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Original Research Article

Correlation of platelet indices with severity and clinical outcome in patients with acute ischemic stroke

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Abstract

Aim and Objectives: To study an association of platelet indices in acute ischemic stroke and compare them with age- and gender-matched controls, to find predictive value of platelet indices in acute ischemic stroke and association of platelet indices for in hospital mortality and morbidity by national institute of health stroke scale (NIHSS) and clinical outcome by modified Rankin score and to study the correlation of MPV with established (Traditional) risk factors for acute ischemic stroke.

Method: 100 consecutive cases of acute ischemic stroke and equal number of age and gender match healthy controls were enrolled in study. Blood sample was collected at time of admission from cases and control for laboratory investigations. Modified Rankin score, ECG, BMI and NIHSS scale score of every patient carried out at time of admission, also modified Rankin score was calculated on day 7 or discharge.

Results: Cases and controls ranged from 55 to 65 years of age with males (55%) outnumbering females (45%) in both groups. Incidence of hypertension, diabetes, alcohol, obesity, dyslipidaemiaas well as mean MPV, PDW, P-lcr and platelet count were more in cases than controls. Platelet indices increased in severe stroke, amongst MPV and platelet count increase was statistically significant. 25% mortality observed in studied cases. MPV and platelet count were increased in death and dependent cases compared to discharge and independent cases while PDW and P-lcr had positive correlation. Acute ischemic stroke associate hyponitremia had higher mortality. Platelet counts increases mortality in positive relation.

Conclusion: Platelet indices can be used as positive predictor for acute ischemic stroke. Mean platelet volume can be used as a prognostic indicator and high mean platelet volume is well correlated with severity and outcome of acute ischemic stroke at the time of admission itself.

Keywords: Platelet indices, acute ischemic stroke, National institute of health stroke scale, Modified Rankin score, Dyslipidaemia, Hyponitremia.

1. Introduction

According to the recently published Global Burden of Disease 2010 Study (GBD 2010) [1], stroke is the second leading cause of death globally and the third leading cause of premature death and disability as measured in DALY(disability adjusted life year). In India, crude prevalence rate of stroke in various studies has been reported as 1.27–2.20/1000 persons with the only exceptions in Parsi community, who showed dramatically high prevalence of 8.42/1000 persons [2]. Indian lifestyle with a carbohydrate rich predominantly vegetarian diet and a sedentary lifestyle, especially in urban areas might be contributing to high prevalence of metabolic syndrome which further predisposes to atherosclerotic diseases like cardiovascular, cerebrovascular and vascular diseases.

Platelets play a major role in pathogenesis of vascular disease. Platelet size and function is measured by Mean Platelet Volume (MPV). Platelet activity is accentuated in acute ischemic stroke due to blood vessel occlusion that leads to ischemia, endothelial damage and new platelet formation. The new younger platelets are larger in size due to increase in α granules and the presence of platelet factor [3]. Thus the mean platelet volume is elevated in ischemic stroke. Studies conducted worldwide,

have found that mean platelet volume has prognostic significance in determining the outcome and severity of stroke.

However the platelet indices - (Platelet - PLT, Mean platelet volume - MPV, Platelet distribution width - PDW and Platelet large cell ratio - PLCR) are the determinants of platelet functionality, among which increased mean platelet volume (MPV) and platelet distribution width (PDW) were found to be attributed in the causation of thromboembolic complications [4,5]. It is also noted that the platelets with increased number and size possibly affect the platelet distribution width contributing in the pathogenesis of vascular complications [6]. Hyperactivity of platelets has an important role in the initiation of thrombosis and atherosclerotic lesions. Larger platelets are more active enzymatically and metabolically and have a higher thrombotic ability as compared to the small sized platelets [7].

The present study was undertaken to find out predictive value of platelet indices in acute ischemic stroke and to correlate platelet indices with severity of acute ischemic stroke by national institute of health stroke scale (NIHSS) and clinical outcome by modified Rankin score.

2. Materials and Methods

After obtaining Institutional Ethics Committee approval and written inform consent from all the patients, this hospital based case control study was conducted in 100 consecutive cases of acute ischemic stroke and were compared with 100 equal number of age and gender matched controls. The inclusion criteria for cases- cases presented with first stroke, previous stroke but not on any anti platelet medication and who were admitted to hospital within 72 hours. Exclusion criteria for cases- cases presented with focal neurological deficit after 72 hours, with intra-cerebral hemorrhage, subarachnoid hemorrhage, acute coronary syndrome, cases with infectious pathology, arthritis, cancer or prior inflammatory pathology, patients on NSAIDS, anti-platelet drugs, warfarin and hormone replacement therapy, patients not willing to participate in the study, patient with valvular heart disease, cong. heart diseases or haemoglobinopathies, severe hepatic or renal impairment, thyroid disorders, pregnant women, inflammatory diseases (like rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease etc.), sepsis, patient with recent history of blood transfusion. Exclusion criteria for controls were subject diagnosed to have acute ischemic stroke at any time in the past, those on NSAIDS, antiplatelet drugs, warfarin and hormone replacement therapy and failure to obtain consent recruitment of controls in: subjects attending out-patient department of hospital for minor ailments or routine medical check-up, subjects from community (Population based) accompanying patients (other than neurological involvement) or amongst office working staff from various department of this institution without having any evidence of acute or chronic neurological disease. The other exclusion criteria were same for controls as that for cases.

A detail history, general and systemic examination was done for all the subjects. Patient with history and clinical feature suggestive of acute stroke within onset of 72 hr; non contrast CT head had been done. Phillips 250 slice machine was used for CT scanning. It easily identifies and differentiate acute ischemic stroke from hemorrhagic stroke. At the time of admission blood sample was collected from cases and control for laboratory investigations (platelet indices, random blood sugar, kidney function test, serum electrolyte, liver function test, lipid profile). Modified Rankin score, ECG, BMI and NIHSS scale score of every patient carried out at time of admission, also modified Rankin score was calculated on day 7 or discharge.

A standard mercury sphygmomanometer was used to measure the blood pressure of participant with regular adult or large adult size cuff, based on the participant's arm circumference. Three readings of each systolic blood pressures (SBPs) and diastolic blood pressures (DBPs) were recorded with an interval of 1minute at least, and an average of the last 2 measurements was used for the data analysis. Systolic blood pressure more than 140mmHg and diastolic blood pressure more than 90 mmHg taken as hypertension. Random blood sugar was observed with help of Glucometer Make-Sure. Blood sugar level <140mg/dl represent good glycemic controls; we take cut off value 140mg/dl. Lipid profile measured with help of Becman Coulter Au 5800 machine Normal value are for Triglycerides (TG) - <150 mg/ dL, Total cholesterol (TC) - <200 mg/dL, High density lipoprotein (HDL) - > 40 mg/ dL, Low density lipoprotein - <140 mg/dL. Body mass index calculated with help of Quetelet index (Body mass index - measured as weight in kg/height in metres^2) and classified with WHO criteria for obesity. Cardiac abnormality was detected by 12 lead ECG, taken with help of EDAN ECG machine. Non contrast computer tomography (NCCT) in ischemic stroke shows loss of gray-white differentiation, sulcal effacement, and hyper attenuated clot in the proximal vessels. NCCT has been reported to have low sensitivity (39%) and high specificity (100%) for detection of ischemic changes. MRI scans was another head imaging involved in study.

Severity of acute ischemic stroke was measured with help of NIHSS. Stroke severity was grouped in minor stroke (1-4), moderate stroke (5-15), moderate to severe stroke (16-20) and severe stroke (21-42). Also, severity of acute ischemic stroke is classified on basis modified Rankin score, it consists of six grades from 0 to 5 and additional category '6', which means death. Clinical outcome measured as independent (modified Rankin score ≤ 2) and

dependent (modified Rankin score ≥ 3) on day 7. Score between 0-2 taken as less sever stroke associated with good prognosis. mRs more than 3 to 6 taken as sever stroke. Various parameters such as smoking, alcohol consumption, hypertension, lipid profile, MPV, PDW, P-lcr and platelet count were compared with controls.

2.1 Statistical analysis

Continuous variables were presented as mean ± SD; categorical variables were expressed in frequency and percentages. Demographic, hemodynamic and clinical parameters were compared between cases and controls also death and discharged patients by performing independent t-test. Categorical variables were compared by performing chi-square test. For small number fisher exant test was applied wherever applicable. Pearson correlation coefficient (μ) was assessed to study nature and magnitude of correlation between platelet indices and lipid level for normalized data and spearman's correlation coefficient (Rho) was calculated for non-normalized data. Multiple logistic regression analysis was performed to identify the risk factor for predicting mortality in patient of acute ischemic stroke. Receiving Operating Characteristic (ROC) Curve analysis was performed to differentiate between presence and absence of acute ischemic stroke. Area under curve, sensitivity, specificity, and cut off value were estimated for all four platelet indices. All tests were two sided, $p<0.05$ was considered as statistically significance. Statistical software 'STATA' version 14.0 was used for data analysis.

3. Observations and Results

In the present study, cases ranged from 55 to 65 years of age with mean age was 59.78 ± 2.80 years. Controls ranged from 55 to 65 years of age with mean age 59.05 ± 3.10 years. Males (55%) were outnumbering females (45%) in cases and control showing ratio 1.22:1. Table 1 show the age and sex distribution of subjects in cases and control.

Table 1: Age and sex distribution of subjects in cases and control

Parameters	Cases (n= 100)	Control (n=100)	p-value
Age(yrs)	59.78 ± 2.80	59.05 ± 3.10	0.0825
Male (110)	60.08 ± 2.87	59.05 ± 3.12	0.2153
Female (90)	59.05 ± 3.12	59.04 ± 3.11	0.9872

The risk factor like smoking and alcohol were taken in both case and controls group as shown in table 2. Hypertension was one of risk factor for ischemic stroke, we compared it in cases and controls and found that the SBP and DBP was significantly increased in cases than controls, ($p<0.0001$). Also, lipid profile found to be significantly elevated in cases ($p<0.0001$). There were no significant differences observed in pulse rate. Biochemical profile in cases and controls were also compared like blood sugar level, kidney function, liver function, serum electrolyte, and lipid profile as depicted in table 3.

Table 2: Relation between smoking and alcoholic in cases and controls

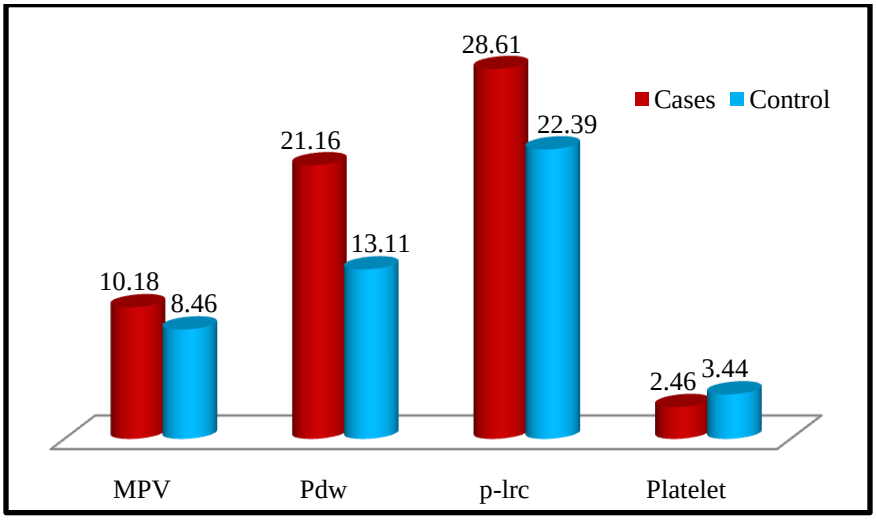
Risk factors	No. of subject	Cases	Controls	p-value
Smoking	Yes (n=34)	16	18	0.590
	No (n=166)	84	82	
Alcohol	Yes (n=36)	23	13	0.066
	No (n=164)	77	87	

Table 3: Hemodynamic, Lipid levels and Clinical parameters in Cases and Controls

Parameters	Cases	Controls	p-value
Pulse (rate /min)	79.16± 6.83	79.9 ±7.45	0.4653, NS
SBP (mmHg)	135.2 ±8.74	126.7± 12.87	<0.0001, HS
DBP(mmHg)	83.5 ±6.28	80.06 ±7.25	0.0004, HS
BMI ($Kg/m^{2)}$	23.29± 2.01	21.05± 2.82	<0.0001, HS
Random Blood Sugar (mg/dl)	134.48 ±10.43	132.97 ±17.14	0.4527, NS
Urea (mg/dl)	27.68± 7.35	28.05± 8.88	0.7539, NS
Na (meq/L)	138.46± 5.98	137.15 ±7.17	0.1625, NS
K (meq/L)	3.68± 0.47	4.17± 3.56	0.1708, NS
TG (mg/dl)	155.22± 17.29	125.88± 26.75	<0.0001, HS
TC (mg/dl)	171.28 ±31.82	144.43± 33.88	<0.0001, HS
HDL(mg/dl)	44.01 ±7.05	62.82± 13.07	<0.0001, HS
LDL	146.53 ±18.50	77.68 ±13.81	<0.0001, HS

Platelet indices were compared in cases and controls as shown in figure 1. Mean MPV, PDW, P-lcr and platelet count was more in cases compared to controls ($p<0.0001$). Platelet indices were change with smoking, alcohol, hypertension, diabetes, and dyslipidaemia in positive correlation but not statistically significant.

Table 1: Comparison of platelet indices between cases and Controls



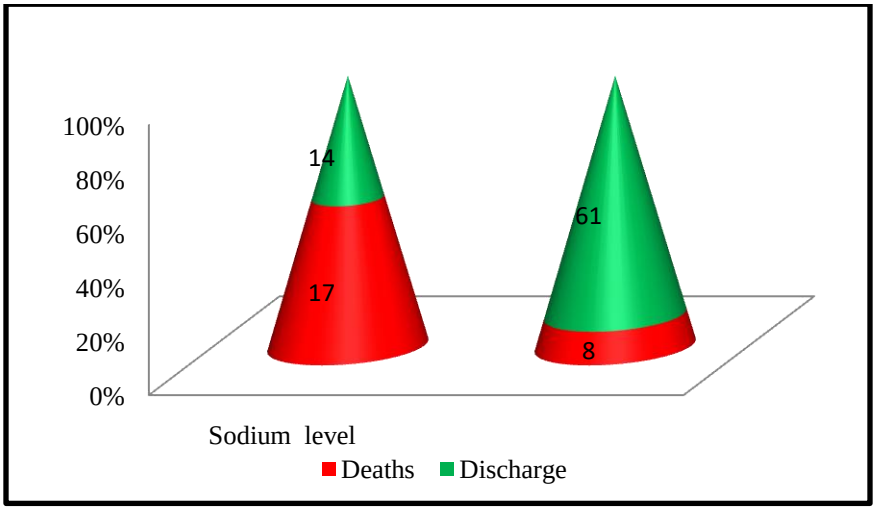
Platelet indices increased in severe stroke, amongst MPV and platelet count increase was statistically significant. As severity increases platelet indices were increases as shown in table 4.

Table 4: Correlation of platelet indices and NIHS score

NIHS score (n=100)	Mpv (fl)	Pdw (fl)	p-rlc (%)	Platelets count ($\times 10^5$ /µL)
1-4 (minor stroke)	9.35± 0.77	12.73± 4.53	27.01± 5.87	1.98± 0.69
5-15 (moderate stroke)	9.85 ±0.70	21.19± 5.98	28.39± 7.10	2.28± 0.60
16-20 (moderate to severe)	10.08± 0.89	21.57± 6.13	27.53± 5.91	2.41± 0.64
21-42 (severe stroke)	10.8 ±1.64	22.26 ±7.22	30.31± 8.37	2.82± 0.55
P-value	0.0027, HS	0.0119, S	0.4289, NS	0.0012, HS

Out of total cases were studied, 75 cases were discharged and 25 cases death. In present study we compared clinical and biochemical parameters to find out its effect on out-come in the form of discharge and death. There were non-significant in these parameters association except hyponitremia. Patient having hyponitremia had higher mortality (p<0.0001), (Figure 2).

Figure2: Serum sodium level in cases and association with its outcome in form of death



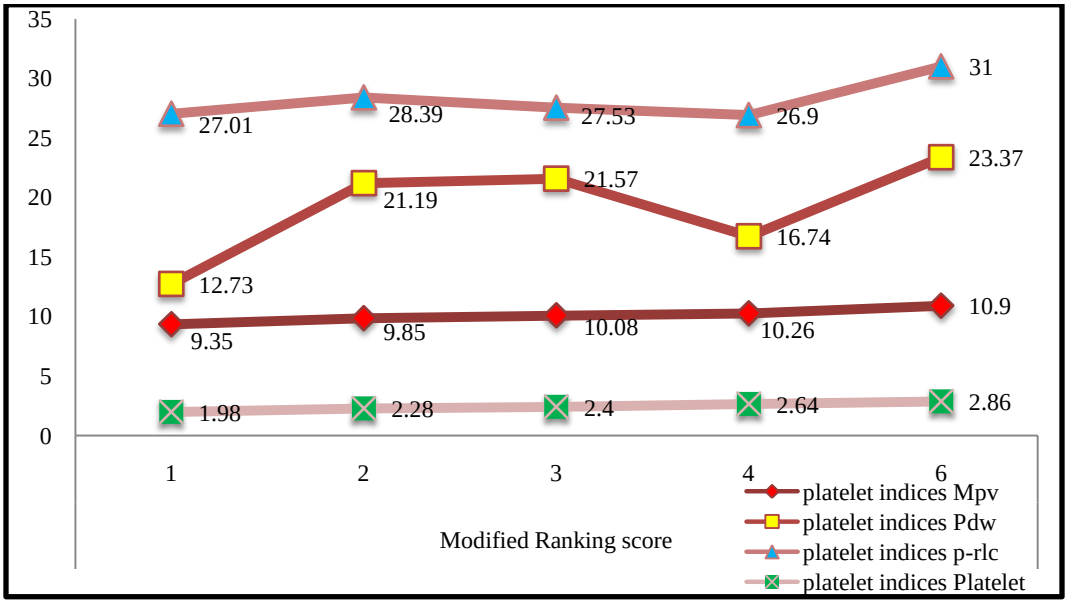
Clinical outcome defined on basis of modified Rankin score which was calculated on day 7 or at the time of discharge, scoring given to discharge patients from 1 to 5 (as there clinical condition at time of discharge) and score 6 given to death patients. 6 patients had score1, 32 patients had score 2, score 3 was seen in 32 patients, score 4 was seen in 5 patients and death (score6) was seen in 25 patients. Table 5 shows the association of platelet indices and clinical outcome. From this table, we found that as MPV, PWD, P-rlc increases, mortality also increases.

Table 5: Association of platelet indices and outcome

Platelet indices	Discharge (n=75)	Deaths (n=25)	p-value
Mpv (fl)	9.94± 0.89	10.90± 1.69	0.0003, HS
Pdw (fl)	20.65± 6.36	22.7 ±7.07	0.1795, NS
p-rlc (%)	27.81± 6.44	31.0± 8.49	0.0520, NS
Platelet ($\times 10^5$ /µL)	2.33± 0.63	2.86± 0.54	0.0004, HS

Platelet indices also compared with modified Rankin score to find out clinical outcome, found that lesser the platelet indices there is better outcome as shown in figure 3. MPV and platelet count increased in dependent cases (9.77 ±0.73 fl and 2.33±0.62 $\times 10^5$/µL) than independent cases (10.43±1.35 fl and 2.61±0.63 $\times 10^5$/µL) with statistically significance. PDW and P-lcr had positive correlation.

Figure 3: Correlation of modified Rankin scores and platelet indices



The multiple logistic regression analysis was done to predict causative independent risk factor of acute ischemic stroke. We found serum sodium < 135 meq/L and high platelet count had statistically significance p<0.001. Other risk factor like smoking, alcohol, hypertension, hyperlipidemia, diabetes, MPV, PDW, and P-lcr had statistically non significance. ROC curve analysis, the area under curve for MPV was 0.902 (95% confidence interval 0.86-0.94) indicating high discriminative value of MPV for predicting sever ischemic stroke from mild stroke. When MPV taken as >9.2fl, a sensitivity of 84% and specificity of 79% found. When we took PDW, P-lcr and platelet counts cut off value as >14.6 fl, >24.1% and >2.7×10^5 /µL area under curve were 0.8378, 0.7545 and 0.7992 respectively.

4. Discussion

The present study was carried out on consecutive 100 patients of acute ischemic stroke admitted in tertiary care and teaching hospital over period of 2 year, age and sex matched control were taken from healthy volunteer accompanied with patient. There was male preponderance in this study similar to all other studies [8,9] except for O'Malley [10] and Pikija *et al* [11] that showed female preponderance. The study excluded patient of young stroke as young stroke has different etiology than atherosclerosis. Smoking, alcoholism, BMI, hypertension, diabetes mellitus, and hyperlipidemia are major risk factor for acute ischemic stroke. Smoking found in 16 cases (16%) and in 18 (18%) controls while alcoholism found in23 (23%) cases and 13 (13%) controls. There was more number of alcoholic in cases group than control but not significantly. There was no statistically significant difference among the two groups with regard to the smoking and alcoholism with p<0.590 and p<0.066 respectively. This finding was compared with the other studies [9, 12].

As hypertension is one of major reversible risk factor for acute stroke, it was compared with cases and control group. Cases had higher systolic blood pressure (SBP) and diastolic blood pressure (DBP) than controls but not a statistical significant value p<0.0004, this was compared with previous studies [9,13,14]. Random blood sugar level was measured in cases and controls. Instead of fasting and post meal level, we took random blood sugar at admission for comparison. There was random blood sugars were increased in cases than controls, increase trend found in glucose level but no significant correlation were found p=0.4527. Most of cases were not taking orally as they were in comorbid state, and on intravenous fluid. It is difficult to

find out diabetic status of such patient. The study found significantly increased in TG, TC and LDL in acute ischemic stroke patient than control group, this result was correlated with the study done by Togha *et al* [15] and Arabadzhieva *et al* [16].

In present study, platelet indices were studied in view of traditional risk factor for ischemic stroke. There was increased platelet indices observed in cases as compare to controls, thus significant correlation of platelet indices with ischemic stroke. Waseem F Al-Tameemi *et al* [17] reported no statistically significant difference in mean platelet volume (MPV), PDW, P-lcr among the case and control groups. Increased MPC will increase the chance of arterial thrombosis and this had been shown also in this study as MPC was higher in group 2 patients when compared with group 1 or control. MPV, PDW and P-lcr were not significantly in this study, may be there indices were checked in stored sample unlike current study, measured it immediately.

We correlated platelet indices with its risk factor. Female have hyper proliferative bone marrow due to iron deficiency anaemia. Female have higher MCV and MPV as compare to male. In current study, there were no statistically significant different observe in female gender. Cigarette smoking's crucial role in disrupting platelet activation and aggregation, as well as other coagulation processing components leading to thrombotic formations has been recently suggested. MPV was significantly raised in smoker than nonsmoker, in present study. PDW, P-lcr and platelet count also increased in positive correlation. Similar results were also reported in other studies [18-20]. Alcohol affects not only platelet production but also platelet function. Alcohol increases MPV and decreases platelets count through depressant action over bone marrow. When comparing platelet indices in alcoholic and non-alcoholic one, there was no any positive or negative correlation found in the study with alcohol consumption. There were increases in MPV in significant manner when platelet indices compared with hypertension. Other parameters were increased in positive relation but not in statistically significance. Present study was consistent with previous studies [21, 22]. Correlation of hyperglycemia with platelet indices found positive co relation of blood sugar with MPV and P-lcr and positive correlation with platelet count with non-significant. We do not found PDW correlation with diabetes mellitus. Hyperlipidemia like increased total triglyceride, total cholesterol, and low density lipoprotein increases platelet indices. The present study found positive significance of MPV with triglyceride and total cholesterol. PDW significantly increase with triglyceride. All platelet indices were increase in hyperlipidemia state. Previous studies [23,24] have found similar results.

Comparison of severity of score with platelet indices, found statistically significant increase in MPV and decrease in platelet counts. PDW also increases in positive correlation but not in statistically significant. P-lcr does not show any relation with NIHSS scores. Hence the present study shows that higher the platelets, severe the ischemic stroke. Total 75 patients were discharged and in 25 patients death occurred. MPV and platelet count were increased in death cases as compared to discharge cases with statistically significance while PDW and P-lcr increased in positive correlation but not statistically significant. Comparison of platelet indices in independent and dependent group found that MPV and platelet count were increased in independent cases than dependent cases with statistically significance and PDW and P-lcr increased in positive correlation but not in statistically significance. This finding of the study correlated with the study done by Shah *et al*[25].

Multiple logistic regression analysis found that hyponitremia (<135 meq /L) and platelet counts were independent risk factor for acute ischemic stroke. ROC curve analysis, the area under curve for MPV was 0.902 indicating high discriminative value of MPV for predicting sever ischemic stroke from mild stroke. These findings were compared with other studies [8,26].

5. Conclusion

Platelet indices is cost effective investigation can be obtained in most health care center. The present study is corroborating other observation that platelet indices are higher in acute ischemic stroke and increase in MPV and platelet count associate with sever ischemic stroke, mortality. Platelet counts can be used as a significant risk factor for acute ischemic stroke and other vascular events independent of other risk factor. Mean platelet volume can be used as a prognostic indicator and high mean platelet volume is well correlated with severity and outcome of acute ischemic stroke at the time of admission itself. The primary goal of biomarker MPV in ischemic stroke patients should be early identification of high risk individuals who can be targeted for aggressive acute management and improved secondary preventive measures. It is not yet clear that increase in platelet indices is cause or effect of ischemic stroke. We propose that MPV may useful as predictor of clinical outcome in acute ischemic stroke.

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