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MEAN PLATELET VOLUME (MPV) AS A RISK STRATIFICATION TOOL AND AN EARLY PROGNOSTIC MARKER IN ACUTE ISCHEMIC STROKE: AN OBSERVATIONAL STUDY FROM TERTIARY CARE HOSPITAL IN NORTH EAST INDIA

General Medicine

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ABSTRACT

Introduction: Stroke is one of the leading causes of disability and death worldwide. A stroke or cerebrovascular accident is defined as "an abrupt onset of neurological deficit that is attributable to a focal vascular cause." A majority of strokes are ischemic in origin (80%), which can be either thrombotic or embolic in nature. Activation of platelets play an important role in the process of atherosclerosis. The mean platelet volume (MPV) is a laboratory marker associated with platelet function and activity. Increased MPV in thromboembolic disease is reflected as an important risk factor. The aim of the study is to assess MPV in acute ischemic cerebrovascular stroke and, furthermore, to find out its diagnostic value in an acute setting to help risk stratification in patients with ischemic stroke. **Material And Methods:** The present study was conducted in Department of General Medicine, SMCH from 1st June 2021 to 31st May 2022, with the aim of evaluating the role of Mean platelet volume (MPV) in determining the severity and prognosis of Acute Ischemic stroke. It was a hospital based observational study comprising of 100 patients diagnosed with acute ischemic stroke who presented to the hospital within 48 hours of onset of symptoms. Equal number of age and sex matched control group was taken after fulfillment of inclusion and exclusion criteria. The diagnosis of stroke was made clinically according to World health organization and confirmed by brain CT and MRI when needed. Blood samples were collected and MPV was assessed within 2 hours after admission. The severity of ischemic stroke was assessed using Modified Rankin scale (MRS). **Results:** In this study, MPV value was found to be significantly high in stroke patients (11.26 ± 1.22 fL) as compared to control group (9.98 ± 1.22 Fl, p value<0.00001). The MPV value was found to be significantly high in patients with higher MRS score in comparison to those with lower scores (p value=0.000011). Higher MPV values were also associated with poorer functional outcome at Day 7, increased length of hospital stay, increased ICU admissions and in-hospital mortality. **Conclusion:** Platelet size (MPV), a marker of platelet function is a physiological variable of hemostatic importance. Higher MPV values were associated with more severe stroke and worser outcome. MPV can predict the outcome among stroke patients in terms of morbidity and mortality. In developing countries with limited resources, MPV can be a useful and cost effective biomarker in evaluation and prognostication of patients admitted to hospital with acute ischemic stroke.

KEYWORDS

Acute ischemic stroke, Mean platelet volume, Modified Rankin scale, mortality.

INTRODUCTION:

A stroke, or cerebrovascular accident, is defined as "an abrupt onset of neurological deficit that is attributable to a focal vascular cause." Thus the definition of stroke is clinical, and laboratory studies including brain imaging are used to support the diagnosis[1]. Stroke occurs when the symptoms and signs last for more than 24 hours or there is evidence of infarction or haemorrhage on brain imaging. The definition excludes Transient ischemic attack (TIA), which is defined as focal neurologic symptoms but lasting less than 24 hrs without evidence of infarction.

The World Health Organization estimates that 15 million strokes occur each year throughout the world. 5 million of them pass away, and another 5 million suffer from permanent disabilities. Even in India, stroke is a leading cause of mortality and disability. The estimated range of the adjusted stroke prevalence rate is 84–262/100,000 in rural areas and 334–424/100,000 in urban areas. According to recent population-based studies, the incidence rate is 119–145/100,000.[2]

Stroke can be as a result of cerebrovascular occlusion or haemorrhage. Ischemic stroke accounts for 85% of all strokes, with the remaining being haemorrhagic. At present, clinical diagnosis relies on history, neurological examination, and neuroimaging. There are several scoring systems used to quantify the degree of severity of stroke like NIH stroke scale and Modified Rankin scale.

Platelets are small (1-4 um in diameter), discoid, nonnucleated structures formed by megakaryocyte fragmentation. Platelets, in addition to being acute phase reactants, are affected by the patient's health and nutritional status. Platelets are composed of up to 65% smooth, disc-shaped cells (discocytes), with the remaining 10-35% being less clearly defined cells (spherical platelets). The morphology of platelets has important implications for both interpreting functional expressions of platelets and measuring platelet size experimentally.[3]

Counter flow centrifugation can be used to separate platelets into fractions based on differences in platelet volume. These differences in platelet volume correlate with differences in density, dense body content, LDH (lactate dehydrogenase) enzymatic activity, platelet aggregation to ADP (adenosine diphospate), and serotonin uptake and release, supporting the relevance of mean platelet volume (MPV) as a measure of platelet functional capability. Platelet size (MPV), as a marker and possibly determinant of platelet function, is thus a physiological variable of hemostatic importance.[4]

Platelet volume is influenced by a variety of intrinsic and extrinsic factors. When the megakaryocyte platelet haemostatic axis (MPHA) is disrupted, hyper-functional platelets form, which may contribute to the development of vascular disease or an acute thrombotic event such as ischemic stroke or myocardial infarction.[5] The mean platelet volume (MPV) is a commonly used laboratory marker for platelet functions, which ranges between 7.5-10.5 fl in a healthy person.[6] Large platelets are more reactive than ordinary platelets, produce more prothrombotic factors, show greater aggregation to adenosine diphosphate (ADP), collagen, or adrenaline, and secrete more thromboxane A2 (TxA2).[7]

Increased platelet size has also been reported in patients with vascular risk factors such as diabetes[8], hypercholesterolemia, and metabolic syndrome. Patients with stroke[9] and acute myocardial infarction had higher MPV values than controls. Furthermore, MPV has been demonstrated to be predictive of stroke in patients who have had previous cerebrovascular episodes, even 3.9 years before the initial

occurrence.[10] Recent developments in clinical laboratory techniques have opened up new avenues for a better knowledge of platelet function in thrombosis, immunology, inflammation, and angiogenesis. As a result, platelet activation is now recognized as a therapeutic target in atherothrombosis, hypertension, and diabetes.

The links between MPV and cerebrovascular accidents and their prognosis have already been called into question. Several studies have found an increase in MPV in various subtypes of brain stroke, both in the acute phase and long after the disease[11].These findings suggest that increased MPV may play an important role in the development or progression of brain stroke. However, no studies in our country have sufficiently assessed the role of MPV during acute ischemic events until now. The aim of this study is to evaluate correlation of MPV in with various risk factors of ischemic stroke, and also to find out its prognostic significance in an acute setting to determine the outcome and severity of stroke.

MATERIALAND METHODS:

The present study is a hospital-based Observational study conducted in the Department of General Medicine, Silchar medical college & hospital, Silchar, Assam over a period of one year from June 2021 to May 2022. A total of 100 cases of acute ischemic stroke who met the selection criteria along with equal number of age and sex matched controls (100) were included in this study. The diagnosis of stroke was performed clinically according to World health organization and confirmed by brain CT or MRI when needed. Blood samples were collected and MPV was assessed within 2 hours of venepuncture to avoid time dependent platelet swelling that occurs in EDTA vials. The severity of ischemic stroke was assessed using Modified Rankin scale (MRS). The mean MPV of stroke patients was calculated and compared with that of controls and further analysis was done to find out any correlation of MPV with various risk factors and outcomes of stroke. The primary outcome of the study was the functional outcome assessed by MRS score, while the secondary outcomes included length of hospital stay, ICU admissions and in-hospital mortality. Statistical analysis was prepared using Microsoft Excel and Statistical Package for Social Sciences (SPSS for Windows, version 20.0 Chicago, SPSS Inc.). The Institutional ethics Committee approved the study after thorough review and written informed consent was taken from all the participants involved in the study.

Inclusion and Exclusion criteria (For cases):

Inclusion Criteria

- Patients presenting with first episode of acute ischemic stroke confirmed by imaging studies [NCCT brain].
- Presentation to the hospital within 48 hours of symptom onset.
- The individuals were included irrespective of sex and socio-economic status.
- Age > 18 years

Exclusion Criteria

- Previous history of cerebrovascular accident or Transient ischemic attacks or recurrent stroke
- Patients with sub-arachnoid, subdural, extradural or intracerebral haemorrhage.
- Patients with history of degenerative neurological diseases or any other CNS diseases.
- Patients presenting to hospital 48 hours after the onset of neurological symptoms.
- Patients on antiplatelet drugs (e.g. aspirin), anti-coagulation therapy, immunosuppressant or recent blood transfusion (within 6 weeks).
- Patients with peripheral vascular disease, acute infections, hepatic or renal disorders, any malignancies, any hereditary platelet disorder or other blood dyscrasias.

Selection Of Controls:

Subjects for the control group were selected randomly from different sectors of the society belonging to diverse socio-economic status who were apparently healthy. The control groups comprised of 100 subjects who were mostly apparently healthy attendants of patients attending the OPD or IPD of the hospital. The subjects selected were age and sex matched with the case group. All individuals of the control group cooperated voluntarily and informed consent was taken.

RESULTS:

Demographic Profile:

The mean age for the study population was 63.25±14.19 years when compared to 62.84 ±13.71 years for the controls. The maximum number of cases being in the age group between 61-70 years (29%), which was followed by age group of 51-60 years (23%). Females (67.06±12.55 years) with stroke were significantly older than males (61.29±14.67 years) with a p value of 0.043. 66% of the study subjects were males while 34% were females. Out of the many risk factors, Hypertension was most prevalent among the study subjects, with 61% among cases and 41% among controls, and a significant p value of 0.007 on comparing. Smoking was placed second with prevalence of 42% among cases and 27% among controls, the difference being statistically significant with p value 0.025. Other risk factors like dyslipidaemia, diabetes Mellitus, Alcoholism were also more prevalent in cases compared to controls. However, the differences were not statistically significant. Mean platelet volume (MPV) has got a statistically significant correlation with ischemic stroke with an average MPV in cases being 11.26±1.22fL compared to 9.98 ±1.22fL in controls (p value<0.00001).

Table 1: Baseline characteristic of Study population:-

CHARACTERISTIC	CASES	CONTROLS	P value
Males (%)	66	66	1.00
Females (%)	34	34	1.00
Mean age (years)	63.25 ± 14.19	62.84 ± 13.71	0.84
Mean age of Males (years)	61.29 ± 14.67	61.64 ± 14.58	0.92
Mean age of Females (years)	67.06 ± 12.55	65.18 ± 11.69	0.84
Hypertension (%)	61	42	0.007*
Diabetes mellitus (%)	34	23	0.084
Dyslipidaemia (%)	29	19	0.097
Smoker (%)	42	27	0.025*
Alcoholic (%)	21	12	0.086
Mean platelet volume (MPV)(fL)	11.26 ± 1.22 (8.9-14.0)	9.98 ± 1.22 (7.5-13.1)	<0.00001 *

Relation Of Mpv With Stroke Risk Factors

The mean MPV of stroke patients aged less than 60 years was 11.13±1.17fL while those aged 60 years or above was 11.34±1.26 fL. There was no statistical difference in MPV values between the two age groups. The females had slightly higher MPV values as compared to the males, but the difference was not statistically significant. The MPV was higher among hypertensives as compared to non-hypertensives and the difference was statistically significant (p value=0.033). The MPV was also higher in diabetics as compared to non-diabetics. However, the difference was not found to be statistically significant. Similarly, no statistically significant difference could be found on comparing MPV between patients with dyslipidaemia and normal lipid profile, smoker and non-smoker or alcoholic and non-alcoholic stroke patients. The results are shown in **Table 2.**

Table 2: Relationship between MPV and risk factors for Acute ischemic stroke

Risk factors	n	MPV (fL)	P value
Gender			
Male	66	11.12 ± 1.31	0.094
Female	34	11.52 ± 1.01	
Age (years)			
<60	38	11.13 ± 1.17	0.42
≥60	62	11.34 ± 1.26	
Hypertension			
Hypertensive	61	11.46 ± 1.29	0.033*
Non-hypertensive	39	10.95 ± 1.05	
Diabetes Mellitus			
Diabetic	34	11.45 ± 1.19	0.27
Non-Diabetic	66	11.16 ± 1.23	
Dyslipidemia			
Yes	29	11.39 ± 1.44	0.53
No	71	11.21 ± 1.12	
Smoking			
Smoker	42	11.49 ± 1.33	0.128
Non-smoker	58	11.09 ±1.12	
Alcoholism			

Alcoholic	21	11.44 ± 1.32	0.484
Non-alcoholic	79	11.21 ± 1.19	

MPV And Severity Of Acute Ischemic Stroke (on admission)

The clinical severity of stroke at presentation was determined by the Modified Rankin's scale(MRS) score, which ranges from score 0- 6, with score 0 implying "No symptoms" and score 6 implying "Death". Moderately severe disability (Score 4) was present in 26% of the cases, moderate disability in 24% followed by severe disability in 20%, slight disability in 18% and No significant disability in 12% of cases. There is a strong co-relation between MPV and severity of stroke (on the basis of Modified Rankin's scale) with a p value=0.000011 which is statistically significant. Thus higher values of MPV are associated with severe forms of stroke as shown in **Table 3**.

Table 3: MPV AND Stroke Severity

MRS SCORE (0-6) (on admission)	No (n=100)	MPV (fL)	P value (ONE WAY ANNOVA)
Score 1 (No Disability)	12	10.4 ±0.89	0.000011* (significant)
Score 2 (Slight Disability)	18	10.54 ±0.91	
Score 3 (Moderate Disability)	24	11.09 ±1.15	
Score 4 (Moderately Severe Disability)	26	11.62 ±1.09	
Score 5 (Severe Disability)	20	12.15 ±1.18	

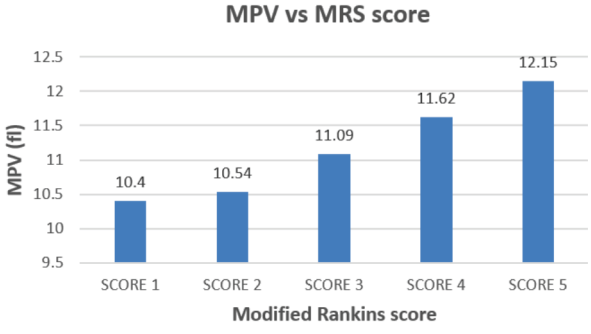

Figure 1: Bar Diagram Showing Comparision Of Mean Platelet Volume With Mrs Score

The correlation of mean platelet volume with the Modified Rankin Scale score was calculated using Pearson formula. A positive correlation was present with R value 0.498, and this correlation was statistically significant with p value <0.00001 as shown in **Table 4** and **Figure 2**.

Table 4: Mean Platelet Volume And Mrs Score Correlation Analysis

MEAN PLATELET VOLUME AND MODIFIED RANKIN SCALE CORRELATION	PEARSON FORMULA	
	R value	0.498
	P value	<0.00001(significant)

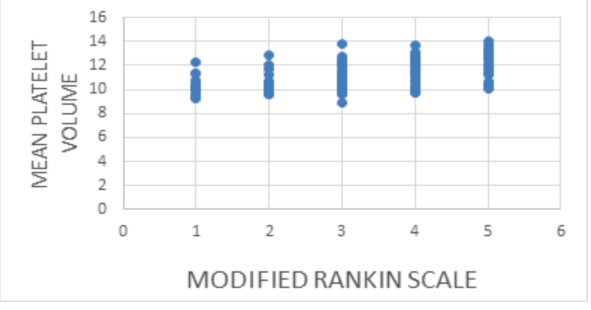

Figure 2: Scatter Plot Showing Correlation Between Mpv And Mrs Score

MPV And Outcome Of Stroke

The primary outcome was the functional outcome as assessed by the modified Rankins scale (MRS) score at discharge or at Day 7 of admission, whichever was earlier. MRS score 0-2 was considered as good outcome while score 3-6 as poor outcome. The secondary outcomes included need for ICU admission, death in hospital and duration of hospital stay. The mean hospital stay for cases was calculated to be 5.71 (=6 days). Prolonged hospital stay was defined as more than 6 days. 43% of patients had a prolonged hospital stay, 31% required ICU admission and 12% was the in-hospital mortality.The various outcomes are depicted in Figure 3.

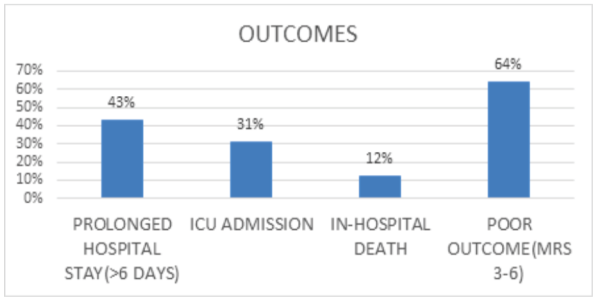

Figure 3: Bar Diagram Showing Distribution Of Cases Based Upon Various Outcomes

MRS score was re-evaluated at Day 7 and compared with MPV values of admission. 36% of stroke patients had a good functional outcome (MRS 0-2) at Day 7, while 64% had a poor outcome (MRS 3-6) including 12% death. The mean MPV in patients with poor outcome at day 7 was significantly higher than those with good outcome (11.70±1.17 vs 10.48 ± 0.88) ($p < 0.001$). Thus higher MPV values at admission were associated with poor functional outcome at one week.

The mean MPV of patients who required ICU admission was significantly higher when compared with those did not require ICU admission (p value=0.001). Out of 100 patients, 57 had duration of hospitalization for ≤ 6 days, while 43 were hospitalized for more than 6 days. The mean MPV values in those with >6 days hospital stay was significantly higher than those with ≤ 6 days hospital stay (p value <0.001). Out of the 100 cases included in the study, there were 12 in-hospital deaths. The mean MPV in these non-survivors was 12.12 ± 0.88 fL while it was 11.14 ± 1.22 fL in survivors (p value=0.003). Higher MPV values were associated with increased duration of hospital stay, ICU admissions and increased in-hospital mortality.

Table 5: MPV AND OUTCOME OF STROKE

OUTCOME	N (no.)	MPV	P value
Functional outcome (at Day 7)			
MRS< 2 (GOOD OUTCOME)	36	10.48 ± 0.88	< 0.001 (Significant)
MRS >3 (POOR OUTCOME)	64	11.70 ± 1.17	
Hospital Stay			
< 6 days	57	10.89 ± 1.10	<0.001* (significant)
> 6 days	43	11.76 ± 1.21	
ICU admissions			
Yes	31	11.89 ± 1.22	0.001* (significant)
No	69	10.98 ± 1.12	
Mortality			
Yes	12	12.13±0.88	0.003* (significant)
No	88	11.14 ± 1.22	

DISCUSSION:

Stroke is a major global health problem. It is the second commonest cause of death and fourth leading cause of disability worldwide. India, like other developing nations, is in the midst of a stroke epidemic, and the burden of stroke is enormous with significant regional variations. Recent advances in clinical laboratory techniques have opened new horizons for a better understanding of the role of platelets in thrombosis, immunity, inflammation and angiogenesis. Platelet size (MPV), a marker and possibly a determinant of platelet function, is a physiological variable of haemostatic importance and is being considered as a newly emerging risk factor for atherothrombosis. Recent studies have suggested a possible correlation between Mean platelet volume (MPV) with Acute ischemic stroke and its severity and prognosis.

In the present study, the mean age of cases was 63.25±14.19 with maximum number of cases being in the age group of 61-70 years (29%), followed by age group of 51-60 years (23%). The mean age of stroke patients in our study was much lower as compared with Western studies like O'Malley et al[7] (79.5± 6.5 years), Pikija et al[12](76 years)

and is comparable with Indian studies done by Patil VC et al[13](62.51±12.72 years) and Ot S et al[14](61.22±11.9 years). This signifies that the mean age of Indian population developing stroke is less when compared with Western population. The disparity in age may be due to higher life expectancy in the West as compared to the developing world. Stroke was found to be more prevalent among male patients (66%) as compared to females (34%). The male preponderance in this study corelate well with all other studies except for O'Malley et al[7] and Pikija et al[12] that showed female preponderance. Males are more prone to develop ischemic stroke than women which may be due to increased prevalence of risk factors like smoking, hypertension, diabetes mellitus in males. Women are less affected probably due to a genetic cause and positive effects of oestrogen on the cerebral circulation, thereby protecting them from ischemic stroke.

Hypertension was found to be the most prevalent risk factor (61%) followed by smoking (42%) in the stroke patients, which were significantly higher than the control group. Other risk factors like dyslipidaemia, diabetes Mellitus, alcoholism were also more prevalent in cases compared to controls, but the differences were not statistically significant. The results were comparable to studies done by Muscari et al(84.7%)[15], Pikija et al[12](82.7%) and Ot S et al[14](64%) which showed hypertension as the most prevalent risk factor. Arterial hypertension predisposes to ischemic stroke by aggravating atherosclerosis and accelerating heart disease, increasing the relative risk for stroke three- to fourfold. The mechanisms of enhanced atherogenesis promoted by cigarette smoking are incompletely understood but include reduced capacity of the blood to deliver oxygen, cardiac arrhythmias, increased blood coagulability, and triggering of arterial thrombosis and arterial spasm.

In this study, the mean MPV was significantly higher among hypertensives as compared to normotensives. This implies that hypertension increases the Mean platelet volume thereby increasing the risk and severity of stroke. Possible mechanism behind it being platelet activation, primarily caused by the effects of the sympathetic and renin-angiotensin systems, shear stress, increased production of reactive oxygen species, altered regulation of calcium signalling, endothelial dysfunction, and decreased nitric oxide bioavailability. Similar observations were made by Coban et al.[16]and Varol et al.[17], who showed significant elevation of MPV in hypertensives as compared with normotensives. However, no significant correlation of MPV was found with respect to other risk factors of stroke such as age, gender, diabetes mellitus, dyslipidaemia, smoking and alcohol intake.

In this study, MPV was found to be significantly higher in stroke patients as compared to the control group. Higher MPV was thus independently associated with acute ischaemic stroke. The findings were consistent with studies like O'Malley et al.[7] and Butterworth et al.[18],which showed raised MPV was independently associated with acute ischemic stroke. There was also a strong correlation seen between MPV and severity of stroke (based on Modified Rankin's scale), with higher MPV values being associated with more severe stroke. This study thus validates the association of MPV in stroke patients as a prognostic marker in terms of functional disability and stroke outcome, which is consistent with studies done by Ghahremanfard F et al [19] and Ot S et al[14].

MPV had an inverse relationship with the outcome at the end of one week. Higher MPV values on admission were associated with poor functional outcome (MRS 3-6) at day 7. The observations were consistent with studies done by S. Greisenegger et al.[20] and Mohamed AA, Elnady HM et al[21] which showed that elevated MPV at presentation in stroke patients was associated with poor functional outcome at 1 week and 3 months respectively. There was also a statistically significant correlation found between MPV and secondary outcomes of strokes, with higher MPV values on admission being associated with prolonged hospital stay, increased need for ICU admission and increased mortality. This signifies that higher MPV on admission was associated with poorer outcome and increased morbidity and mortality.

The findings in our study suggest that larger platelets play a role in the development of cerebral thrombosis. These findings are likely to represent changes occurring during thrombopoiesis, and large platelets may promote the thrombotic event in a susceptible individual. The increase in MPV could have contributed to the development of the stroke rather than being a result of the acute event. Our findings suggest that there is an independent relationship between MPV and stroke, and that elevated MPV may be considered a risk factor for acute ischemic stroke. One could argue that increased MPV and platelet reactivity are simply markers for a more severe stroke and a more pronounced acute-phase reaction. This study included patients who presented within 48 hours of the onset of their stroke, and a sample of MPV was taken immediately upon admission. Because platelets have a life span of 8–10 days, the increased MPV at admission suggests that the increase must have occurred prior to the stroke. Over 90% of the platelet population whose distribution was assessed following a stroke was already in circulation prior to the vascular occlusion. Platelet size is determined at the progenitor cell level (i.e., the megakaryocyte), and recent research has found that cytokines like interleukin-3 and interleukin-6 influence megakaryocyte ploidy and can lead to the production of more reactive, larger platelets. Because the megakaryocyte determines platelet volume, the evidence of change in platelet volume in stroke presented in our study suggests that stroke may be preceded by changes in megakaryocytes. As a result, it is reasonable to speculate that a proinflammatory state preceding the cerebrovascular event may confer a higher MPV and a prothrombotic condition. More likely, our findings indicate that patients who later suffered a severe stroke had an increased MPV, indicating higher platelet reactivity, prior to the stroke. Exact mechanism by which elevated MPV might play a role in development or progression of cerebrovascular accidents are not completely understood, but there are possible explanations:

1. First, platelet activity is increased with ischemic stroke as evidenced by increased levels of soluble platelet P selectin and thromboxane A2, which are considered atherogenic factors.
2. Second, cytokines such as interleukin 3,6, which play an important role in the pathophysiology of ischemic stroke, influence megakaryocyte ploidy, which in turn affects platelet size and can lead to production of more reactive and large platelets, and so proinflammatory conditions before ischaemic stroke may lead to higher MPV, which in turn leads to prothrombotic conditions.
3. Finally, large platelets may be a consequence of secretion and metabolism of biologically active substances during aging, diabetes, high blood pressure, and obesity and consequently cause an increased risk of ischemic stroke.

CONCLUSION:

It can be concluded from the present study that raised MPV is independently associated with acute ischemic stroke suggesting a role for larger platelets in the genesis of cerebral thrombosis. MPV can act as prognostic marker in acute ischemic stroke and can help in prognosticating and predicting the severity and outcome of stroke. MPV can prognosticate patients with acute ischemic stroke in terms of functional outcome, need for ICU admission, duration of hospital stay as well as mortality. These findings thus raise the potential importance of MPV as non-invasive, easily measurable, inexpensive test for early detection and risk stratification of cerebrovascular stroke. Further research is required to accurately determine the role of MPV in stroke pathology, outcome and importantly, in individuals at risk of stroke. It is expected that the present study will encourage newer studies and research works related to the above subject with a much more expanded approach and for a considerable duration to further cement the role of MPV in patients suffering from stroke.

Conflicts Of Interest: Authors declare no conflict of interest exist.

Ethical consideration: Ethical clearance was obtained from Institutional Ethical committee of Silchar medical College.

Informed consent- Due consent was obtained from the patients for the work.

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