Original Research Article

The Association between Platelet Lymphocyte Ratio and In-Hospital Outcomes in Patients with First Attack of Acute ST-elevation Myocardial Infraction following Thrombolysis with Streptokinase in a Tertiary Care Hospital

Abstract

Introduction: Platelet Lymphocyte ratio (PLR) has been found to be a good predictor of future adverse cardiovascular outcomes in patients with ST-segment elevation myocardial infarction (STEMI).**Aim:** Investigation was done in the aim to detect the role of Platelet Lymphocyte ratio (PLR) in predicting in-hospital adverse cardiac events in patients with STEMI thrombolysed with streptokinase in a tertiary care hospital. **Methods:**This cross sectional descriptive study carried out in the Department of Cardiology,Mymensingh Medical College Hospital, Mymensinghfor fifteen-month duration from January, 2018 to March, 2019, in STEMI patients, who were thrombolysed with inj. Streptokinase (STK) had blood samples at admission, analyzed complete blood counts for PLR calculation. They were grouped into two, low and high PLR, taking 150 as cut-off. Chi square test was used to compare rate of adverse events and death in hospital stay. Logistic regression analysis was used to estimate predictive ability of PLR for in-hospital cardiac events. **Results:** A total of 79 (%) patients among 217 patients had complications. Patients in high PLR group had higher rate of complications (63.6% vs. 21.4%, p <0.001) in hospital than those in low PLR group. Arrhythmias (13.0% vs. 5.0%, p <0.036), Heart failure (45.5% vs. 15.0%, p=0.001), Cardiogenic shock (10.4% vs.3.6%, p <0.001), Death (9.1% vs. 6.4%, p=0.473), occurred more in high PLR group. Mean PLR was significantly different between Group-I and group-II (96.21±27.79 vs. 233.21±88.20, p<0.001). Multivariate regression analysis showed PLR an independent predictor of in-hospital adverse cardiac events (at 10% level of significance, p = 0.001). **Conclusion:** High admission PLR is an independent predictor for in-hospital adverse cardiac events in patients hospitalized for STEMI thrombolysed with streptokinase.

Key Words: PlateletLymphocyte ratio, Adverse cardiac events, STEMI, Thrombolysis, Streptokinase.

Introduction

"Acute coronary syndrome (ST elevation myocardial infarction, Non ST elevation myocardial infarction, Unstable angina) is the leading cause of death in developed countries & second leading cause of death in developing countries & by the year 2020 Ischaemic heart disease will hold the first place in the WHO list of leading cause of disability"[1]."Coronary artery disease (CAD) is a major cause of death and is a global health problem reaching epidemic in both developed as well as in developing countries"[2]. Bangladesh is a small country with vast population. Cardiovascular diseases are becoming a significant burden on health care services in Bangladesh. The prevalence of CAD in Bangladesh has been reported to be 0.33% to 19.6% in different studies. "Despite marked disparity in values, there seems to be a rising prevalence and mortality from CAD"[3].

Acute myocardial infarction patients constitute a large proportion of admissions in coronary care unit and their management and risk stratification is of immense importance. "In most cases, STEMI is due to rupture of an inflamed thin capped fibro-atheroma containing a lipid rich necrotic core with superimposed thrombosis which results coronary artery occlusion" (Stone, 2008). "It is well known that inflammation and thrombosis play a crucial role in the pathophysiology of STEMI"[4]"Vulnerable plaque, characterized by thin fibrous caps, large lipid core,macrophage infiltration and neo-vascularization,is closely related to inflammation"[5-6]."The majority of acute coronary syndromes can be attributed to plaque vulnerability".[7,43,44,45].

Platelets are a pivotal component in the process of inflammation and thrombosis. "Higher platelet counts may increase thrombocyte activation and aggravate the release of inflammatory mediators,prompting a harmful inflammatory process[8]. In contrast,lymphocytes have been shown to modulate the immunologic response at all stages of the atherosclerotic process. "The association between lower lymphocyte counts and risk of adverse CV outcomes has also been confirmed in previous studies"[9-10].

"High PLR was related to increased inflammatory activity and aggravated pro-thrombotic status due to megakaryocytic proliferation and relative thrombocytosis in high –risk with ACS"[11-13]."Therefore,High platelet counts have been shown to development of no-reflow via micro-vascular plugging,thrombus formation, and vasoconstriction"[14-15]. "Leukocytes play a major role in both initiation and progression of atherosclerosis, and have been implicated in acute rupture of atherosclerotic plaques with superimposed thrombus formation"[16-21]."Lymphocyte is also a major part of chronic inflammation in the atherosclerotic process. Lymphocyte may express interleukin 10, which plays a significant role in transmigration of mononuclear cells and tissue inhibitor of metalloproteinase" 1[22]. "Hence, a lower lymphocyte count may be associated with adverse cardiovascular outcomes[23].Lower lymphocyte levels were associated with advanced heart failure[17, 24] and mortality[20] in STEMI patients".

Higher levels of PLR were also reported to be associated with the slow flow/no-reflow phenomenon[25-26], increased SYNTAX score[25] impaired infarct-related artery patency[27], stent restenosis[28], contrast-induced nephropathy[29],recurrent non-fatal myocardial infarction[30] and worsening in-hospital and long-term mortality in STEMI[31-33]."PLR may be associated with clinical outcomes such as all-cause mortality, recurrent myocardial infraction, heart failure, serious cardiac arrhythmias, and ischemic stroke in patient with STEMI because an increased PLR was shown to be related to inflammation and atherosclerosis"[34].Investigation was done in the aim to detect the role of Platelet Lymphocyte ratio (PLR) in predicting in-hospital adverse cardiac events in patients with STEMI thrombolysed with streptokinase in a tertiary care hospital.

Methodology

This cross sectional descriptive type of study was carried out in the Department of Cardiology,Mymensingh Medical College Hospital, Mymensingh. The total study duration wassince January 2018 to March 2019. Patient admitted into the Department of Cardiology, MMCH with ST Elevation Myocardial Infraction. Patients with first attack of ST Elevation Myocardial Infraction within 12 hours of onset of chest pain who fulfilled the inclusion and exclusion criteria of study.Non**-**randompurposive sampling method was obtained.Patients with first attack of ST elevation myocardial infarction who were present within 12 hours of onset of chest pain & who were thrombolysed were included in the study.

Patients having previous history of myocardial infarction, having major non-cardiovascular disorder such as sepsis or clinical evidence of active infection, recent (three months) surgery or trauma, recent (three months) steroid therapy and patient at age (less than 25 years and more than 75 years) (Total male: 140 & female: 77), having renal impairment, hepatic insufficiency, bleeding diathesis, inflammatory disease, malignancy, having contraindication to thrombolytic therapy and those who do not willing to enroll in study were excluded from the study.

Considering inclusion and exclusion criteria sample population was divided into two groups -

- **Group-I :** Patients with Platelet Lymphocyte Ratio (PLR) <150.
- **Group-II :** Patients with Platelet Lymphocyte Ratio (PLR) >150.

Thesample size was determined by following formula:

$$n = Z^2pq/d^2$$

p = Prevalence or proportion of occurrence.

The proportion of patients with AMI events is

30% (0.30) (Chowdhury, et al., 2015)

q = 1-p

Z = Z value of normal standard distribution. (At 5% level of significance or 95% of confidence level, Z = 1.96)

d (e) = Acceptable error. It is usually set as 5% (0.05%)

n = Sample size.

Therefore, $n = (1.96)^2 \times 0.30 \times 0.70/ (0.05)^2$

$= 3.84 \times 0.21/0.0025$

$= 322$

After calculation of thesample size (initially 322)242 patients were taken but among them, 12 patients shifted to PCI capable center as a pharmaco-invasive strategy, 5 patients died immediately after or during thrombolysis and 8 patients dropped out due to incomplete data. Finally, 217 cases were feasible to be included in the study.

Data were collected by direct interview from patient or attendant and their responses were organized through a structured case record form.After collection data were processed and analyzed by computer software SPSS (Statistical package for social science) Version 22.0. Level of significance was considered as p value less than 0.05 ($p < 0.05$).Continuous data were expressed as mean ± SD &categorical data as frequency and percentage. Categorical data were analyzed with χ^2 test. Student's "t" test was used for analysis of continuous variables. Comparison between groups was done by unpaired t-test. Multivariate regression analysis was done to find out the association of in-hospital adverse cardiac events with platelet lymphocyte ratio and other compounding variables.
Proper safety measures were ensured in every steps of the study.There was no potential conflict of interest in this study and was entirely an academic research project.

A 12 lead standard surface ECG on admission was done within 10 min of arriving patient at CCU. Troponin-I ELISA assay kit was used for quantitative determination of cardiac troponin I in human whole blood serum / plasma specimens. Platelet Lymphocyte Ratio (PLR)level was estimated during estimation of Complete Blood Count (CBC) by Automated Haematology Analyzer.

Echocardiograms were subjected to careful visual analysis to detect regional contractile abnormalities. LV end-systolic and end-diastolic volumes and LVEF was estimated by Teicholtz method. 2D and Doppler echocardiography imaging were performed to screen for wall motion abnormalities, mitral annular calcification, valvular stenosis and

regurgitation. LV wall thickness, diameters, volumes and EF were measured according to American society of Echocardiography (ASE) recommendations. According to LVEF the LV systolic functions were divided into-

Normal LV systolic function	>55%
Mild LV systolic dysfunction	45-54%
Moderate LV systolic dysfunction	30-44%
Severe LV systolic dysfunction	<30%

Facilities available in the Department of Cardiology, MMCH (ECG, Echocardiography) were used. Haematological & Biochemical investigations were carried out in the Department of Clinical Pathology, MMCH and Emergency Biochemistry Lab, Dept. of Cardiology, MMCH.

After collection, data were checked for omission, inadequacy, irrelevancy and inconsistency. Omissions were corrected by retaking history or reexamining the patient. Irrelevant and inconsistent data were discarded.

Variables of the study:

Demographic variables:

- Age
- Sex

Risk factors variables:

- HTN
- DM
- Smoking
- Dyslipidaemia
- Family History of Coronary Artery Disease
- BMI (kg/m^2)

Investigation variables:

- ECG
- Troponin-I
- CBC
- Echocardiography

Outcome variables:

- Arrhythmias
- Heart Failure
- Cardiogenic shock
- Hospital Stay
- In hospital death.

Results

The main objective was to investigate the association between Platelet-Lymphocyte Ratio (PLR) and In-hospital Outcome in patients with first attack of Acute ST-Segment Elevation Myocardial Infarction (STEMI) Thrombolysed with Streptokinase. Total sample population were 247 but 30 patients was drop out due to referred, death immediately after admission, absconded or not done investigation. So ultimately total 217 patients were taken as sample population.

Total study populations were 217. Among them 64.5% patients were in Group-I: Platelet Lymphocyte Ratio (PLR) <150, n = 140 (male 129, female 11) & 35.5% patients were in Group-II: Platelet Lymphocyte Ratio (PLR) >150, n= 77 (male 69, female 8).

Table 1: Baseline characteristics of the study population (n=217)

	Group-I (n=140)	**Group-II (n=77)**	**p-Value**
Age	50.78±11.41	55.00±9.98	0.031[s]
Sex			
Male Female	129 (92.1%) 11 (7.9%)	69 (89.6%) 8 (10.4%)	0.528[ns]
BMI	23.75± 2.15	23.47± 2.14	0.568[ns]
Risk Factors			
Hypertension	19 (13.6)	27 (35.1)	0.001[s]
Diabetes	13 (9.3)	16 (20.8)	0.017[s]
Smoking	116 (82.9)	54 (70.1)	0.029[s]
Family H/O IHD	9 (6.4)	7 (9.1)	0.473[ns]
Sedentary Life	41 (29.3)	31 (40.3)	1.007[ns]
Involved Wall in AMI			
Anterior Ext-Ant Inferior Lateral Ant-Septal Ant-Inf	43 (30.7) 22 (15.7) 68 (48.6) 0 (0) 4 (2.9) 3 (2.1)	20 (26.0) 17 (22.1) 35 (45.5) 1 (1.3) 4 (5.2) 0 (0)	0.325[ns]
Troponin-I	25.83±19.35	28.99±20.24	0.261[ns]

Chi square & Un-paired t-tests were done accordingly.

s means significant
ns means Non-significant.

Group-I **:** Patients with Platelet Lymphocyte Ratio (PLR) <150
Group-II **:** Patients with Platelet Lymphocyte Ratio (PLR) >150

The Table shows the baseline characteristics of the study population. The mean ages of Group-I was 50.78 ± 11.41 years and Group-II was 55.00 ± 9.98 years. Analysis revealed statistically Significant ($p < 0.05$) mean age difference between the study groups. Majority of the study population were male. But gender was not found to be statistically significant ($p>0.05$). BMI showed slightly overweight study population but no statistical significance was found among the groups. Among the risk factors smoking was found to be the highest number followed by hypertension and diabetes. All these risk factors had statistically significant difference among the groups ($p<0.05$). Although sedentary life and family H/O IHD were found to have a substantial number but they were statistically insignificant ($p>0.05$). Among the involved walls due to myocardial infarction inferior involvement was the highest followed by anterior and extensive anterior but no statistical significance couldn't be drawn among the groups. Troponin-I was also found to be statistically non-significant between the groups ($p>0.05$)

Table 2: Platelet Lymphocyte Ratio (PLR) among the study population (n=217)

	Group-I (<150)	Group-II (>150)	Total
PLR	140 (64.5)	77 (35.5)	217 (100.0)

Table 2 shows that total study populations were 217. It was observed that in 140 (64.5%) of the study population the PLR level was <150 and 77 (35.5%) of study population the PLR level was>150.

Table 3: In-hospital outcome analysis among the study population (n=217)

		Study population				p-value
		Group-I (<150)		Group-II (>150)		
		Count	%	Count	%	
Complications	Yes	30	21.4	49	63.6	0.001[s]
	No	110	78.6	28	36.4	
Hospital Stay		4.04±1.31		4.81±1.73		0.001[s]
Arrhythmia	Yes	7	5.0	10	13.0	0.036[s]
	No	133	95.0	67	87.0	
Heart failure	Yes	21	15.0	35	45.5	0.001[s]
	No	119	85.0	42	54.5	
Cardiogenic shock	Yes	5	3.6	8	10.4	0.043[s]
	No	135	96.4	69	89.6	

Death	Yes	9	6.4	7	9.1	0.473^{ns}
	No	131	93.6	70	99.9	

Chi-square& Unpaired t- tests were done accordingly.

smeans significant

ns means Non-significant.

Group –I : Patients with Platelet Lymphocyte Ratio (PLR) <150

Group –II : Patients with Platelet Lymphocyte Ratio (PLR) >150

Above table shows outcome of study population according to Platelet Lymphocyte Ratio (PLR) level. Complications occurred in Group-I 21.4% and that is Group-II 63.6%, which was statistically significant (p<0.05). Arrhythmias, Heart failure, Cardiogenic shock occurred in 5.0%, 15.0%, 3.6%,in group- I where as in group-II Arrhythmias Heart failure, Cardiogenic shock, occurred in 13.0%, 45.5%, 10.4%,respectively, which were statistically significant (p< 0.05). Regarding death occurred in 6.4% in Group-I where as in Group-II 9.1% which were statistically not significant (p>005). The mean duration of hospital stays in Group-I was (4.04±1.31) days & in group-II was (4.81±1.73) days. p-Value of hospital stay was statistically significant (p<0.05).

Table 4: Left ventricular ejection fraction among Heart Failure patients of study population (n=59)

Heart failure	**Study population**		**p-Value**
	Group-I (PLR <150) n1=23	**Group-II (PLR >150) n2=36**	
Ejection fractionin percent	51.41±11.39	46.08±8.21	0.001^{s}

Unpaired t-test was done to measure the level of significance.

n1=number of heart failure patient in group –I.

n2=number of heart failure patient in group-II.

Table 4shows left ventricular mean ejection fraction among patients who developed heart failure. In Group-I mean ejection fraction was (51.41±11.39) % and in Group-II mean ejection fraction was (46.08±8.21) %. From above table, P-value of two groups was statistically significant (p<0.05).

Table 5: Killip class among heart failure patients of Study Population (n=59)

Killip Class	**Study population**				p- Value
	Group-I (PLR<150)		**Group-II (PLR>150)**		
	Frequency	**%**	**Frequency**	**%**	

I	1	4	1	3	0.001[s]
II	12	52	9	25	
III	4	18	17	47	
IV	6	26	9	25	
Total	23	100.0%	36	100.0%	

Chi-square test was done.

Table 5 shows Killip class among study population who developed heart failure. In Group-I Killip Class= 1, Killip Class=2, Killip Class=3, Killip Class=4 were 4.0%, 52.0%, 18.0%,26.0% patients where as in Group- II that was 3.0%, 25.0%, 47.0%, 25.0% patients. From above table, p- value of two group was statistically significant (p<0.05).

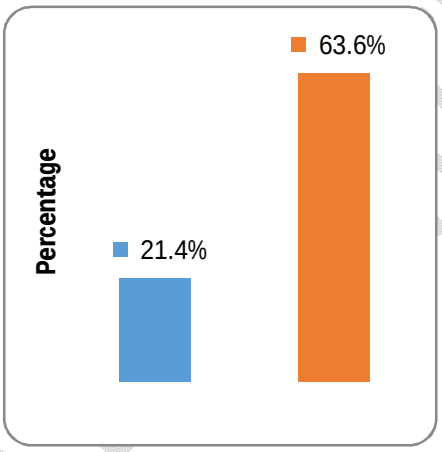

Figure 1: In-hospital adverse outcomes in two groups.

Group-I : Patients with Platelet Lymphocyte Ratio <150.

Group-II : Patients with Platelet Lymphocyte Ratio >150.

This figure (**Figure 1**) shows in Group-I, 21.4 % patients developed in-hospital adverse cardiac events, and in Group-II, 63.6% patients developed adverse cardiac events.

Table 6: Multivariate regression analysis for evaluating PLR to predict In-hospital adverse cardiac events compared to other predictors:

Model		**Unstandardized Coefficients**		**Standardized Coefficients**	**T**	**Sig.**
		B	**Std. Error**	**Beta**		
1	(Constant)	2.583	.573		4.505	.000

	Age	-.004	.003	-.089	-1.328	.186
	Sex	-.097	.123	-.057	-.783	.434
	Smoking	.051	.086	.044	.591	.555
	HTN	.039	.081	.033	.479	.633
	DM	-.054	.093	-.038	-.578	.564
	Dyslipidemia	.090	.070	.087	1.282	.201
	Family H/O IHD	-.029	.122	-.016	-.236	.813
	Sedentary life	-.080	.067	-.078	-1.184	.238
	BMI	-.014	.016	-.060	-.877	.381
	PLR	-.002	.000	-.380	-5.727	<.001**
a. Dependent Variable: Complications						

In the above table, logistic regression was used to study the impact of PLR level and other confounders like age, sex, smoking, hypertension, diabetes, dyslipidemia, sedentary life and body mass index (BMI) in predicting in-hospital outcomes in first attack of ST-segment elevation myocardial infarction patients thrombolysed with streptokinase. After performing the multivariable logistic regression analysis, it was found that Platelet Lymphocyte Ratio (PLR) contributed to predict adverse In-hospital cardiac events with p value001. From the above parameters, it is found that PLR level is the most independent predictor of adverse In-hospital cardiac events.

Discussion

Majority of patients of both groups were 45-55 years.Few studies of similar type reported the mean age of the patients were 58.1(±9.1)years, 57.58(±9.23) years, 62(±12) years respectively[36-38]. This finding is almost similar to the present study.

In our study, out of 217 cases, 198 (91.24%) were male. In a similar study it was found 84.80 % cases were male"[32]. So, like other studies, males were predominant in our study also.

In this study smoking status was statistically significant (p<0.05) between two groups of the study population. A study conductedin NICVD, Dhaka, reported that commonest risk factor of AMI was smoking and it was 73.33%[39].

In this study, hypertension was statistically significant (p< 0.05) risk factor.Astudy of similar type and reported that near half of their study population were hypertensive[40]. Anotherconducted study regarding risk factor assessment for coronary artery disease and reported that majority of the study population were hypertensive[39].

In this study, diabetes mellitus was found statistically significant (p<0.05). Although in both group, non-diabetic patients were predominant. Similar findings were found in other study[40].

It was observed that in 140(64.5%) of study population PLR level were <150 and 77(35.5%) of study population PLR level were >150. "In our study the mean Platelet Lymphocyte Ratio (PLR) were statistically significant (P<0.05). Similar conducted studywith nearly similar to the present study"[36].

On evaluation of In-hospital outcomes of study population revealed Group-II population developed statistically significantmore in-hospital adverse cardiac events than its counterpart.

Our study showed that during hospital stay composite end-point rates of arrhythmia and Heart failure were statistically significant (p=0.024). In similar study reported that rate of heart failure in low PLR group was significantly higher thanhigh PLR group (p<0.05)[41].

Regarding sub-group analysis of heart failure among study population showed majority resided in Killip class II & III. Our study showed that low PLR associated with lower Killip class and high PLR associated with worst Killip class, which was statistically significant.A similar study reported that patients in the highest PLR tertile had a worse presentation than those in lowest PLR tertile[42].Our study also found that the mean LV systolic function was more depressed in more PLR group that that of lower PLR group and hence the outcome.

The rate of cardiogenic shock among studypopulation was statistically significant. The PLR may be associated with clinical outcomes (such as all- cause mortality, recurrent myocardial infraction, heart failure, serious cardiac arrhythmia,and ischemic stroke) in patients with STEMI, because an increased PLR was known to be related to inflammation and atherosclerosis[36].

In our study, we found that the in-hospital mortality rates among the study population was not statistically significant. A study on prognostic value of PLR in patients with STEMI revealed that the in-hospital mortality rates were significantly more in high PLR group than that oflow PLR group[40].In our study the mean duration of hospital stay (in Days) were also found significantly higher in high PLR group than low PLR group.

From the above discussion we found that patient with admission high platelet lymphocyte ratio (PLR) with first attack of acute STEMI who were thrombolysed with streptokinase had higher risk for development of in-hospital cardiovascular events (heart failure, arrhythmia, cardiogenic shock) and increased hospital stay. Thus platelet lymphocyte ratio (PLR) had positive correlation with in-hospital adverse cardiac events in patients with first attack of acute STEMI.

Conclusion

The present study concluded that admission Platelet lymphocyte ratio (PLR) associated with In-hospital adverse cardiac events following thrombolysis in patients with first attack of ST-segment elevation myocardial infarction (STEMI). This study positively correlated with in-hospital adverse cardiac events in STEMI patients following thrombolysis. Thus high PLR is a strong and independent predictor of in-hospital adverse cardiac events in STEMI patients treated with thrombolytic.The study team also showed that this simple, widely available and inexpensive test might help to identify STEMI patients who are at a higher risk of in-hospital death and developing major adverse cardiovascular events (MACE) and may help in risk stratification of these cases. We think that the significant findings of our analysis can serve as a guide for future clinical practice. The research team also recommended that aggressive treatment strategy including early PCI and closer surveillance should be offered to acute myocardial infarction patients with high PLR levels, as these patients are more prone to develop short term and long term adverse cardiac events like heart failure, arrhythmia, cardiogenic shock and even sudden cardiac death.

Ethical Approval and Consent:

Ethical clearance was obtained from the Institutional Review Board of MMCH to undertake the present study. Informed written consent was obtained from each subject who voluntarily provided consent to participate in the study. The ethical issues were addressed accordingly. Strict confidentiality and security of data related to patient was maintained.

Disclaimer (Artificial intelligence)

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Limitations of the study

This study was not without limitations. The limitations of the study were as follows

- This study was conducted in only one center (DepartmentofCardiology, Mymensingh Medical College Hospital) and majority of study population was male. Thus, these results need to be re-evaluated in other health care center by inclusion of male and female in large numbers.
- The sample size was small and study period was short.
- We used streptokinase as thrombolytic regimen in all of our patients. Streptokinase has lower potency compared to the other clinically available thrombolytic drugs in restoring flow in the culprit coronary artery. Streptokinase is the only readily available thrombolytic routinely used in our center.
- Though re-infraction or ongoing MI is an important outcome in STEMI patients but it could not be evaluated due to technical problem.
- We did not compare the prognostic value of PLR with other inflammatory markers like hs-CRP, pro-BNP and etc.

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