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ORIGINAL RESEARCH

To explore the association of platelet to lymphocyte ratio and development of in hospital adverse cardiac events in patients with acute coronary syndrome (ACS)

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Abstract

Aim: To explore the association of platelet to lymphocyte ratio and development of in hospital adverse cardiac events in patients with acute coronary syndrome (ACS).

Material and Methods: The present prospective observational hospital based study, was conducted in Department of Internal Medicine, Government Medical College and Hospital, Jammu for a period of one year. The study population included in the trial were the patients diagnosed with acute coronary syndrome, who were of more than 18 years of age, of either sex, presenting to Medicine OPD and Emergency ward, after considering the inclusion and exclusion criteria. In emergency department, a 2.5 ml of blood was drawn from every patient who presumed to have ACS under aseptic technique from peripheral veins. Total and differential leukocyte counts were measured by an automated hematologyanalyzer. Routine biochemical tests were performed by standard techniques. PLR calculated as the ratio of platelet count to lymphocyte count.

Results: Patients were divided into 2 groups based on PLR level cut-off value of 116: <116 group1 and ≥116 group 2. The mean value of c-reactive protein in PLR<116 was 0.47±0.34, and in PLR ≥116 was 0.62±0.36 with statistically significant difference. In-hospital mortality among the study subjects in PLR<116 was in only one subject (1.85%) and in PLR ≥116 was in 9 subjects (19.57%). The difference in-hospital mortality among the study subjects was statistically significant among study groups (p<0.01).

Conclusion:The combination of PLR and other traditional markers might be of great significance in identifying high-risk patients and providing timely intervention strategies to improve the prognosis of acute coronary syndrome.

Keywords: Platelet, Lymphocyte, ACS

Introduction: Acute Coronary Syndrome (ACS) refers to spectrum of clinical presentations ranging from those of ST- segment myocardial infraction (STEMI) to presentations found in non ST-segment elevation myocardial infraction (NSTEMI) or in Unstable Angina **(Kumar A, Cannon CP, 2009)[1].**Acute coronary syndrome (ACS) is characterized by ruptured, vulnerable plaque and the subsequent intraluminal thrombus formation, resulting in the termination of blood flow and it might cause myocardial infarction **(Meeuwsen JAL *et al.*, 2017)[2].** The clinical presentation of acute coronary syndromes (ACS) is broad. It ranges from cardiac arrest, electrical or haemodynamic instability with cardiogenic shock (CS) due to ongoingischaemia or mechanical complications such as in severe mitral regurgitation, to pain free interval at the time of presentation **(Roffi M *et al.*, 2016)[3].** Although endothelial damage has been known as the triggering factor for the formation of atherosclerotic plaques, inflammatory process is responsible in the initiation and progression of the atherosclerosis**.** Platelet to lymphocyte ratio (PLR) is a new prognostic marker that integrates the risk prediction of these two parameters. It gives an idea about both the aggregation and inflammation pathways, and it may be more valuable than either platelet or lymphocyte count alone in the prediction of coronary atherosclerotic burden **(Libby P *et al*., 2009)[4].** A full blood count is a routine, automated, inexpensive, easy test that provides information about red blood cells and white blood cells as well as platelets. The platelet-lymphocyte ratio (PLR) novel inflammatory marker, which may be used in many diseases for predicting inflammation and mortality and is calculated as the ratio of the platelet to lymphocyte count (obtained from the same blood sample) **(Balta S &Ozturk C, 2015**)[5]. The combination of neutrophil and lymphocyte parameters has a better prognostic value than each parameter separately **(Duffy BK et al., 2006)[6].** NLR is related to the progression of coronary atherosclerosis, and also it is a predictor of all-cause mortality and cardiovascular events in patients undergoing

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angiography or cardiac revascularization. (Kalay Net al. 2012; Wang X et al. 2014)[7,8]. NLR is described as a predictor of in-hospital and 6-month mortality in patients who undergo PCI. The higher NLR is associated with diabetes and heart failure(Tamhane UU et al. 2008)[9]**.**The value of NLR is important in predicting short- and longterm mortality in patients with ST-segment elevation (STEMI)**(NúñezJ** et al., 2008; Akpek M et al., 2012; Sahin DY et al., **2013)[10-12]**and with non-NSTEMI**(**Azab B et al., 2010**)[13].**Preprocedural elevated NLR is also linked to an increased risk of significant ventricular arrhythmias during PCI (Chatterjee S et al., 2011**)[14].** The roles of PLR and other complex markers of systemicinflammatory response are related to the prognosis of ACS. PLR correlates with a greater overall mortality in patientswith NSTEMI **(A zab B et al., 2012)[15].**The high PLR correlates with the recurrence of myocardial infarction, stroke, and subsequent heart failure**(Sun XP et al., 2017)[16]**. PLR isalso helpful in predicting long-term results of percutaneousinterventions and it can help select patients with a higher riskof no-reflow syndrome after p PCI (Yildiz A et al., 2015; Vakili H et al., 2017)[17,18].Hence, present study was carried out to evaluate the association between PLR and all-cause mortality or CV events in patients with ACS.

Material And Methods: Thisprospective study was conducted in the Department of Internal Medicine, Government Medical College and Hospital, Jammu for a duration of one year, was conducted w.e.f 1st November 2020 to 31st October 2021.Ethical clearance was taken from the Institute's Ethical committee before commencement of the study.

Inclusion Criteria:

1. Patients more than 18 years of age
2. Patients diagnosed with acute coronary syndrome, presenting to Medicine OPD and Emergency of GMCH and Super Speciality Hospital, Jammu.

Exclusion Criteria:

1. Age<18 years
2. Hematological disease like myeloma, leukemia, lymphomas, hemophilia, etc.
3. Autoimmune disease like Pernicious anemia, ITP, HUS, etc
4. CKD with GFR <60 ml/min/1.73m2
5. Chronic liver disease
6. Severe valvular heart disease
7. History or imaging evidence of heart failure previously
8. Ischemic heart diseases within 1 month
9. Active infections
10. History of corticosteroid or cytotoxic drugs intake within 6 months
11. Blood product transfusion in past 6 weeks

Study Tools: Baseline blood investigations, ECG, Cardiac Troponin markers, Angiography, proforma, Echocardiography.

Methodology: In emergency department, a 2.5 ml of blood was drawn from every patient who presumed to have ACS under aseptic technique from peripheral veins.Total and differential leukocyte counts were measured by an automated hematolo gyanalyzer (Mindray BC-5800 Auto hematologyAnalyzer). Routine biochemical tests were performed by standard techniques.PLR calculated as the ratio of platelet count to lymphocyte count. All enrolled patients detailed history was recorded, clinical examination and necessary investigations were performed. Informed consent was obtained. Association of Platelet to Lymphocyte Ratio and development of major in hospital adverse cardiac events in patients with acute coronary syndrome were studied by applying appropriate statistical analysis.

Statistical analysis: Data so collected was tabulated in an excel sheet, under the guidance of statistician. The means and standard deviations of the measurements per group were used for statistical analysis (SPSS 22.00 for windows; SPSS inc, Chicago, USA). Difference between two groups was determined using student t-test as well as chi square test and the level of significance was set at $p < 0.05$.

Results: In present study, total of 100 subjects were involved. Patients were divided into 2 groups based onPLR level cut-off value of 116: <116 group1 and ≥116 group 2. In group1 there were 54 subjects and ingroup 2 there were 46 patients.(graph 1)

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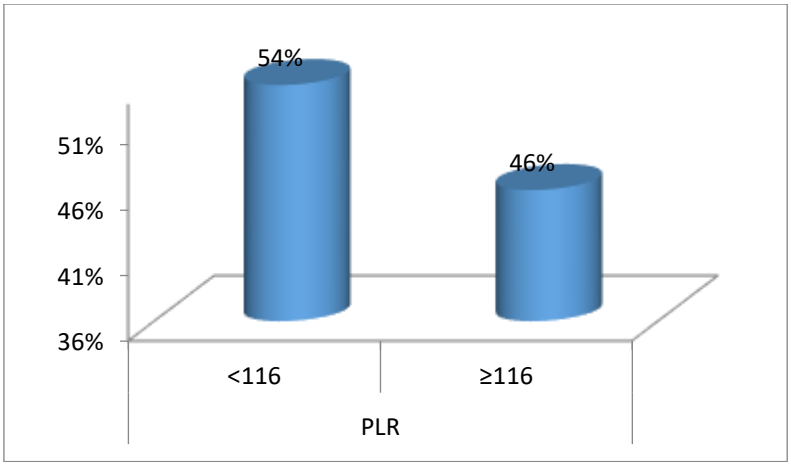

Graph 1: Distribution of study subjects according to PLR

In group1, mean age among the study subjects was 57.21±11.68 and in group2 mean age among the study subjects was 65.84±12.47. In group 1 (PLR<116), the no. of male patients was more, i.e., 38 (70.37%), and females were 16 (29.63%). In group 2 (PLR≥116), the no. of male patients was more (n=34, 73.91%), then females (n=12, 26.09%). Complete blood count profile of patients was recorded in both groups. There was a statistically significant difference between levels of hemoglobin (p=0.042), neutrophils (p<0.01), Lymphocyte (p=0.003), Platelets (p=0.001) and neutrophil lymphocyte ratio (p<0.01), between two groups. Only difference in WBC count was not significant between group 1 (PLR<116) and group 2 (PLR≥116). The mean value of c-reactive protein in PLR<116 was 0.47±0.34, and in PLR ≥116 was 0.62±0.36. The difference was statistically significant (p=0.023).(Table 1)

Table 1: CBC profile among the study subjects according to PLR

Parameters	PLR				t test	P value
	<116		≥116			
	Mean	SD	Mean	SD		
Hb (g/dl)	13.79	1.72	12.81	1.93	3.14	0.042*
WBC (10^3/μL)	11.68	2.77	12.05	3.15	2.23	0.16
Neutrophil (10^3/μL)	7.34	3.02	9.87	3.61	9.53	<0.01*
Lymphocyte (10^3/μL)	2.72	0.68	1.58	0.43	7.11	0.003*
Platelet (10^3/μL)	227.41	48.22	281.04	61.36	8.22	0.001*
NLR	2.58	0.75	6.91	3.39	11.29	<0.01*
CRP (mg/dl)	0.47	0.34	0.62	0.36	4.13	0.023*

statistically significant

In PLR<116 group, ST-segment elevation was present in 33 subjects (61.11%) and Non-ST-segment elevation was in 21 patients (38.89%). In PLR≥116 group, ST-segment elevation was present in 28 subjects (60.87%) and Non-ST-segment elevation was in 18 patients (39.13%). The difference was not significant. (Table 2)

Table: 2 Acute coronary syndrome among study subjects according to PLR

Syndrome	PLR				Chi Square	P value
	<116		≥116			
	N=54	%	N=46	%		
ST-segment elevation	33	61.11	28	60.87	0.54	0.72
Non-ST-segment elevation	21	38.89	18	39.13		

Study subjects were classified according to Killip class. In PLR <116 group, there were 11 (20.37%) subjects in class I, 18 (33.33%) in class II, 25 (46.3%) in class III and there was no subject in class IV. In PLR ≥116 group, there were 5 (10.87%) subjects in class I, 12 (26.09%) in class II, 27 (58.7%) in class III and there were 2 (4.35%) subject in class IV. The difference was statistically significant (p=0.046). (Table 3)

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Table: 3 Killip class among study subjects according to PLR

Killip Class	PLR				Chi Square	P value
	<116		≥116			
	N=54	%	N=46	%		
Class I	11	20.37	5	10.87	7.18	0.046*
Class II	18	33.33	12	26.09		
Class III	25	46.30	27	58.70		
Class IV	0	0.00	2	4.35		

In-hospital mortality among the study subjects in PLR<116 was in only one subject (1.85%) and in PLR ≥116 was in 9 subjects (19.57%). The difference in-hospital mortality among the study subjects was statistically significant among study groups (p<0.01). (Table 4)

Table: 4 In-hospital mortality among the study subjects according to PLR

Mortality	PLR				Chi Square	P value
	<116		≥116			
	N=54	%	N=46	%		
Yes	1	1.85	9	19.57	19.83	<0.01*
No	53	98.15	37	80.43		

*: statistically significant

DISCUSSION: Patients were divided into 2 groups based onPLR level cut-off value of 116: <116 group1 and ≥116 group 2. In group1 there were 54 subjects and ingroup 2 there were 46 patients.Following were the main observations of the present study. In group1 mean age among the study subjects was 57.21±11.68years and in group2 mean age among the study subjects was 65.84±12.47years.Patients with PLR ≥ 116 were significantly older.There was a statistically significant difference between mean age among the study subjects of bothgroups. (p=0.006). These findings were in accordance to result of **Kurtul A et al., (2014)[19],** who found that when patients were divided in to two groups according to PLR level, the mean age in group 1 was 58±12 years and in group 2 was 65±13 years, and the difference was statistically significant (p <0.001).

In group 1 (PLR<116), the no. of male patients was more, i.e., 38 (70.37%), and females were 16 (29.63%). In group 2 (PLR≥116), the no. of male patients was more (n=34, 73.91%), then females (n=12, 26.09%). Though the difference was not statistically significant. The result of present study was similar to findings of trial done by Oylumlu Met al., **(2015)[20],** who found that no. of male patients was more than in comparison to female patients.But according to study **ofKurtul A et al., (2014)[19],** there was a female predominance.The relationship between white blood cell count andincreased cardiovascular risk is well established. While highneutrophil counts reflect the inflammatory response, low lymphocyte counts reflect poor general health and physiologic stress **(**Gibson PH et al., 2010)[22].Complete blood count profile of patients was recorded in both groups. There was a statistically significant difference between levels of haemoglobin (p=0.042), neutrophils (p<0.01), Lymphocyte count (p=0.003), Platelets count (p=0.001) and neutrophil lymphocyte ratio (p<0.01), between two groups. Only difference in WBC count was not significant between group 1 (PLR<116) and group 2 (PLR≥116). According to Oylumlu Met al., (2015)[23], there was statistically significant difference in Lymphocyte count, Platelets count and neutrophil lymphocyte ratio between three groups, but difference between level of haemoglobin and WBC count was not significant among groups. In study done by **Kurtul A et al., (2014)[19],** there was a statistically significant difference in level of haemoglobin between two groups (p<0.001). The mean value of c-reactive protein(CRP) in PLR<116 was 0.47±0.34, and in PLR ≥116 was 0.62±0.36. The difference was statistically significant (p=0.023). But according to study done by **Oylumlu Met al., (2015)[20],** there was no significant difference in CRP levels among the groups. The mean level of Left ventricular ejection fraction (%)in PLR <116 was 49.2±7.30, and in PLR≥116 was 45.5±8.24, the difference was statistically significant (p= 0.007). Same were the findings of **Kurtul A et al., (2014)[19],** they found that mean level of Left ventricular ejection fraction (%) in PLR <116 was 49± 10 and in PLR≥116 45± 11, the difference was statistically significant (p<0.001). According to **Oylumlu M et al., (2015) [20],** there was statistically significant difference in mean levels of Left ventricular ejection fraction (%) among the groups.

In PLR<116 group, ST-segment elevation was present in 33 subjects (61.11%) and Non-ST-segment elevation was in 21 patients (38.89%). In PLR≥116 group, ST-segment elevation was present in 28 subjects (60.87%) and Non-ST-segment elevation was in 18 patients (39.13%). The difference was not significant. Similar were the findings of **Kurtul A et al., (2014)**and**Oylumlu M et al., (2015)[19,20],** they also did not found any significant difference. The Killip classification is a system used in individuals with an acute myocardial infarction (heart attack), taking into account physical examination and the development of heart failure in order to predict and stratify their risk of mortality. Individuals with a low Killip class are less likely to

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die within the first 30 days after their myocardial infarction than individuals with a high Killip class **(Killip T et al., 1967)[21].**Study subjects were classified according to Killip class. In PLR <116 group, there were 11 (20.37%) subjects in class I, 18 (33.33%) in class II, 25 (46.3%) in class III and there was no subject in class IV. In PLR ≥116 group, there were 5 (10.87%) subjects in class I, 12 (26.09%) in class II, 27 (58.7%) in class III and there were 2 (4.35%) subject in class IV. The difference was statistically significant (p=0.046). In-hospital mortality among the study subjects in PLR<116 was in only one subject (1.85%) and in PLR ≥116 was in 9 subjects (19.57%). The difference in-hospital mortality among the study subjects was statistically significant among study groups (p<0.01). Similar were the findings of Kurtul A et al., (2014)[19].

Limitations: This study has few limitations. First, this was a single center prospective study with a small study population. Second, we analyzed only the admission PLR, PLR may change dynamically with different clinical outcomes during the course of the disease, the lack of follow-up data of PLR is a notable drawback. The use of a single blood sample at admission does not anticipate the persistence of PLR over time. So multi center studies with larger sample size should be done.

Conclusion: High level of physiologic stress meanhigh levels of cortisol and catecholamine, which can translated into a lower lymphocyte count. In addition, high platelet countsmay represent higher propensity to form platelet-richthrombi on atherosclerotic plaques, leading to worse outcomes. Elevated PLR may indicate excess thrombotic status. In present study there was a statistically significant difference in mean age, hemoglobin level, neutrophils count, Lymphocyte count, Platelets count, neutrophil lymphocyte ratio, c-reactive protein, Triglyceride levels, Left ventricular ejection fraction (%), Killip class and In-hospital mortality among the study subjects, among the study groups. The combination of PLRand other traditional markers might be of great significancein identifying high-risk patients and providing timelyintervention strategies to improve the prognosis of acute coronary syndrome. We found PLR to be a risk variable for in-hospital mortality inpatient with ACS. Further large-scale, prospective, and multicenter studies are needed to clarify and confirm the associationbetween the PLR and in-hospital mortality in patients with ACS.In conclusion, different from other inflammatory markers andassays, PLR is an inexpensive and readily available biomarkerthat may be useful for cardiac risk stratification in patients withACS.

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