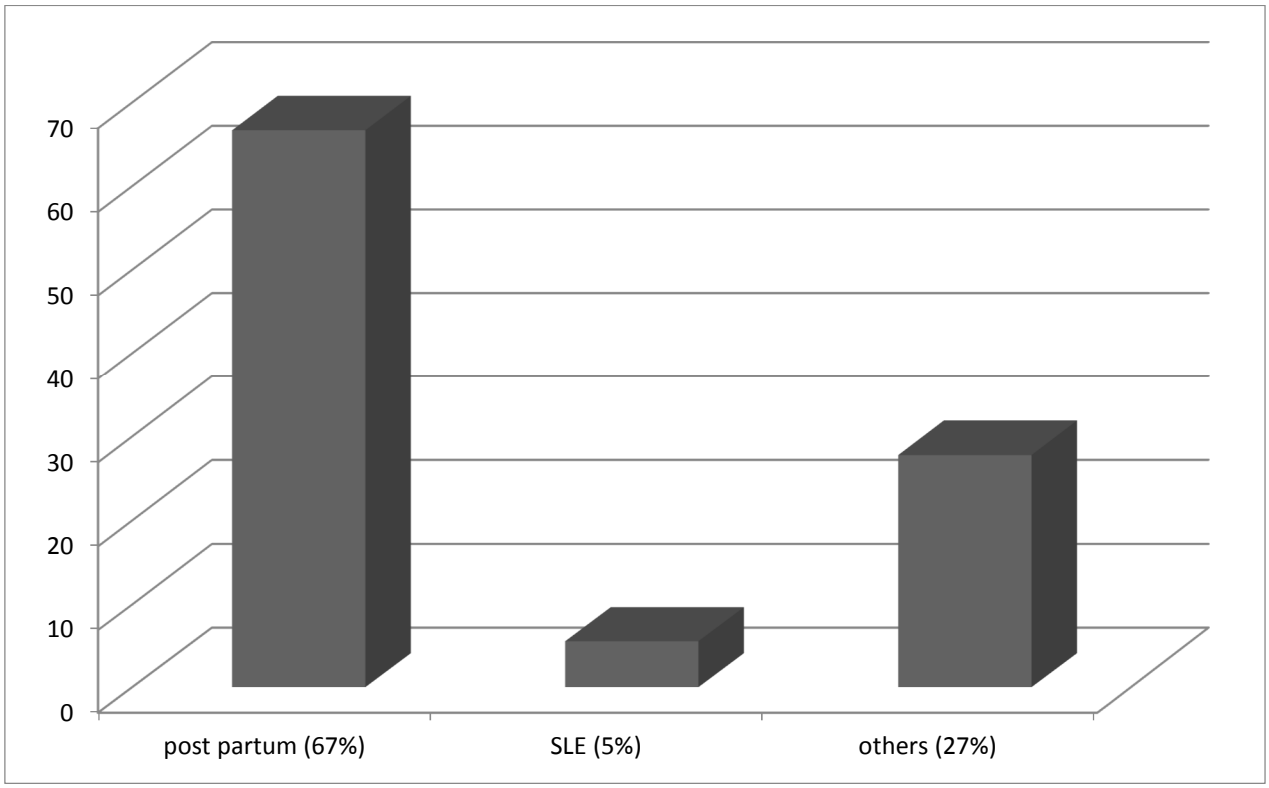

Figure.13: Etiological distribution in females

Etiological Distribution in males:

Total number of males included in the study were 58 out of which, 29 of them had consumed alcohol at some of time in their life. The cause attributed to CVST in these patients was alcohol **(figure.14)**.

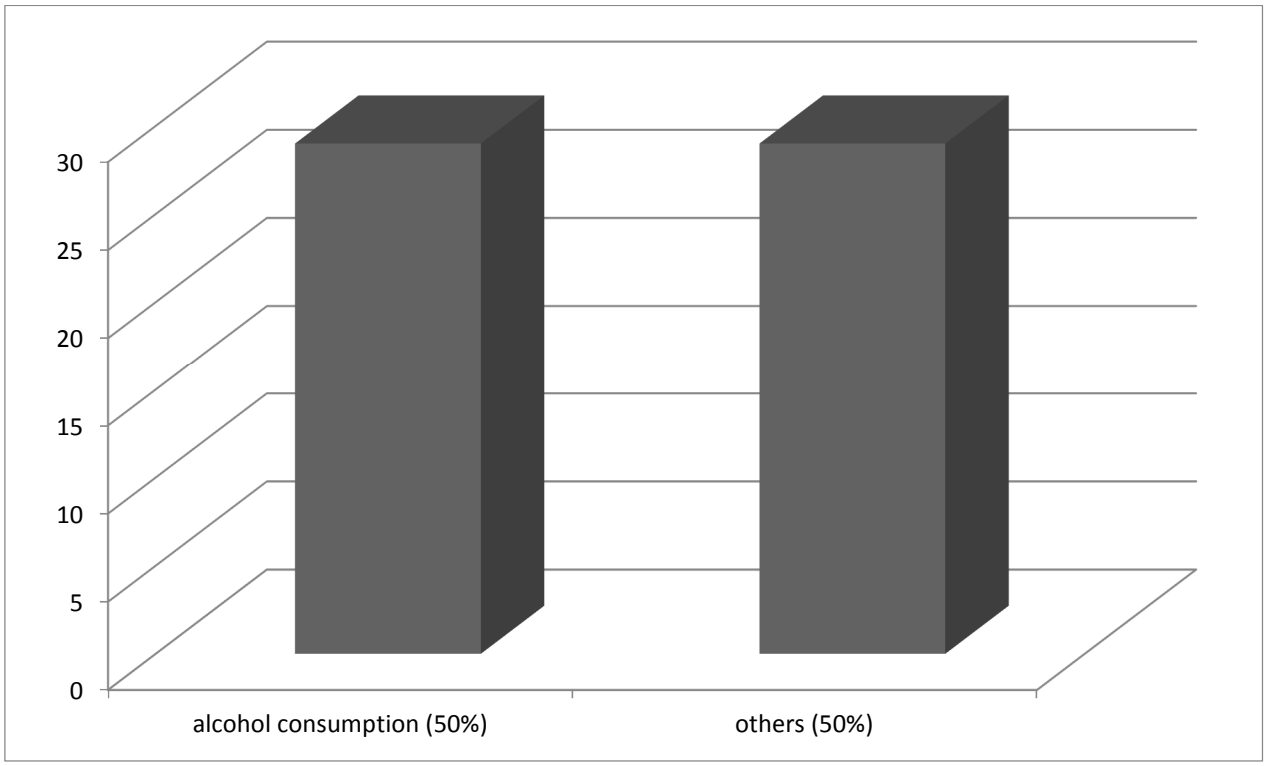

Figure.14: Etiological distribution in males.

CLINICAL SEVERITY DISTRIBUTION ACCORDING TO mRS:

Most of the patients presented with mRS score 1 or 3. 26.6% patients presented with mRS score 1 with no clinical disability despite symptoms and were able to carry on their activities without any assistance. While 27.7% patients presented with mRS score 3 who were moderate disability, requiring some but able to walk without assistance. None of the patients fell into the score of 0 (asymptomatic) as all of them had a wide spectrum of symptoms ranging from a mild headache to coma(**table.5 and figure.15).**

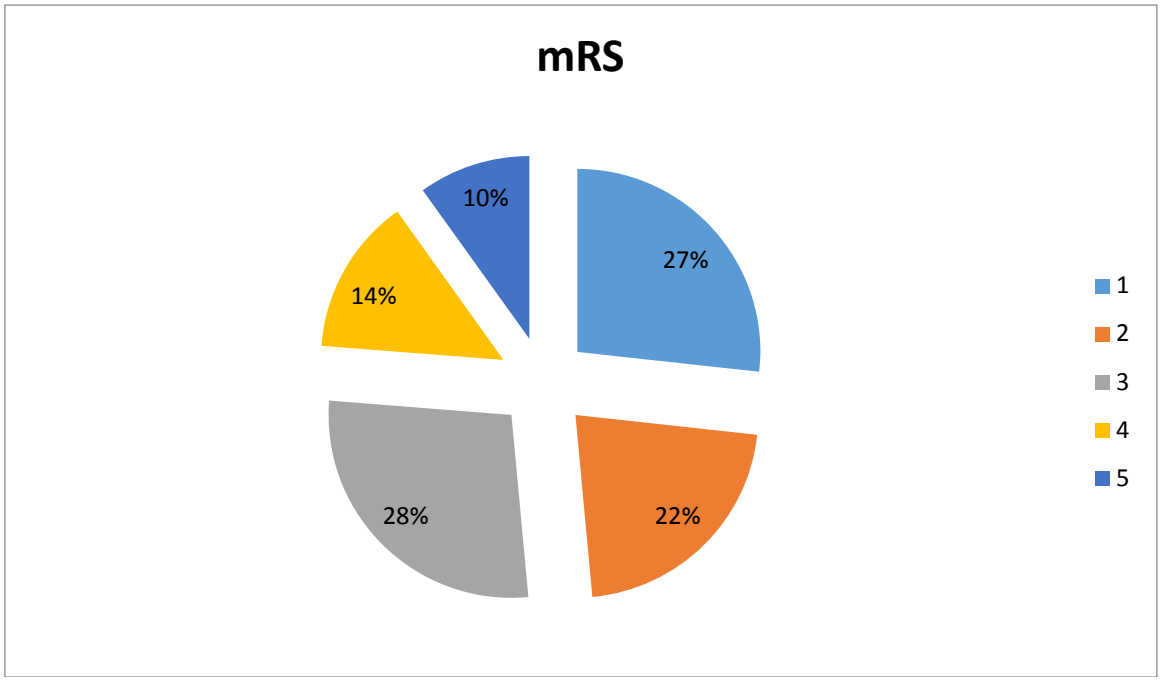

Figure.15: mRS severity distribution

Table.5: mRS severity distribution

mRS	Frequency	Percent
1.00	25	26.6
2.00	21	22.3
3.00	26	27.7
4.00	13	13.8
5.00	9	9.6
Total	94	100.0

CLINICAL SEVERITY DISTRIBUTION ACCORDING TO ISCVT:

The novel scoring system based on the large scale research on cerebral venous and sinus thrombosis, ISCVT ranges from 0 to 9. Even the original research has not witnessed a solid number of patients presenting with a score >6. Even in our study, the maximum representation is by a score 1 accounting for 30.9% and the least representation by score 6 with only 2 (2.1%) patients **(table.6 and figure.16)**.

Table.6: ISCVT severity distribution

ISCVT	Frequency	Percent
.00	26	27.7
1.00	29	30.9
2.00	20	21.3
3.00	8	8.5
4.00	9	9.6
6.00	2	2.1
Total	94	100.0

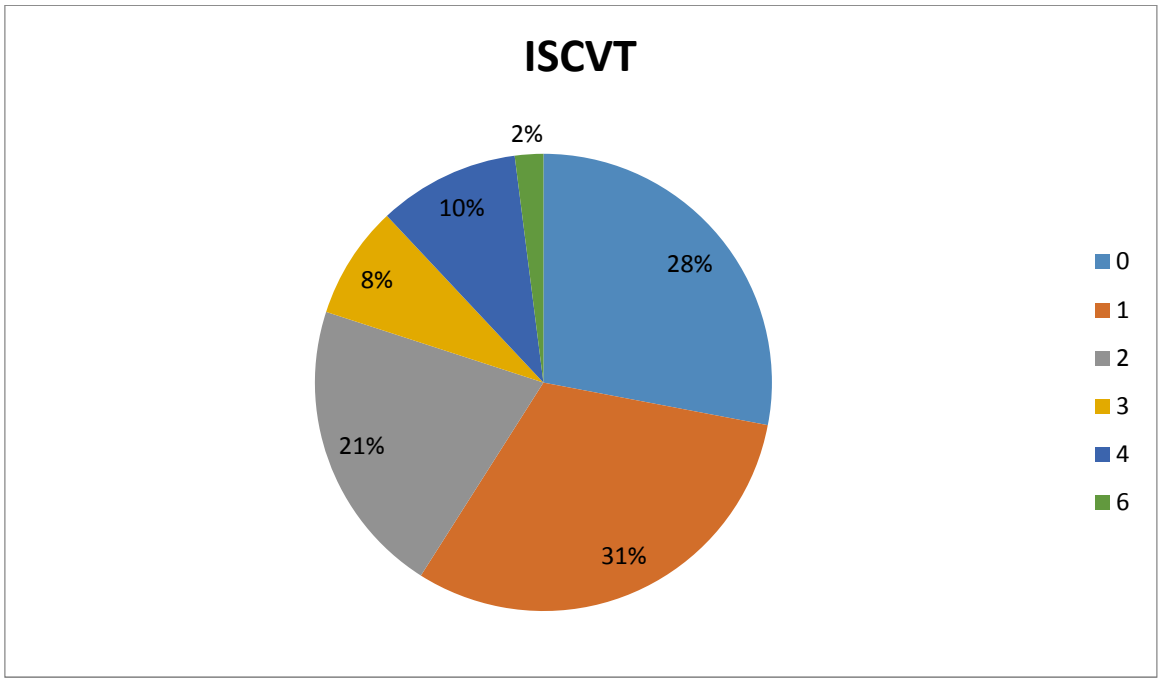

Figure.16: ISCVT severity distribution.

CORRELATION BETWEEN mRS AND NLR:

Correlation was done between mRS clinical severity and neutrophil to lymphocyte ratio. Out of 94 patients who presented with a various mRS scores, the least NLR was 3.17 and the highest was 9.69. A mean NLR of 5.589(±1.351 SD; 5.312 – 5.865 of 95% CI) was obtained **(table.7 and figures 17, 18).** The results were statistically significant with F value of 55.757. As the NLR increased, there was an increase in clinical severity by mRS score with $p<0.05$.

Table.7: Correlation between mRS and NLR

		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum	F value
						Lower Bound	Upper Bound			
NLR	1.00	25	4.2532	.68869	.13774	3.9689	4.5375	3.17	5.73	55.757**
	2.00	21	4.9690	.50749	.11074	4.7380	5.2001	3.95	5.78	
	3.00	26	5.9981	.79795	.15649	5.6758	6.3204	4.14	8.28	
	4.00	13	6.7777	.84802	.23520	6.2652	7.2901	5.99	8.52	
	5.00	9	7.8489	.95843	.31948	7.1122	8.5856	6.58	9.69	
	Total	94	5.5891	1.35120	.13937	5.3124	5.8659	3.17	9.69	

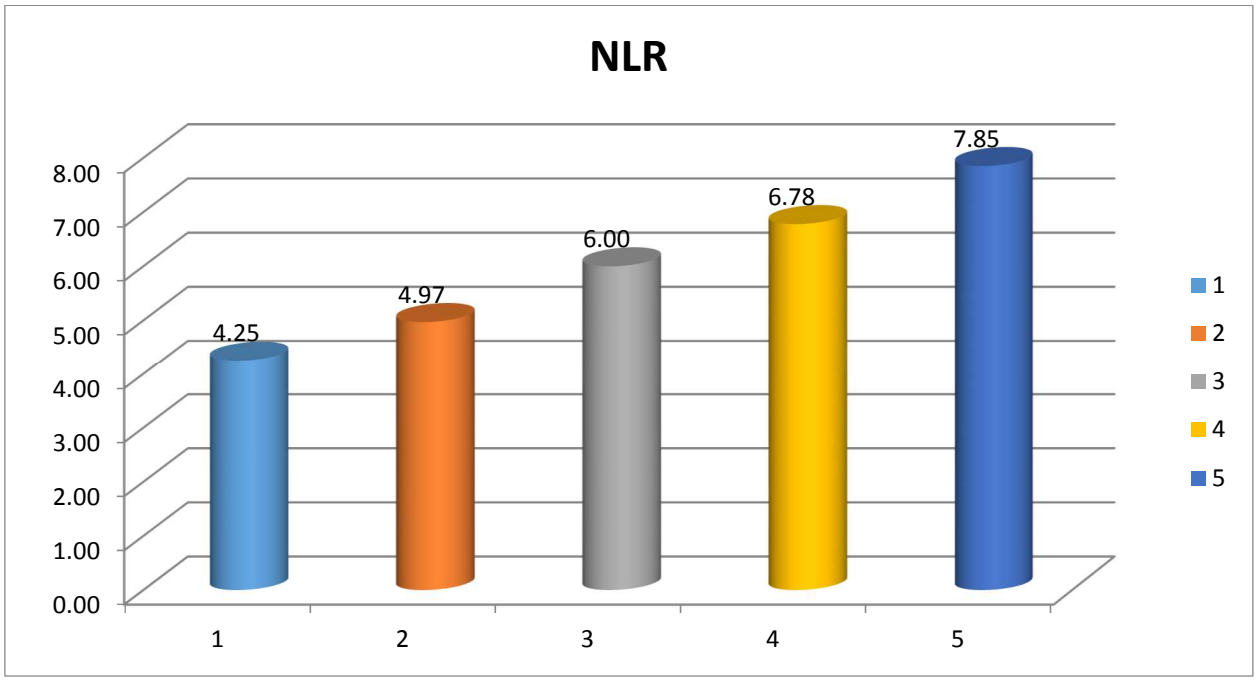

Figure.17: Correlation between mRS and NLR

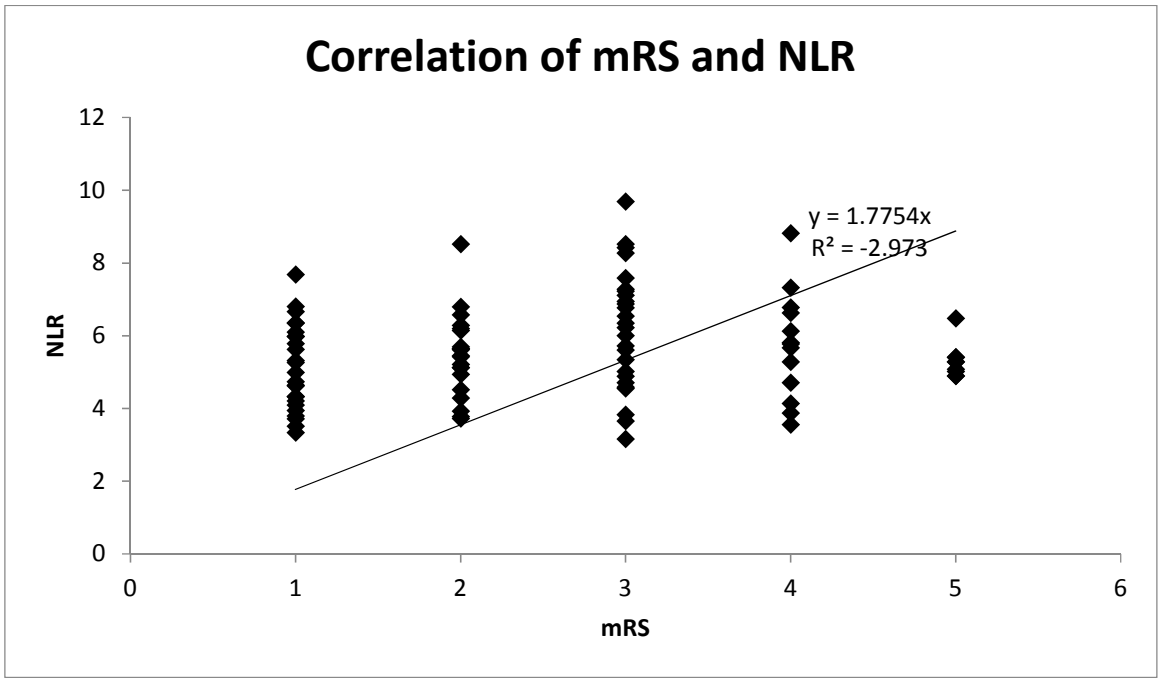

Figure.18

CORRELATION BETWEEN mRS AND PLR:

Correlation was done between mRS clinical severity and platelet to lymphocyte ratio. Out of 94 patients who presented with a various mRS scores, the least PLR was 94.62 and the highest was 259.87. A mean PLR of 161.898(±26.182 SD; 156.536 – 167.261 of 95% CI) was obtained **(table.8 and figures 19, 20).** The results were statistically significant with F value of 28.7. As the PLR increased, there was an increase in clinical severity by mRS score with $p<0.05$.

Table.8: Correlation between mRS and PLR

		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum	
						Lower Bound	Upper Bound			F value
PLR	1	25	141.8584	14.00279	2.80056	136.0783	147.6385	94.62	154.04	28.700**
	2	21	149.0448	12.64684	2.75977	143.2880	154.8015	104.71	159.74	
	3	26	166.7415	16.87630	3.30972	159.9251	173.5580	150.52	214.53	
	4	13	181.6969	15.37974	4.26557	172.4030	190.9908	165.45	210.97	
	5	9	204.9678	35.31352	11.7711	177.8234	232.1122	129.11	259.87	
	Total	94	161.8984	26.18169	2.70043	156.5359	167.2609	94.62	259.87	

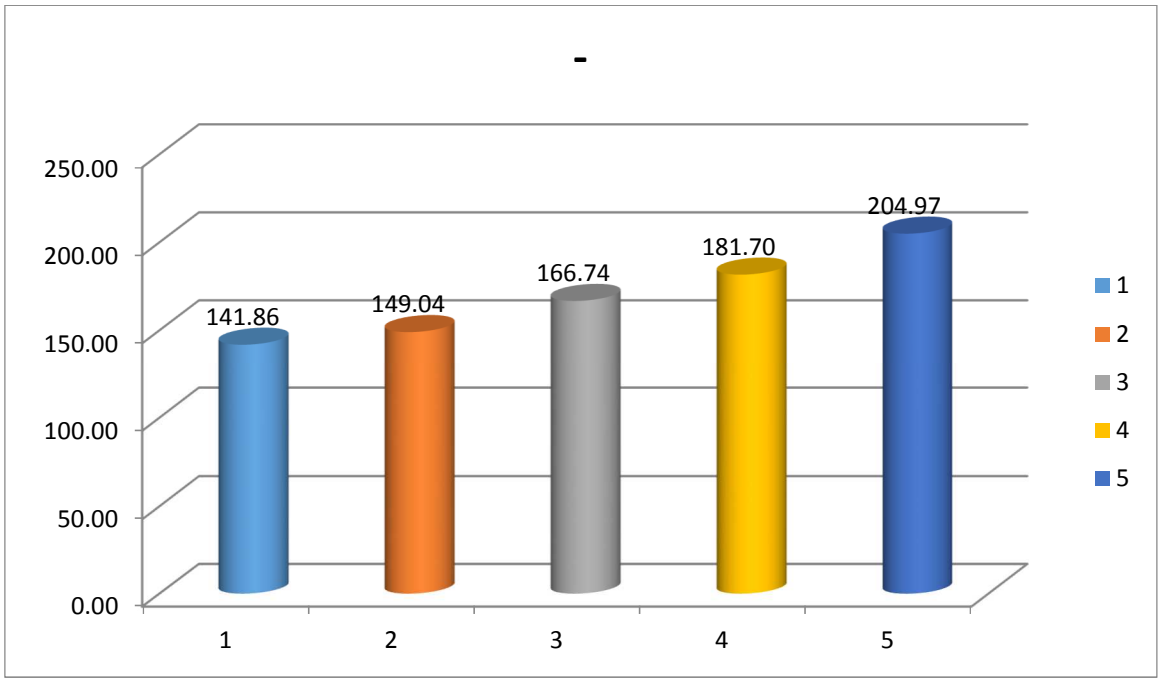

Figure.19: Correlation between mRS and PLR

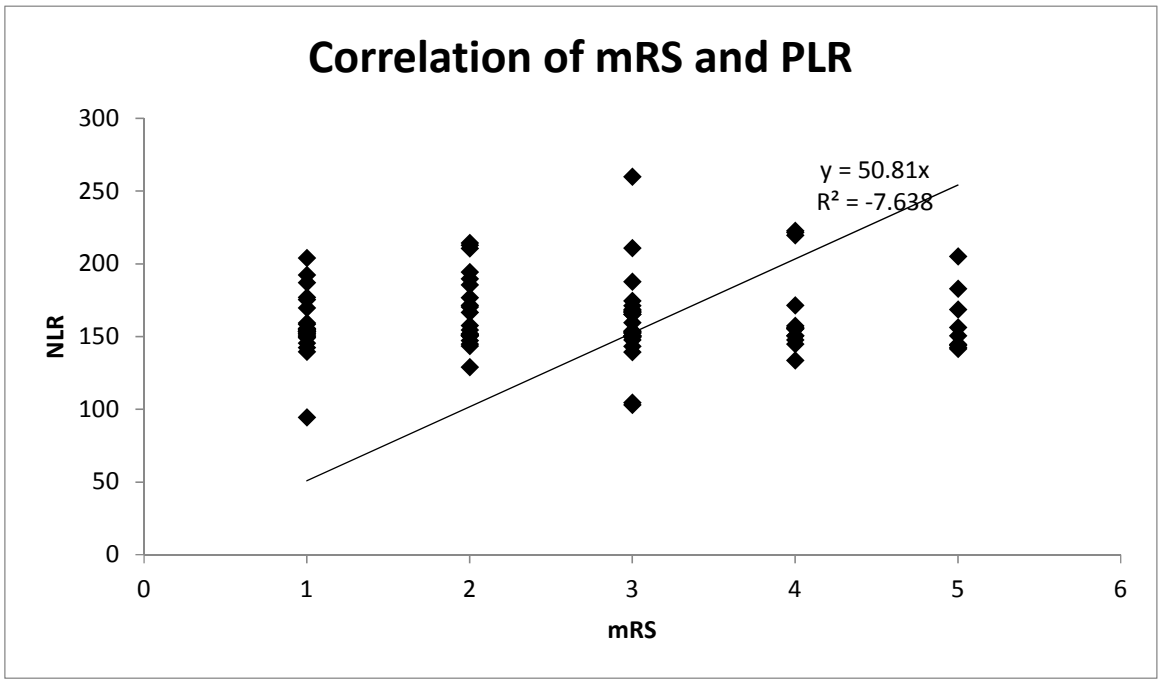

Figure.20

CORRELATION BETWEEN ISCVT AND NLR:

Correlation was done between ISCVT clinical severity and neutrophil to lymphocyte ratio. Out of 94 patients who presented with a various ISCVT scores, the least NLR was 3.17 and the highest was 9.69. None of the patients presented with score 5. A mean NLR of 5.589(±1.351 SD; 5.312 – 5.865 of 95% CI) was obtained **(table.9 and figures 21, 22).** The results were statistically significant with F value of 36.462. As the NLR increased, there was an increase in clinical severity by ISCVT score with $p<0.05$.

Table.9: Correlation between ISCVT with NLR

		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum	
						Lower Bound	Upper Bound			
NLR	0	26	4.4850	.63747	.12502	4.2275	4.7425	3.34	5.81	36.462**
	1	29	5.0569	.87955	.16333	4.7223	5.3915	3.17	6.67	
	2	20	5.9670	.66550	.14881	5.6555	6.2785	4.14	6.95	
	3	8	7.2288	.85401	.30194	6.5148	7.9427	6.13	8.52	
	4	9	7.7811	1.11258	.37086	6.9259	8.6363	6.48	9.69	
	6	2	7.4600	.18385	.13000	5.8082	9.1118	7.33	7.59	
	Total	94	5.5891	1.35120	.13937	5.3124	5.8659	3.17	9.69	

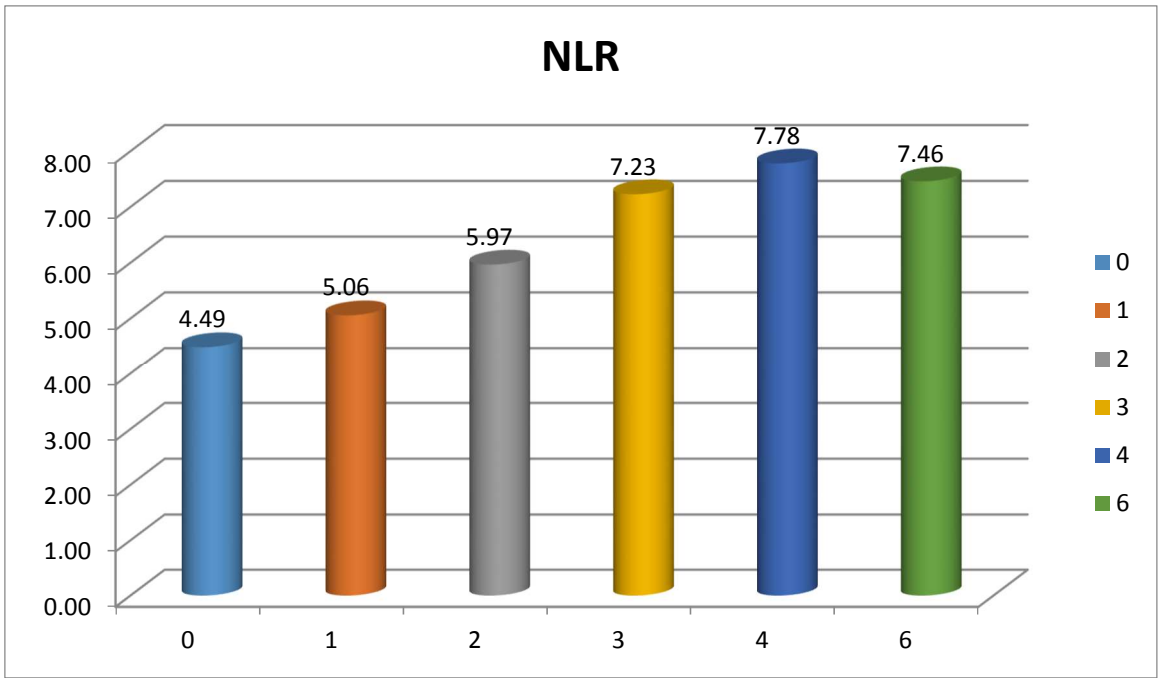

Figure.21: Correlation between ISCVT and NLR

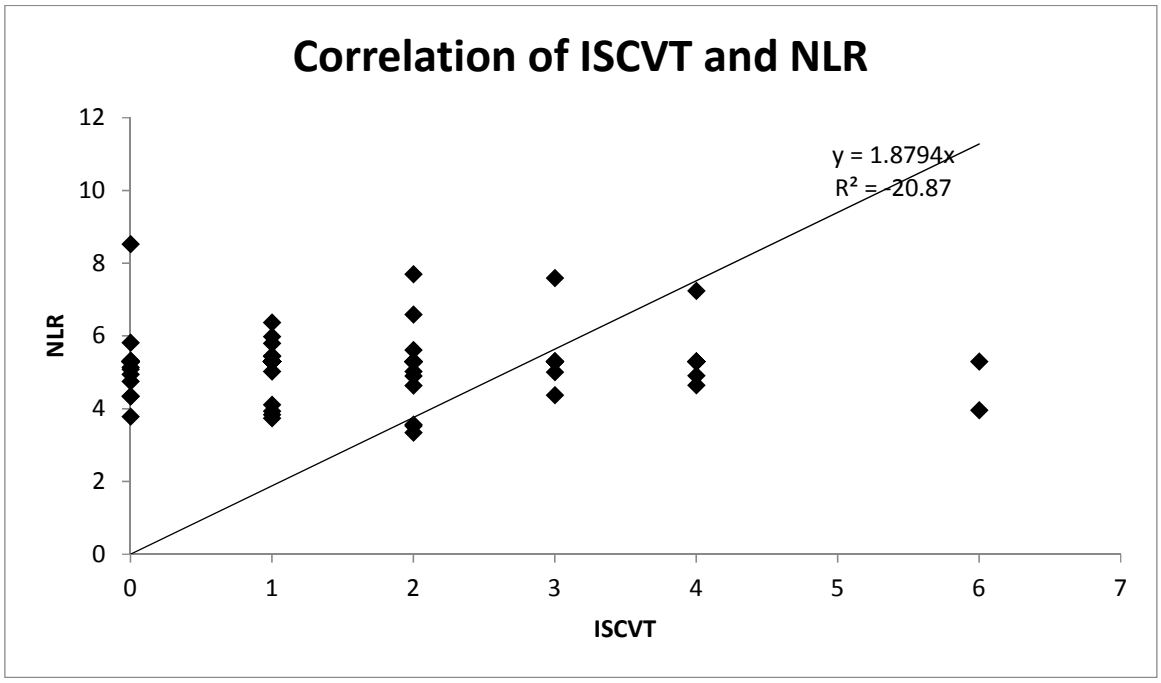

Figure.22

CORRELATION BETWEEN ISCVT AND PLR:

Correlation was done between ISCVT clinical severity and platelet to lymphocyte ratio. Out of 94 patients who presented with a various ISCVT scores, the least PLR was 94.62 and the highest was 259.87. None of the patients presented with score 5. A mean PLR of 161.989(±26.181 SD; 156.536 – 167.261 of 95% CI) was obtained **(table.10 and figures 23, 24).** The results were statistically significant with F value of 26.947. As the PLR increased, there was an increase in clinical severity by ISCVT score with $p<0.05$.

Table.10: Correlation between ISCVT and PLR

		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum	
						Lower Bound	Upper Bound			
PLR	0	26	143.6988	15.0905	2.9595	137.6036	149.7940	94.62	157.18	26.947**
	1	29	150.9586	12.1318	2.2528	146.3439	155.5733	104.71	168.61	
	2	20	167.9140	14.4962	3.2414	161.1296	174.6984	152.91	212.90	
	3	8	191.0763	17.0799	6.0386	176.7971	205.3554	171.28	214.53	
	4	9	207.2989	24.8747	8.2916	188.1784	226.4193	176.90	259.87	
	6	2	175.9500	66.2417	46.840	419.2086	771.1086	129.11	222.79	
	Total	94	161.8984	26.1816	2.7004	156.5359	167.2609	94.62	259.87	

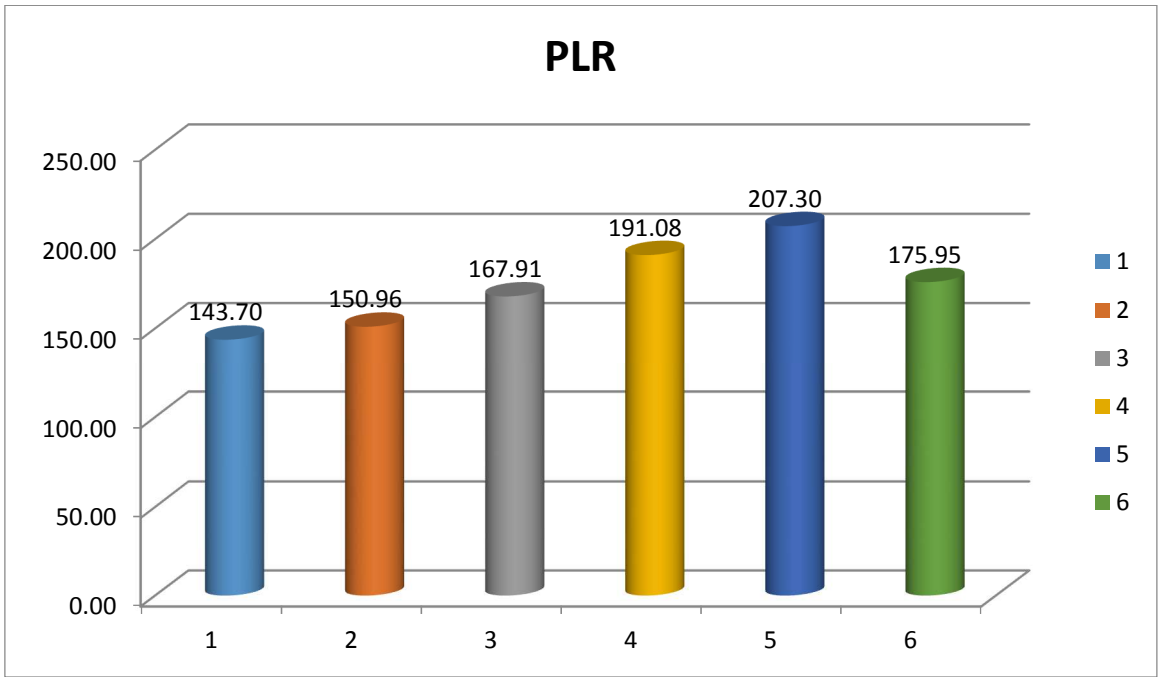

Figure.23: Correlation between TSCVT and PLR

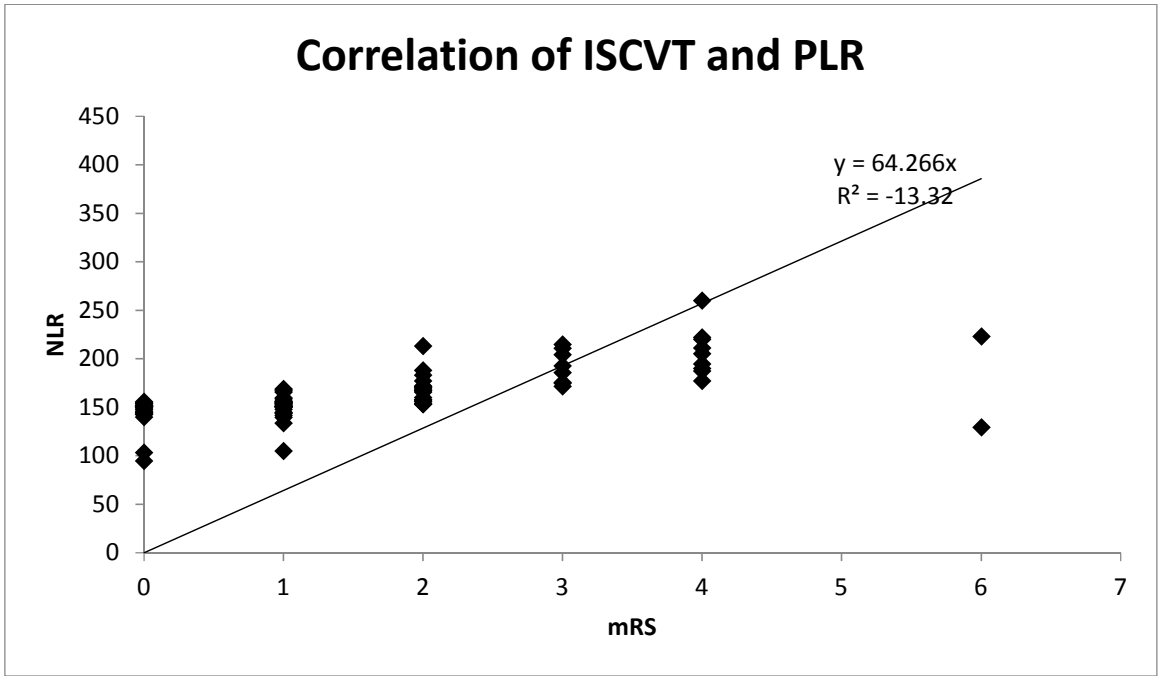

Figure.24

DISCUSSION

Diagnosis of CVST becomes crucial, due to its dreadful complications and as resolution of symptoms and disease activity occurs with prompt treatment. Therefore, a simple diagnostic and a prognostic tool will be helpful in identifying the patients with CVST even before radiological diagnosis. As the patients have vague clinical presentations like headache, blurring of vision or seizures, without any localizing features, a biomarker can help categorize these patients of having a more insidious disease.

In our study, consisting of 96 patients, 2 were excluded during the study as they satisfied the exclusion criteria only after investigations. One was a 56 year old female excluded to a haematological malignancy and the other was a 45 year old male excluded due to anteroinferior wall STEMI. The remaining 94 were included for statistical analysis. The majority of them were males (61.7%) among which most of them had consumed alcohol at some point of time in their life. This suggests the relation between alcohol and thromboembolism which need further studies. The remaining 38.3% were females. The age group with maximum representation was between 18 and 28 consisting of 33 patients of which 27 were females. 24 females from this age group were post-partum and the remaining had some underlying conditions contributing to CVST. This data highlights that the

post-partum period posed a higher risk than pregnancy for the development of the thrombus. The age group with male predominance was between 39 and 48 years containing 29 males out of 30 patients and most of them had consumed alcohol in their life. 3 patients died within few hours of presentation. The first patient was a 27/f, the other two were males of 47 and 49 years old. Out of 94, 14 patients including those who died had central vein of Galen thrombosis.

Patients presented with a wide spectrum of symptoms ranging from headache to coma. At a primary care level where the scope for radiological diagnosis is remote, the symptoms like headache or blurring of vision or giddiness might be overlooked or symptomatically treated which leaves the actual disease process unaddressed. But the patients with severe symptoms like seizures or loss of consciousness will be referred to higher centres. If left untreated, even the milder forms of the disease will progress to involve the dural sinus and cerebral venous system extensively which could prove fatal. With the above data, including post partum period in females or alcohol history in males and with a strong clinical suspicion, a simple yet valuable biomarker might reveal a lethal disease process. Markers such as ESR are nonspecific while CRP is expensive. So, in search of a more affordable, readily accessible and acceptable biomarker, the ratios were formulated. Neutrophil to lymphocyte ratio and platelet to lymphocyte ratios are better compared to discrete values like platelet and neutrophil counts. The ratios

have different cut off values in different disease but researches in CVST have evaluated the most common cut off values of 3 for NLR and 130 for PLR. As was evident from the data collected, all radiologicaly proven CVST patients had a raise in NLR (value > 3 – abnormal) and PLR (value >130 – abnormal). So when the ratios are more than these values in patients with a relevant history and vague clinical presentations, CVST can be suspected and investigated for. In our study the least NLR was found to be 3.17 and the maximum value was 9.69 with a mean of 5.589 (±1.351 SD). The least PLR was 94.62 and the maximum was 259.87 with a mean of 161.898 (± 26.182 SD).

The study not only calculated the ratio cut offs for CVST but also assessed the severity of the disease using Modified Rankin Scale and International Study of Cerebral Vein and Dural Sinus Thrombosis scoring which predicts the mortality rate at six months post CVST. Though single post event mRS is used in this study, a series of values and a structured questionnaire is required to predict the long term outcome. mRS and ISCVT was calculated for all the patients included in the study. The distribution of the study population for scores 1, 2, 3, 4 and 5 of mRS were 26.6%, 22.3%, 27.7%, 13.8% and 9.6% respectively. The maximum representation was with a score of 3 defining moderate disability; requiring some help, but able to walk without assistance. The distribution of the patients for scores 0, 1, 2, 3, 4, 6 of ISCVT were 27.7%, 30.9%, 21.3%, 8.5%,

9.6% and 2.1% respectively. Though the ISCVT score ranges from 0-9, the patients presented with scores only from 0 – 6, with maximum representation of score 1 out of which 24 were males. Male gender accounts for a score of 1. 20 out of 24 such patients had a score of 1 just because of male gender. The next highest representation was observed for a score of 0 accounting for 27.7% out of which only one was a male. 23 females who had ISCVT score of 0 were between 18-28 years of age and in post-partum period perhaps suggesting a favorable outcome in post-partum CVST.

In this study, the post event single mRS value and ISCVT are used to assess the severity and has been correlated with NLR and PLR. The correlation between NLR and mRS yielded a positive result.

Correlation between mRS and NLR:

NLR was lower with a mean of 4.2532 (±0.688 SD) for mRS score 1. The mean values got higher when higher scores of mRS giving a linear relationship between mRS and NLR **(figure.13).**

Correlation between mRS and PLR:

PLR values showed a linear relationship with mRS. The mean values of 141.858 (± 14.003 SD) and 204.968 (± 35.314 SD) corresponding to scores 1 and 5 respectively **(figure.15)**

Correlation between ISCVT and NLR:

Both of them showed a linear relationship with mean values of 4.485 (± 0.637 SD) and 7.46 (±0.184 SD) corresponding to scores 0 and 6 respectively.

Correlation between ISCVT and PLR:

There was a better correlation between ISCVT and PLR as most of the patients with a score of 0 had their respective PLRs at the lower range. 5 patients even had their PLR less than that of the original cut off value of 130 and all the 5 of them scored 0 in ISCVT.

The available data therefore suggests a linear direct relationship between mRS and NLR; mRS and PLR; ISCVT and NLR; ISCVT and PLR. As mRS and ISCVT are already predictive markers of outcome in patients post CVST, the relationship between the scores and the ratios shows that NLR and PLR can be used as surrogate markers in CVST.

CONCLUSION

CVST is a life threatening disease with wide spectrum of vague symptoms. In order to prevent under-diagnosis by health care professionals where radiological investigations are unavailable, an accessible, acceptable and affordable biomarker can be help in prompt referral without time delay. Satisfying these criteria are the neutrophil to lymphocyte and platelet to lymphocyte ratios. This study shows that these ratios can be used as markers of CVST and also predict the future outcome in these patients. Thus, whenever a patient presents with a vague neurological symptom, a haemogram can be done at a primary care level to calculate the ratios and promptly refer the patient to higher centre if the ratios are suggestive of CVST.

LIMITATIONS

- Multiple values of NLR and PLR during the course of hospital stay would lead to a better prediction of the prognosis in the patients.
- The calculated ratios must be correlated with mRS assessed during multiple points of time post CVST.
- The normal values of NLR and PLR used were taken from the studies done in other ethnic groups.
- Several multi centric trials using NLR and PLR of Indian population reference range have to be conducted as Indian genotype has vast differences from that of the ethnic groups.
- A novel risk prediction score can be derived using the available data.
- Several other new ratios including MLR (monocyte lymphocyte ratio) can be added in future studies to derive a new risk prediction score.

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ANNEXURES

PROFORMA

Name: Age/gender:

IP no:

Address:

Co morbidities:

Drugs for chronic inflammatory conditions	
Thromboembolic conditions (others)	
Coronary Artery Disease	
Stroke	
Malignancy	
Steroid consuption	

Clinical severity scores:

mRS	
ISCVT	

Lab parameters (Hemogram):

Total count	
Platelet count	
Absolute neutrophil count	
Absolute lymphocyte count	
NLR	
PLR	

Etiology:

INFORMATION SHEET

We are conducting a study on **"NEUTROPHIL TO LYPMHOCYTE RATIO AND PLATELT TO LYMPHOCYTE RATIO AS PREDICTIVE MARKERS OF CLINICAL SEVERITY IN CEREBRAL VENOUS AND SINUS THROMBOSIS"** among patients attending Rajiv Gandhi Government General Hospital, Chennai and for that your specimen may be valuable to us.

The purpose of this study is to assess the significance of Neutrophil to Lymphocyte ratio and Platelet to Lymphocyte ratio in patients with Cerebral Venous and Sinus Thrombosis.

We are selecting certain cases and if you are found eligible, we may perform extra tests and special studies which in anyway do not affect your final report or management.

The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time. Your decision will not result in any loss of benefits to which you are otherwise entitled.

The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of investigator

Date:

Place:

Signature of participant

Dr. KISHWANTH R

PATIENT CONSENT FORM

Study detail: **NEUTROPHIL TO LYPMHOCYTE RATIO AND PLATELT TO LYMPHOCYTE RATIO AS PREDICTIVE MARKERS OF CLINICAL SEVERITY IN CEREBRAL VENOUS AND SINUS THROMBOSIS**

Study centre: Rajiv Gandhi Government General Hospital, Chennai.

Patient's name:

Patient's age:

Identification number:

Patient may check these boxes.

- I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction. ☐
- I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ☐
- I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study, I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data results that arise from this study. ☐
- I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or wellbeing or any unexpected or unusual symptoms. ☐
- I hereby consent to participate in this study. ☐
- I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological, biochemical and radiological tests. ☐

Signature/Thumb impression of the patient

Signature of Investigator
Dr. KISHWANTH R

ஆராய்ச்சி தகவல் தாள்

ஆராய்ச்சி தலைப்பு: பெருமூளை இரத்த உறைவு தீவிரத்தின்

குறிப்பான்களாக நியூட்ரோபில் லிம்போசைட் விகிதம்

மற்றும் பிளேட்லெட் லிம்போசைட் விகிதம்

ஆய்வாளர் பெயர் : மரு. கிஷ்வந்த்

ஆய்வு நிலையம் : பொது மருத்துவ துறை, சென்னை மருத்துவ கல்லூரி சென்னை

இந்த ஆய்வில் தங்களை பங்கேற்க அழைக்கிறோம். இந்த தகவல் அறிக்கையில் கூறப்பட்டிருக்கும் தகவல்கள் தாங்கள் இந்த ஆயிராய்ச்சியில் பங்கேற்கலாமா அல்லது வேண்டாமா என்று முடிவு செய்ய உதவியாக இருக்கும்.

இந்த படிவத்தில் உள்ள தகவல்கள் பற்றி உள்ள சந்தேகங்களை தயங்காமல் கேட்கலாம்.

இந்த ஆய்வில் உங்களுக்கு தேவையான ரத்த பரிசோதனைகளும்,இதர ஆய்வுகளும் செய்யப்படும்.

நீங்களும் இந்த ஆராய்ச்சியில் பங்கேற்க நாங்கள் விரும்புகிறோம். அதனால் தங்கள் நோயின் ஆய்வறிக்கையோ அல்லது சிகிச்சையோ பாதிப்புக்கு ஏற்படாது என்பதையும் தெரிவித்து கொள்கிறோம்

முடிவுகள் அல்லது கருத்துக்கள் வெளியிடும் போது தங்களின் பெயரையோ அல்லது அடையாளத்தாயோ வெளியிடமாட்டோம் என்பதையும் தெரிவித்துக்கொள்கிறோம்

இந்த சிறப்பு பரிசோதனைகளின் முடிவுகளை ஆராய்ச்சியின் போது அல்லது ஆராச்சியின் முடிவின் போது தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்து கொள்கிறோம்

ஆராய்ச்சியாளர் கையொப்பம் பங்கேற்பாளர் கையொப்பம்

ஆராய்ச்சி ஒப்புதல் படிவம்

ஆராய்ச்சி தலைப்பு: பெருமூளை இரத்த உறைவு தீவிரத்தின்
குறிப்பான்களாக நியூட்ரோபில் லிம்போசைட் விகிதம்
மற்றும் பிளேட்லெட் லிம்போசைட் விகிதம்

ஆய்வாளர் பெயர் : மரு. கிஷ்வந்த்

பங்கு பெறுபவரின் பெயர் :
பங்கு பெருவரின் ஏன் :
பங்கு பெறுபவர் இதனை குறைக்கவும்

- மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. எனது சந்தேகங்களை கேட்கவும் அதற்கான விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டது
- நான் இவ்வாய்வில் தன்னிச்சையாக தன் பங்கேற்கிறேன். எந்த காரணத்தினாலோ எந்த கட்டத்திலும் எந்த சட்ட சிக்கலுக்கு உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகி கொள்ளலாம் என்று அறிந்து கொண்டேன்
- இந்த ஆய்வின் சம்பந்தமாகவோ, இதை சார்ந்த மேலும் ஆய்வு மேற்கொள்ளும் போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என்பதை அறிந்து கொண்டேன். நான் ஆய்வில் இருந்து விலகி கொண்டாலும் இது பொருந்தும் என அறிகிறேன்
- இந்த ஆய்வின் மூலம் கிடைக்கும் தகவல்களையும், பரிசோதனை முடிவுகளையும் மற்றும் சிகிச்சை தொடர்பான தகவல்களையும் மருத்துவர் மேற்கொள்ளும் ஆய்வில் பயன்படுத்திக்கொள்ளவும் பரிசுரிக்கவும் என் முழு மனதுடன் சம்மதிக்கிறேன்.
- இந்த ஆய்வில் பங்குகொள்ள ஒப்புக்கொள்கிறேன். எனக்கு கொடுக்கப்பட்ட அறிவுரைகளின்படி நடந்துகொள்வதுடன் இந்த ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்று உறுதியளிக்கிறேன்.

பங்கேற்பாளர் கையொப்பம்: இடம் மற்றும் தேதி

கட்டைவிரல் கை ரேகை

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To

DR. KISHWANTH R
I Yr. PG in MD GENERAL MEDICINE
INSITUTE OF INTERNAL MEDICINE
MADRAS MEDICAL COLLEGE
CHENNAI – 600 003
Dear Dr. KISHWANTH R

The Institutional Ethics Committee has considered your request and approved your study titled **"NUTROPHIL TO LYMPHOCYTE RATIO AND PLATELET TO LYMPHOCYTE RATIO AS PREDICTIVE MARKERS OF CLINICAL SEVERITY IN CEREBRAL VENOUS SINUS THROMBOSIS" - NO.22042018**

The following members of Ethics Committee were present in the meeting held on **03.04.2018** conducted at Madras Medical College, Chennai 3

1. Prof.P.V.Jayashankar :Chairperson
2. Prof.R.Jayanthi,MD.,FRCP(Glasg) Dean,MMC,Ch-3 : Deputy Chairperson
3. Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3 : Member Secretary
4. Prof.N.Gopalakrishnan,MD,Director,Inst.of Nephrology,MMC,Ch : Member
5. Prof.S.Mayilvahanan,MD,Director,Inst. of Int.Med,MMC, Ch-3 : Member
6. Prof.A.Pandiya Raj,Director, Inst. of Gen.Surgery,MMC : Member
7. Prof.Shanthy Gunasingh, Director, Inst.of Social Obstetrics,KGH : Member
8. Prof.Rema Chandramohan,Prof.of Paediatrics,ICH,Chennai : Member
9. Prof. S. Purushothaman, Associate Professor of Pharmacology, MMC,Ch-3 : Member
10. Prof.K.Ramadevi,MD., Director, Inst. of Bio-Chemistry,MMC,Ch-3 : Member
11. Prof.Bharathi Vidya Jayanthi,Director, Inst. of Pathology,MMC,Ch-3: Member
12. Thiru S.Govindasamy, BA.,BL,High Court,Chennai : Lawyer
13. Tmt.Arnold Saulina, MA.,MSW., :Social Scientist
14. Thiru K.Ranjith, Ch- 91 : Lay Person

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary – Ethics Committee

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Instances where selected sources appear:

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PLAGIARISM CERTIFICATE

This is to certify that this dissertation work titled "**NEUTROPHIL TO LYPMHOCYTE RATIO AND PLATELT TO LYMPHOCYTE RATIO AS PREDICTIVE MARKERS OF CLINICAL SEVERITY IN CEREBRAL VENOUS AND SINUS THROMBOSIS"** of the candidate **Dr. KISHWANTH R** with registration Number **201711008** for the award of **M.D.** in the branch of **GENERAL MEDICINE.** I personally verified the urkund.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows 4% of plagiarism in the dissertation.

Guide & Supervisor sign with Seal

MASTER CHART

Age	gender	mRS	ISCVT	WBC	neutrophil	ANC	Lymphocyt	ALC	platelets	NLR	PLR	galen vein	outcome
24	f	2	0	14500	74.9	10860	17.1	2480	302000	4.37	121.77		
26	f	1	0	9200	80.12	7371	16.21	1491	203000	4.94	136.51		
23	f	2	0	7400	74.31	5498	17.12	1266	199000	4.34	157.18		
23	**f**	**4**	**3**	**14000**	**86.16**	**12062**	**10.11**	**1415**	**298000**	**8.52**	**210.6**	**yes**	**protein c deficiency**
24	f	3	0	12000	82.26	9853	11.12	1694	262000	5.81	154.66		
37	**f**	**5**	**6**	**20000**	**85.24**	**17048**	**11.23**	**2246**	**290000**	**7.59**	**129.11**	**yes**	**died**
19	f	1	0	8500	76.89	6535	15.21	1285	190000	5.08	147.86		
28	f	1	0	6500	79.26	5152	18.28	1188	183000	4.33	154.04		
32	f	3	1	11000	80.1	8811	13.38	1471	230000	5.98	156.31		
27	f	1	0	9100	78.35	7129	20.46	1861	286000	3.83	153.68		
22	f	2	0	12300	81.51	10025	17.56	2159	328000	4.64	151.92		
18	f	1	0	12000	76.1	9120	20.1	2412	250000	3.78	103.2		
20	f	1	0	10100	81.1	8191	17.1	1727	259000	4.74	149.97		
30	f	2	0	8500	81	6885	15.23	1294	196000	5.32	151.46		
22	f	1	0	8800	82	7216	15.98	1406	210000	5.13	149.35		
27	f	1	0	11800	79.7	9409	17.2	2029	192000	4.63	94.62		
25	f	1	0	7500	81.1	6082	16.21	1215	176000	5	144.85		
36	f	5	3	7100	85.37	6061	11.11	788	157000	7.69	204.16	yes	
31	f	2	0	7100	79.58	5650	16.23	1152	175000	4.9	151.9		
20	f	2	1	7600	80.88	6146	14.88	1130	176000	5.43	155.75		
26	f	1	0	6800	75.15	5110	20.14	1369	198000	3.73	144.63		
30	f	3	1	8300	83.56	6935	14.42	1196	185000	5.79	154.68		
26	f	2	0	7700	80.7	6213	16.5	1270	187000	4.89	147.24		
33	f	3	1	13000	80.23	10429	14.78	1912	305000	5.45	159.51		
28	**f**	**3**	**1**	**16200**	**80.2**	**13284**	**14.6**	**2365**	**391000**	**5.61**	**165.32**	**yes**	**ocp intake**
37	**f**	**5**	**4**	**15300**	**81.21**	**12425**	**11.23**	**1718**	**326000**	**7.23**	**189.75**	**yes**	**sle**
26	f	3	0	7800	79.23	6177	15.76	1229	185000	5.02	150.52		
23	f	2	0	8100	81.45	6597	16.23	1314	198000	5.02	150.68		
18	f	1	0	5400	76.13	4111	19.36	1045	149000	3.93	142.58		
24	f	1	0	5800	79.78	4627	19.45	1128	170000	4.1	150.7		
31	f	1	0	6300	74.11	4668	21.02	1323	190000	3.52	143.61		
25	f	4	2	14300	79.26	11334	12.49	1786	316000	6.36	176.93		
21	f	1	0	8600	75.12	6460	21.1	1814	253000	3.56	139.74		
25	f	1	0	5400	74	3996	22.1	1193	170000	3.34	142.49		
19	**f**	**2**	**0**	**9500**	**76.23**	**7241**	**19.3**	**1833**	**285000**	**3.95**	**155.48**		**sle**
25	f	5	3	16000	78.24	12518	11.89	1902	366000	6.58	192.42	yes	
44	m	2	1	9200	81.03	7454	15.3	1407	212000	5.29	150.67		
33	m	3	2	9100	80.75	7348	13.12	1193	254000	6.15	212.9		
41	m	3	2	14000	84.19	11786	12.1	1694	310000	6.95	183		

32	m	3	3	8200	86.23	7070	10.41	853	183000	8.28	214.53	yes	
24	m	3	1	14300	79.21	11327	12.46	1781	299000	6.35	167.88		
36	m	3	2	8600	80.25	6901	12.26	1054	198000	6.54	187.85		
45	m	1	1	7900	72.13	5698	15.69	1239	183000	4.59	147.69		
34	m	3	1	9700	82.49	8001	12.36	1198	202000	6.67	168.61		
19	**m**	**5**	**4**	**10100**	**82.11**	**8293**	**11.28**	**1139**	**296000**	**7.28**	**259.87**		**homocystenemia**
20	m	2	1	9500	81.26	7719	14.98	1423	221000	5.42	155.3		
42	m	2	1	10200	74.15	7563	13.12	1338	204000	5.65	152.46		
41	m	1	1	7900	80.41	6352	14.41	1138	176000	4.52	150.68		
29	m	3	1	13400	82.46	11049	13.52	1811	302000	6.1	166.75		
45	m	3	2	9000	82.12	7390	12.12	1090	187000	6.77	171.55	yes	
46	m	1	1	9600	82	7872	14.3	1372	211000	5.73	153.79		
41	m	3	2	13200	83.43	11012	13.13	1733	289000	6.35	166.76		
39	m	2	1	14000	81.26	11376	17.26	2416	253000	4.71	104.71		
35	m	4	2	15000	83.23	12484	13.23	1984	337000	6.29	169.85		
40	m	3	3	14300	82.65	11818	12.46	1781	311000	6.63	174.62	yes	
37	m	4	4	16200	86.12	13951	10.1	1636	319000	8.52	194.48	yes	
41	m	5	4	6900	88.12	6080	10	690	153000	8.82	221.73		
23	m	1	1	8200	82.64	6776	15.26	1251	187000	5.41	149.48		
49	m	1	1	16900	72.01	12169	17.1	2889	386000	4.21	133.61		
36	m	3	2	8400	84.18	7071	12.36	1038	175000	6.81	168.59		
44	m	4	3	9900	86.1	8523	12.1	1197	210000	7.12	175.43		
30	m	2	0	8600	79.13	6805	16.78	1443	210000	4.71	145.53		
44	m	2	2	9100	79.35	7220	15.46	1406	215000	5.13	152.91		
41	m	2	2	7900	81.23	6417	14.23	1124	177000	5.7	157.47		
43	m	3	1	8300	80.76	6703	15.46	1283	195000	5.22	151.98		
48	m	4	2	9600	82.31	7901	13.21	1268	216000	6.23	170.34		
46	m	4	4	8900	83.13	7398	12.26	1091	193000	6.78	176.9		
33	m	2	2	11000	81	8910	14	1540	246000	5.78	159.74		
42	m	3	2	12300	83.56	10277	13.46	1655	284000	6.2	171.6		
49	**m**	**5**	**4**	**9900**	**89.1**	**8820**	**9.2**	**910**	**200000**	**9.69**	**219.78**	**yes**	**died**
36	m	2	1	7200	79.12	5696	16.13	1161	175000	4.9	150.73		
35	m	3	2	8700	80.45	6999	14.23	1238	190000	5.65	153.47		
43	m	5	4	15400	88.16	13576	10.45	1609	330000	8.43	205.1		
20	**m**	**3**	**1**	**11500**	**79.03**	**9088**	**15.04**	**1729**	**261000**	**5.29**	**150.95**		**homocystenemia**
41	m	1	1	9300	70.12	6521	22.12	2057	287000	3.17	139.52		
39	m	1	1	8100	75.12	6084	20.16	1632	231000	3.72	141.54		
43	m	1	1	8000	76.54	6123	20.13	1610	231000	3.8	143.47		
34	m	3	1	8200	80.1	6568	14.23	1166	181000	5.63	155.23		
32	m	2	2	7700	79.24	6101	14.82	1141	175000	5.35	153.37		
43	m	3	1	8200	80.06	6564	14.23	1166	185000	5.62	158.66		

41	m	4	3	9600	84.23	8086	12.23	1174	201000	6.88	171.28	yes
32	m	3	2	9000	80	7200	14.1	1269	200000	5.67	157.6	
37	m	4	2	7800	79.3	6185	13.2	1029	172000	6.01	167.15	
29	m	1	1	7100	75.64	5370	19.46	1381	200000	3.88	144.82	
42	m	4	2	8300	79.45	6594	13.26	1100	182000	5.99	165.45	
47	**m**	**5**	**6**	**6900**	**82.1**	**5664**	**11.2**	**772**	**172000**	**7.33**	**222.79**	**died**
42	m	4	4	11000	85.1	9361	13.12	1443	270000	6.48	187.11	
36	m	3	2	6400	79.1	5062	19.1	1222	190000	4.14	155.48	
24	**m**	**1**	**1**	**5900**	**75.3**	**4442**	**20.6**	**1215**	**175000**	**3.66**	**144.03**	**polycythemia vera**
37	m	3	2	6900	79.7	5499	15.12	1043	163000	5.27	156.27	
34	m	2	1	7400	78.13	5781	17.1	1265	196000	4.56	150.19	
40	m	2	1	8200	78.12	6405	18.2	1492	229000	4.29	153.48	
43	m	4	4	6400	83.14	5320	12.23	782	165000	6.8	210.97	
45	m	4	3	7200	80.4	5788	13.1	943	175000	6.13	185.57	yes