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Original Research Article

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

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Abstract

Background: Cerebral venous and sinus thrombosis (CVST) is a rare stroke mainly affecting young and middle-aged adults, particularly women, due to pregnancy, puerperium, and oral contraceptives. The study investigates whether NLR and PLR can be used as predictive markers of CVST and whether these ratios and clinical severity scales correlate. **Materials and Methods:** This prospective observational study was conducted for twelve months at the Institute of Internal Medicine. Ninety-four radiological diagnosed CVST patients with various manifestations were included after applying preliminary exclusion criteria based on history. The study population underwent a detailed history and clinical examination, and patients were included based on specific criteria and informed consent. **Result:** In the study, males were higher (61.7%) than females (38.3%). Males were more likely to have CVST, while females were more likely to have postpartum, SLE, and other conditions. Patients with ISCVT had symptoms ranging from mild headache to coma, with a maximum representation of 1 (30.9%) and a minimum representation of 6 (2.1%). The mean NLR and PLR of 94 patients were statistically significant, with an F value of 55.757 and a p0.05 increase in clinical severity by the mRS score. The mean NLR and PLR scores of 94 patients were 5.589 and 259.87, respectively, with an F value of 36.462 and 26.947. As the PLR increased, clinical severity by ISCVT score increased with p0.05. **Conclusion:** The neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios can be used as markers of CVST and predict the future outcome in patients with vague neurological symptoms.

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] 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. Diagnosing and confirming cerebral venous and sinus thrombosis (CVST) can be challenging due to the vague clinical symptoms that overlap with other cerebrovascular events, such as headache to coma.

In recent years, advancements in diagnostic techniques and early anticoagulation treatment have significantly reduced mortality rates in patients with CVST. Despite this, many patients who recover from the disease without an apparent physical disability may still experience residual chronic symptoms such as headaches, neuropsychological issues, and other similar problems. These long-term symptoms can significantly impact a patient's quality of life and require appropriate management and care.[5] Therefore, radiological imaging techniques are necessary to diagnose and confirm CVST. For physicians working at hospitals where the scope for imaging techniques is remote, a common, easily available surrogate marker would help them diagnose CVST and would help in prompt referral to a higher centre for definitive treatment.[6-8] Rather than discrete values like platelet count, leucocyte count, platelet and red cell distribution width, and hs-CRP, which can get influenced by several parameters, ratios like

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neutrophil to lymphocyte ratio and platelet to lymphocyte ratio give a more reliable prediction.[9]

As CVST is both an inflammatory and a thrombotic event, NLR and PLR are better predictors than hs-CRP or RDW/PDW in recent studies. According to ongoing research, NLR has a higher negative predictive value, and PLR has a higher positive predictive value.[5] The study aimed to evaluate the potential of Neutrophil-to-Lymphocyte Ratio (NLR) and Platelet-to-Lymphocyte Ratio (PLR) as predictive markers of Cerebral Venous Sinus Thrombosis (CVST). Also, to investigate the association between these ratios and CVST, correlate the ratios with mRS and ISCVT scores, and determine if the ratios can be used as a predictive marker.

MATERIALS AND METHODS

This prospective observational study was in the Institute of Internal Medicine, Rajiv Gandhi Government General Hospital (RGGGH), Madras Medical College, Chennai from 2018-2020.

Inclusion Criteria

Males and females aged between 18 and 60 with radiologically confirmed Cerebral Venous Sinus Thrombosis (CVST) were included.

Exclusion Criteria

Patients with known thromboembolic disorders, chronic inflammatory conditions, exogenous steroid use, known Coronary Artery Disease (CAD) cases, and previous stroke were excluded.

Ninety-four radiological diagnosed CVST patients with various manifestations were included after applying preliminary exclusion criteria based on history. The study focused on patients with radiologically confirmed Cerebral Venous Sinus Thrombosis (CVST) admitted to IIM, RGGGH. A thorough history and a detailed clinical examination were performed on the study population. Patients were included in the study after obtaining informed consent and meeting the established criteria. The Glasgow Coma Scale (GCS), Modified Rankin Score (mRS), and ISCVT risk scores were determined at the bedside for those included in the study. A complete blood count was performed at the first presentation, and Neutrophil-to-Lymphocyte Ratio (NLR) and Platelet-to-Lymphocyte Ratio (PLR) were calculated.

All collected data were entered into a Microsoft Excel sheet. Subsequently, the calculated ratios were correlated with mRS and ISCVT scores. One-way ANOVA was used to analyze the data for both NLR and PLR ratios. The results of the ANOVA analysis are presented in a table format, which includes the sample size (N), mean, standard deviation (STD), 95% confidence interval for the mean, and the minimum-maximum values for each group. The F-value and p-value for each group are also provided.

RESULTS

In the study, the percentage of males was higher (61.7%) compared to females (38.3%). The largest representative age group was those between 18 and 28 years (35.1%), and the least representative group was between 48- and 58 years (2%).

Of 58 males, 29 had consumed alcohol at some time. The cause attributed to CVST in these patients was alcohol. Out of 36 females, 24 were postpartum (within seven days post-delivery), two were diagnosed with SLE, and 10 had conditions like protein c deficiency, oral contraceptive pills intake and others.

Most patients presented with an mRS score of 1 or 3. 26.6% of patients presented with an mRS score of 1 with no clinical disability despite symptoms. While 27.7% of patients presented with mRS score three who were moderate disability, requiring some but able to walk without assistance. None of the patients scored 0 (asymptomatic) as they all had a wide spectrum of symptoms ranging from mild headache to coma.

The novel scoring system based on large-scale research on cerebral venous and sinus thrombosis, ISCVT, ranges from 0 to 9. The original study has not witnessed many patients with a score >6. The maximum representation is by a score of 1 (30.9%), and the least by a score of 6 with only 2 (2.1%) patients [Table 1].

Table 1: Demographic data of the study

		Frequency	Percentage
Gender	Male	58	61.7
	Female	36	38.3
Age group	18-28	33	35.1
	29-38	29	30.9
	39-48	30	31.9
	49-58	2	2.1
mRS	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
ISCVT	.00	26	27.7
	1.00	29	30.9
	2.00	20	21.3
	3.00	8	8.5

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	4.00	9	9.6
	6.00	2	2.1

Table 2: Correlation of mRS between NLR and PLR

		N	Mean STD	95% Confidence interval for the mean		Min-Max	F value
				Lower Bound	Upper Bound		
NLR	1.00	25	4.2532± 0.68869	3.9689	4.5375	3.17-5.73	55.757**
	2.00	21	4.9690± 0.50749	4.7380	5.2001	3.95-5.78	
	3.00	26	5.9981± 0.79795	5.6758	6.3204	4.14-8.28	
	4.00	13	6.7777± 0.84802	6.2652	7.2901	5.99-8.52	
	5.00	9	7.8489± 0.95843	7.1122	8.5856	6.58-9.69	
PLR	1	25	141.8584± 14.00279	136.0783	147.6385	94.62-154.04	28.7**
	2	21	149.0448± 12.64684	143.2880	154.8015	104.71-159.74	
	3	26	166.7415± 16.87630	159.9251	173.5580	150.52-214.53	
	4	13	181.6969± 15.37974	172.4030	190.9908	165.45-210.97	
	5	9	204.9678± 35.31352	177.8234	232.1122	129.11-259.87	

Out of 94 patients who presented with 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. The results were statistically significant, with an F value of 55.757. As the NLR increased, there was an increase in clinical severity by mRS score with $p<0.05$.

Out of 94 patients who presented with 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. The results were statistically significant, with an F value of 28.7. As the PLR increased, there was an increase in clinical severity by mRS score with $p<0.05$ [Table 2].

Table 3: Correlation of ISCVT between NLR and PLR

		N	Mean ± STDV	95% Confidence interval for the mean		Min-Max	F value
				Lower Bound	Upper Bound		
NLR	0	26	4.4850 ±0.63747	4.2275	4.7425	3.34-5.81	36.42**
	1	29	5.0569 ±0.87955	4.7223	5.3915	3.17-6.67	
	2	20	5.9670 ±0.6650	5.6555	6.2785	4.14-6.95	
	3	8	7.2288 ±0.85401	6.5148	7.9427	6.13-8.52	
	4	9	7.7811± 1.11258	6.9259	8.6363	6.48-9.69	
	6	2	7.4600 ±0.18385	5.8082	9.1118	7.33-7.59	
PLR	0	26	143.6988± 15.0905	137.6036	149.7940	94.62-157.18	26.94**
	1	29	150.9586± 12.1318	146.3439	155.5733	104.71-168.61	
	2	20	167.9140± 14.4962	161.1296	174.6984	152.91-212.90	
	3	8	191.0763± 17.0799	176.7971	205.3554	171.28-214.53	
	4	9	207.2989± 24.8747	188.1784	226.4193	176.90-259.87	
	6	2	175.9500 ±66.2417	419.2086	771.1086	129.11-222.79	

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

Out of 94 patients who presented with various ISCVT scores, the least PLR was 94.62, and the highest was 259.87. A mean PLR of 161.989(±26.181 SD; 156.536 – 167.261 of 95% CI) was obtained. The results were statistically significant, with an F value of 26.947. As the PLR increased, there was an increase in clinical severity by ISCVT score with $p<0.05$ [Table 3].

DISCUSSION

Diagnosis of CVST becomes crucial due to its dreadful complications and as the resolution of symptoms and disease activity occurs with prompt treatment. Therefore, a simple diagnostic and predictive tool will help identify patients with CVST even before radiological diagnosis. As the patients have vague clinical presentations like headaches, blurring of vision or seizures without localizing features, a biomarker can help categorize these patients as having a more insidious disease. The study conducted by Johansson et al,[10] discovered that high alcohol consumption in men was linked to a heightened risk of VTE. Interestingly, our current research also found that most study participants were male (61.7%), with a significant proportion of them having a history of alcohol consumption. On the other hand, the remaining 38.3% of participants were female.

The present study's findings corroborate the earlier observation that postpartum women face a higher risk of developing venous thromboembolism than pregnancy.[11] Specifically, the age group between 18 and 28 years had the highest representation in our study, with 33 patients, out of which 27 were females. Of these 27 females, 24 were postpartum, and the remaining had underlying conditions contributing to cerebral venous sinus thrombosis.

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The standardized incidence ratio for venous thromboembolism in pregnant or postpartum women was 4.29, indicating a significantly higher risk of developing thrombus among postpartum women than pregnant women.[12] These findings highlight the need to closely monitor postpartum women for venous thromboembolism and implement preventive measures, such as prophylactic anticoagulation, when necessary.

Early diagnosis of CVST is crucial to prevent fatal outcomes. The symptoms of CVST are diverse, ranging from mild to severe, which could be easily ignored or treated symptomatically. Severe symptoms like seizures or loss of consciousness require referral to higher centres. Patients with milder symptoms, if left untreated, can progress to involve the dural sinus and cerebral venous system extensively, leading to fatal outcomes. A simple biomarker could be valuable in the early detection of CVST, especially in patients with a postpartum period in females or an alcohol history in males. In this regard, using simple and affordable biomarkers such as the NLR and PLR has been evaluated in CVST. These ratios are better indicators than discrete values like platelet and neutrophil counts, which are nonspecific or expensive. Researchers have established cut-off values of 3 for NLR and 130 for PLR in CVST.[13,14] The data collected in this study also showed that all patients with radiologically proven CVST had an abnormal rise in both NLR and PLR, which indicates the potential usefulness of these ratios as a screening tool for CVST.

Our study determined the cut-off values for NLR and PLR in CVST. It assessed the disease severity using the Modified Rankin Scale (mRS) and International Study of Cerebral Vein and Dural Sinus Thrombosis scoring (ISCVT). The study found that all radiologically proven CVST patients had a rise in NLR and PLR, with a mean NLR of 5.589 and a mean PLR of 161.898. The study predicted the mortality rate six months post-CVST and used mRS and ISCVT to assess patient outcomes. However, a series of values and a structured questionnaire is required for long-term outcome prediction. The study found that most patients had moderate disability, as evidenced by a maximum representation of mRS score 3 (27.7%). This is consistent with previous studies showing that most patients with CVST experience residual neurological deficits, ranging from mild to severe, depending on the location and extent of the thrombosis.[15]

The study also identified a group of 23 females between the ages of 18-28 who had ISCVT scores of 0 and were in the postpartum period. This finding is noteworthy as previous studies have suggested that postpartum CVST may have a more favourable outcome than other causes of CVST.[16,17] In this study, the researchers utilized the mRS and ISCVT scoring systems to evaluate the severity of post-CVST events and examined their correlation with NLR and PLR ratios. The results indicated a positive correlation between NLR and mRS, with lower NLR values associated with an mRS score of 1 and higher NLR values associated with higher mRS scores. Similarly, a linear relationship was observed between PLR values and mRS scores, with lower PLR values corresponding to an mRS score of 1 and higher PLR values corresponding to an mRS score of 5.

Furthermore, the study showed that both ISCVT and NLR values were linearly related, with lower NLR values associated with an ISCVT score of 0 and higher NLR values associated with an ISCVT score of 6. Similarly, a direct correlation was observed between ISCVT scores and PLR values, with most patients having a score of 0 and their respective PLRs in the lower range, and some even having PLRs below the original cut-off value 130.

Limitations

Multiple values of NLR and PLR during 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 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 the Indian population reference range have to be conducted as the Indian genotype has vast differences from that of the ethnic groups. A novel risk prediction score can be derived using the available data. Several new ratios, including MLR (monocyte lymphocyte ratio), can be added in future studies to derive a new risk prediction score.

CONCLUSION

CVST is a life-threatening disease with a wide spectrum of vague symptoms. To prevent under-diagnosis by health care professionals where radiological investigations are unavailable, an accessible, acceptable and affordable biomarker can be helpful in prompt referral without 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 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 a higher centre if the ratios suggest CVST.

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