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ORIGINAL PAPER

STUDY OF PROGNOSTIC VALUE OF HAEMATOLOGICAL INDICES IN ACUTE CORONARY SYNDROME

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ABSTRACT

BACKGROUND:

Coronary artery disease, caused by atherosclerosis, is the leading cause of death worldwide, with an estimated prevalence of 54.5 million in India, as on 2016. One in 4 deaths in India are now because of Cardiovascular diseases, with ischemic heart disease and stroke responsible for >80% of this burden.[1]

Atherosclerosis is a systemic, lipid-driven immune inflammatory disease. The chronic low-grade inflammation plays a key role in the initiation and development of the atherosclerotic plaque, which subsequently leads to the plaque's instability with a thrombus formation.[2]
Few haematological indices have been described in the prognostic value in patients with ACS such as White Blood Cell Count (WBC), Neutrophil to Lymphocyte Ratio (NLR), monocyte

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to lymphocyte ratio (MLR), Red Cell Distribution Width (RDW), Platelet to Lymphocyte Ratio (PLR), Platelet Distribution Width (PDW) and Mean Platelet Volume (MPV).

In recent years, strong interest has arisen in these indices, given that they may provide independent information on pathophysiology, risk stratification, and optimal management.[3] The main advantage of haematological indices is that they are relatively inexpensive and thus widely and easily available in daily clinical practice.

STUDY METHODS:

Case records of all Acute coronary syndrome patients, above 18 years of age, admitted to St. John's medical college hospital during the year 2019-2021, were reviewed in the study. Four haematological indices were recorded, namely total leukocyte count, neutrophil to lymphocyte ratio (NLR), monocyte to lymphocyte ratio (MLR) and platelet to lymphocyte ratio (PLR). All patients were divided into three categories on the basis of admission TLC as <10000; 10000-15000 and >15000/cu mm. NLR, MLR and PLR were calculated with admission differential leucocyte count and were divided into tertiles as low, intermediate and high. Each variable was compared with Left Ventricular Ejection Fraction (LVEF), presence of heart failure, NT-pro BNP (N-terminal prohormone Brain Natriuretic Peptide) and severity of coronary artery disease. The data was analysed using appropriate statistical method

RESULTS

In our study we found significant correlation of all the haematological indices (Total leucocyte count, NLR, MLR and PLR) with left ventricular ejection fraction (LVEF) with values being higher in patients with LVEF less than 40%. Also the indices NLR, MLR and PLR significantly correlated with presence of clinical heart failure, elevated NT pro BNP.

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Although our study did not show significant correlation between the indices and angiographical grading of severity of Coronary artery disease (CAD) or mortality, there was significant, although weak correlation with SYNTAX score of CAD. Also the haematological indices were found to be higher in patient with significant coronary artery disease.

CONCLUSION:

From our study we conclude that the haematological indices are good markers to indicate myocardial damage in Acute coronary syndrome with values being higher in extensive myocardial damage presenting as heart failure and echocardiographically having severe LV systolic dysfunction.

To find correlation between the angiographic severity of CAD and mortality probably study with a larger sample size will help.

KEY WORDS: Acute coronary syndrome, Leucocytosis, neutrophil to lymphocyte ratio (NLR), monocyte to lymphocyte ratio (MLR), platelet to lymphocyte ratio (PLR).

INTRODUCTION

Coronary heart disease, most commonly caused by atherosclerosis, is the leading cause of death worldwide. In 2016, the estimated prevalence of coronary vascular diseases (CVD) in India was estimated to be 54.5 million. One in 4 deaths in India are now because of CVDs with ischemic heart disease and stroke responsible for >80% of this burden.[1]

Atherosclerosis is a systemic, lipid-driven immune inflammatory disease. The chronic low-grade inflammation plays a key role in the initiation and development of the atherosclerotic plaque, which subsequently leads to the plaque's instability with a thrombus formation.[2]

Few hematological indices have been described in the prognostic value in patients with Acute coronary syndrome (ACS) such as White Blood Cell Count (WBC), Neutrophil to Lymphocyte

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Ratio (NLR), monocyte to lymphocyte ratio (MLR), Red Cell Distribution Width (RDW), Platelet to Lymphocyte Ratio (PLR), Platelet Distribution Width (PDW) and Mean Platelet Volume (MPV).

In recent years, strong interest has arisen in these indices, given that they may provide independent information on pathophysiology, risk stratification, and optimal management.[3] The main advantage of hematological indices is that they are relatively inexpensive and thus widely and easily available in daily clinical practice.

AIMS AND OBJECTIVES OF THE STUDY:

1. Correlation between leucocytosis and heart failure, LVEF, NT-proBNP and severity of coronary artery disease
2. Correlation between NLR and heart failure, LVEF, NT-proBNP and severity of coronary artery disease
3. Correlation between MLR and heart failure, LVEF, NT-proBNP and severity of coronary artery disease
4. Correlation between PLR and heart failure, LVEF, NT-proBNP and severity of coronary artery disease

INCLUSION CRITERIA: All patients, aged more than 18 years, with acute coronary syndrome, who were admitted in St. John's medical college hospital, from the year 2019 to 2021.

EXCLUSION CRITERIA: Hematologic disease, chronic kidney disease, chronic liver disease, tumour, autoimmune disease, acute and chronic infectious disease.

SAMPLE SIZE AND DURATION OF STUDY:

We included 285 patients admitted with Acute coronary syndrome, in St. John's medical college hospital from the year 2019 to 2021.

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METHODOLOGY:

Case records of all the included patients was reviewed in the study. Four hematological indices were recorded, namely total leukocyte count, neutrophil to lymphocyte ratio (NLR), monocyte to lymphocyte ratio (MLR) and platelet to lymphocyte ratio (PLR). All patients were divided into three categories on the basis of admission TLC as <10000; 10000-15000 and >15000/cu mm. NLR, MLR and PLR were calculated with admission differential leucocyte count and were divided into tertiles as low, intermediate and high. Each variable was compared with LVEF, presence of heart failure, NT-proBNP and severity of coronary artery disease. The data was analysed using appropriate statistical method

STATISTICAL ANALYSIS:

Data has been presented as frequencies and percentage for categorical variables. Differences between groups was assessed by Chi square test and analysis of variance (ANOVA). Correlation between continuous variables will be determined by Pearson correlation coefficient and independent sample T test.

RESULTS:

1. DEMOGRAPHIC CHARACTERISTICS OF SAMPLE:

After reviewing records of 2 years and excluding patients with sepsis, based on procalcitonin value or clinical suspicion of sepsis, 285 patients were included.

Age distribution: The median age of our study population was 60 years

67.5% patients were male and 32.5% were females

2. CLINICAL CHARACTERISTICS

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Of the total smaple size, 63.5 % patients had clinical heart failure and 41.3% had Left ventricular ejection fraction (LVEF) less than 40%.

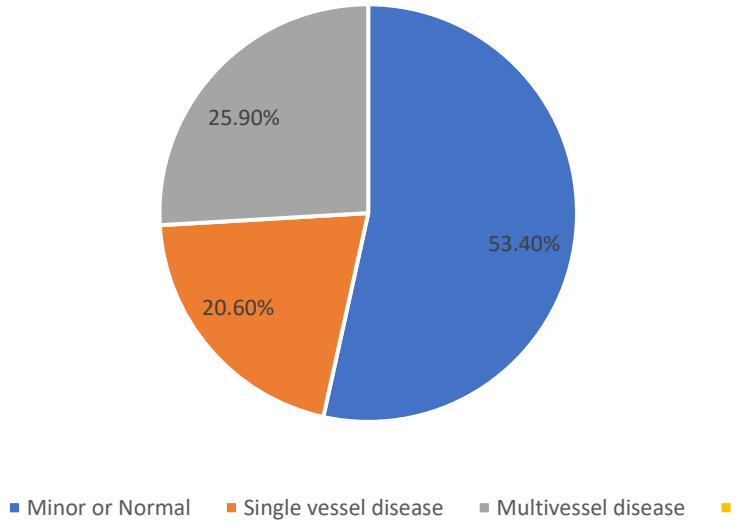
35.4% patients had LVEF between 40-50% and 23.2% had LVEF >50%

Mortality was 3.4%

Severity of Coronary artery disease (CAD)

- by Coronary angiogram: Out of the total sample size 189 patients underwent Cath Coronary angiogram, out of which 53.5% patients were found to have minor disease or normal coronaries, 20.6% patients had single vessel disease and 25.9 % patients had multivessel disease (Fig. 1).

Figure 1: CAD severity by Coronary angiogram



- by SYNTAX score grading: Out of the total patients who underwent CAG, SYNTAX score was calculated in patients with significant CAD. 77.1% (81 patients) had low score (less than 18), 20% (21 patients) had intermediate score (18-27) and 2.9% (3 patients) had high SYNTAX score (>27).

3. CORRELATION WITH HAEMATOLOGICAL INDICES:

a. Total Leucocyte count

- Total Leucocyte count Tertiles:
  After exluding the cases with sepsis 99 patients (36%) had TLC less than 10,000/cu.mm, 117 patients (42.5%) had TLC between 10000 to 15000cu.mm and 59 patients (21.5%) had TLC > 15000 cu.mm.(Fig 2).

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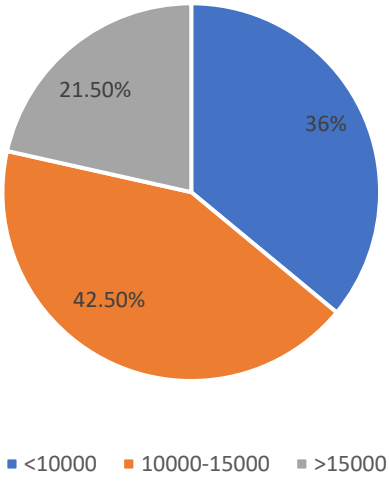
Figure 2:TLC Tertiles (distribution)



- **Correlation of Total Leucocyte count with Heart Failure, LVEF, SYNTAX score and CAG severity:**

Table 1: P values for correlation of Total lleucocyte count with HF, LVEF, CAG severity.

Parameter	Heart failure	CAG severity	SYNTAX score	LVEF grading(less than 40%)
Correlation with TLC (p value)	p= 0.182	p= 0.325	p =0.992	P < 0.001

TLC values did not show significant correlation with Heart failure CAG severity or SYNTAX score. IT however showed significant correlation with LVEF, with mean TLC being significantly higher in patients with LVEF < 40%.

b. Correlation of haematological indices ratio with Heart Failure (HF), NT proBNP, LVEF, CAD severity (one way ANOVA non parametric/ Independent samples T-test):

Table 2: P values for correlation of haematological indices with HF, LVEF, CAG severity and Mortality

Haematological ratio	HF	NT proBNP	LVEF	CAG severity	SYNTAX score	Mortality
NLR	p<0.001	p<0.001	p<0.001	p=0.012	p=0.212	p=0.295
MLR	p=0.012	p=0.004	p=0.01	p=0.058	p=0.012	p=0.731

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PLR	p<0.001	p=0.006	p=0.001	p=0.142	p=0.784	p=0.172

Table 3: Correlation matrix values for correlation of haematological indices with HF, LVEF, CAG severity and Mortality.

			NLR	MLR	PLR
NT PRO BNP	Spearman's rho		0.732	0.605	0.575
	df		19	19	19
	p-value		**< 0 .001**	**0.004**	**0.006**
SYNTAX SCORE 2	Spearman's rho		0.217	0.246	0.085
	df		98	98	97
	p-value		**0.03**	**0.014**	**0.401**
LVEF	Spearman's rho		-0.127	-0.125	-0.141
	df		236	235	235
	p-value		**0.051**	**0.054**	**0.03**

Table 4: Correlation of Haematological indices with Heart Failure

Independent Samples T-Test					
		Statistic		**p**	
NLR	Mann-Whitney U		6221	< .001	
MLR	Mann-Whitney U		7041	0.012	
PLR	Mann-Whitney U		6514	< .001	
Note. $H_a\ \mu_{No} \neq \mu_{Yes}$					

There was found to be significant correlation between the hematological indices ratio of NLR, MLR and PLR with heart failure, with values being higher in patients who had clinical heart failure ($p< 0.05$).

Also the NT pro BNP levels were higher in patients with higher NLR, MLR and PLR ($p <0.05$)

Patients with LVEF lesser than 40% were found to have higher values of NLR, MLR and PLR ($p<0.05$)

The correlation between SYNTAX score on coronary anngiogram and NLR, MLR is positive, weak but significant. So patients with higher SYNTAX score had higher haematological indices ratios.

CORRELATION WITH SEVERITY OF CAD:

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c. **Table 5:** One way ANOVA – non parametric for correlation of haematological indices with severity of CAD.

Kruskal-Wallis							
		χ^2		df		p	
NLR		8.82		2		0.012	
MLR		5.7		2		0.058	
PLR		3.9		2		0.142	

There is significant difference in the median of NLR between CAG severity categories.

d. **Table 6:** Pairwise comparison of CAG severity categories with NLR - Dwass-Steel-Critchlow-Fligner pairwise comparisons

Pairwise comparisons - NLR							
				W		p	
Minor disease or normal		Single vessel disease		-3.49		0.036	
Minor disease or normal		Multi vessel disease		-3.278		0.053	
Single vessel disease		Multi vessel disease		0.625		0.898	

By pairwise comparison the NLR ratio shows weak but significant difference between Minor/normal disease versus single vessel disease (p = 0.053).

Table 7: Correlation of haematological indices and CAD severity by Independent Samples T test

Independent Samples T-Test									
				Statistic		df		p	
NLR		Student's t		4.26	[a]	177		< .001	
MLR		Student's t		2.918	[a]	176		0.004	
PLR		Student's t		-0.477		176		0.634	
Note. H_a μ Minor or normal $\neq$ μ Single or multi vessel									

When NLR and MLR was compared between minor or no CAD versus significant CAD (single or multivessel disease), the difference was found to be statistically significant.

PLR showed no significant correlation with CAG severity.

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DISCUSSION:

In our study population the mean age was 60 years and the majority of patients were males (67.5%). Majority of ACS patients had total leucocyte count more than 10,000 cu.mm (63% cases). Several studies have reported positive associations between elevated leukocyte count and the incidence of coronary diseases or with mortality from coronary heart disease.[6,7]

There is evidence that chronic inflammation is involved in all stages of coronary atherosclerosis, from initial endothelial dysfunction and plaque disruption to clinical manifestation of acute atherothrombotic events. Our result is in line with a study by Prasad. A et.al, which showed that among the various inflammatory markers, the leukocyte count and whole subtypes of white blood cell counts including neutrophils, monocytes, and lymphocytes are associated with increasing cardiovascular events.[4,5]

In our study, although TLC values did not show statistically significant correlation with heart failure, angiographic severity of coronary artery disease or SYNTAX score, it however showed significant correlation with left ventricular ejection fraction (LVEF), with mean TLC being significantly higher in patients with severe left ventricular systolic dysfunction (LVEF < 40%). There was found to be significant correlation between the haematological indices ratio of NLR (Neutrophil Lymphocyte Ratio), MLR (Monocyte Lymphocyte Ratio) and PLR (Platelet Lymphocyte Ratio) with heart failure. All the values being higher in patients who had clinical heart failure ($p< 0.05$). Also the NT pro BNP levels were higher in patients with higher NLR, MLR and PLR ($p <0.05$). Patients with severe LV systolic dysfunction (LVEF lesser than 40%) were found to have higher values of NLR, MLR and PLR ($p<0.05$)

Several studies have proposed hypotheses to explain the mechanism of increased myocardial injury, including a leukocyte-mediated hypercoagulable state,[8] leukocyte mediated no-

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reflow,[9] and indirect cardiotoxicity mediated through proinflammatory cytokines.[10] Elevation in WBC count was also found to be associated with reduced epicardial blood flow and myocardial perfusion, thromboresistance (arteries open later and have a greater thrombus burden), and a higher incidence of new congestive heart failure and death[11] and was an independent predictor of long-term mortality in both non-STEMI and STEMI patients.[12]

Neutrophils are seen as a marker of ongoing inflammation and lymphocytes as a marker of regulatory pathways. Neutrophil-to-lymphocyte ratio (NLR) as an indication of systemic inflammation positively correlated with myocardial damage but negatively correlated with myocardial function.[13] Recent accumulating evidence points that high NLR to be independently and strongly associated with increased risk of complications and mortality post-acute MI[14,15,16], also in patients after thrombolysis[17] and coronary intervention.[18]

Similarly, the role of monocyte infiltration of the arterial wall in the development of atherosclerotic plaques is well recognized.[19] In addition, few studies have showed that monocytes are associated with the onset of myocardial infarction and left ventricular remodeling.[20,21] Recent meta-analysis by Quan et al suggested that lower LMR value might be associated with higher short-term and long-term mortality/MACE in ACS patients. Especially for younger ACS patients, low LMR was more closely associated with poor prognosis.[22]

MLR was also found to be independently correlated with the severity of coronary lesion in NSTEMI patients and has better performance to reflect the severity of coronary lesion than NLR and an independent predictor for in-hospital and long-term MACE in patients with NSTEMI[13] and even in patients with STEMI after primary PCI.[23]

Platelets also play a pivotal role in the pathophysiology of atherosclerotic CAD. Interactions between platelets, leukocytes, and endothelial cells together lead to the destabilization of

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atherosclerotic plaques. Gary et al reported that higher platelet counts may lead to the elevation of blood viscosity and promote inflammation.[24] Azab et al found that Platelet Lymphocyte Ratio (PLR) was associated with short-term and long-term mortality in patients after NSTEMI,[25] and a similar relationship was also reported for STEMI.[26] It was also found to be associated with in-hospital MACEs and CAD severity assessed according to the Gensini Score among 502 patients with acute MI.[27] Also, high pre-intervention PLR and NLR, especially when combined, were found to be an independent predictor of long-term adverse clinical outcomes such as all-cause mortality, cardiac death, and myocardial infarction in patients with unstable angina and NSTEMI who have undergone successful PCI with DES.[28]

In our study the correlation between SYNTAX score on coronary anngiogram and NLR, MLR is positive, weak, but significant. So patients with higher SYNTAX score had higher haematological indices ratios, indicating more severe coronary artery disease. There is significant difference in the median of NLR between angiographically graded severity of coronary artery disease. By pairwise comparison the NLR ratio shows weak but significant difference between Minor/normal disease versus single vessel disease ($p = 0.053$). When NLR and MLR was compared between minor or no CAD versus significant CAD (single or multivessel disease), the difference was found to be statistically significant. So the hematological indices were higher in presence of significant coronary artery disease.

CONCLUSION:

In our study we found significant correlation of all the hematological indices (Total leucocyte count, NLR, MLR and PLR) with left ventricular ejection fraction (LVEF) with values being higher in patients with LVEF less than 40%

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Also the indices NLR, MLR and PLR significantly correlated with presence of clinical heart failure, elevated NT pro BNP.

Although our study did not show significant correlation between the indices and angiographical grading of severity of CAD or mortality, there was significant, although weak correlation with SYNTAX score of CAD. Also the hematological indices were higher in the presence of significant coronary artery disease.

These observations provide a potential explanation for the higher mortality rate observed among AMI patients with elevated WBC counts and helps explain the growing body of literature that links inflammation and cardiovascular disease. These are inexpensive and routine tests which will help us in finding high risk patients for better management.

LIMITATION:

A larger sample size would help to bring about the statistically significant correlation in areas where only weak association was noted. Since during the study period the Covid pandemic had hit the world, there were limitations with regards to number of patients getting admitted and number of planned coronary angiograms and other procedures being done. All the patients included in the study did not undergo coronary angiogram due to various issues like acute kidney injury, financial constaraints, discharge against medical advice. Also though patients with sepsis were excluded in our study, not all cases underwent objective serum procalcitonin measurement and in cases where this marker was not done, clinical decision was used to exclude sepsis.

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