Association between Platelet to Lymphocyte Ratio and In Hospital Adverse Out Comes In Patients with Acute Coronary Syndrome

A thesis submitted to the Iraqi board for medical specialization in partial fulfillment of the requirement for the degree of the fellowship in internal medicine

By

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Abstract:

Background: Patients with acute coronary syndrome may expose to adverse outcome that seriously endanger their life, recognizing those patients at higher risk earlier may be lifesaving. There are many risk scoring systems developed to identify patients at high risk. Many inflammatory markers show prognostic value in patients with acute coronary syndrome. Many studies have concluded that the platelet lymphocyte ratio is associated with adverse cardiac events among patients with acute coronary syndrome, but local data is limited.

Aim of the study: this study was aimed to explore the association of platelet to lymphocyte ratio and development of major adverse cardiac event in patients with acute coronary syndrome.

Patients and methods: A Total of two hundred eighteen patients with acute coronary syndrome were included in this study. Platelet to lymphocyte ratio was measured at admission using automated hematology analyzer. All patients admitted to cardiac care unit for follow up and management. Any adverse outcome were observed.

Results: the mean platelet to lymphocyte ratio and mean neutrophil to lymphocyte ratio was significantly high among patients with acute coronary syndrome who suffer in hospital complications in comparison to patients who had no complications (167.7± 86.8 vs 99.3±35.1 p value <0.001).

Conclusion: complications rate was higher in patients with acute coronary syndrome who had high platelet to lymphocyte ratio and high neutrophil to

lymphocyte ratio. These finding may be valuable in risk stratification of patients with acute coronary syndrome.

Introduction:

Coronary heart disease (CHD) is a leading cause of death worldwide [(1)], Iraq rank twenty second in age-adjusted CHD mortality rates with 187.65 death per 100000 populations. [(2)]

For this increasing threat to the world's health, researchers are working to develop a greater understanding of the mechanisms of CHD.

Our understanding of atheromatous CHD has evolved beyond the view that these lesions consist of a lifeless collection of lipid. Evidence accumulated from autopsy showed that only (25 to 33%) of a lethal coronary thrombi occurred at sites of the most stenotic segments in the infarct related coronary artery. [(3)] Today we appreciate a more complex interaction between endothelial cells and the blood cells, which makes us better understand the molecular bases of CHD. Current evidence supports a major role for inflammation in all phases of the atherosclerotic process. Substantial molecular data implicate inflammatory pathways in early atherogenesis, in the progression of lesions, and finally in the thrombotic complications of this disease. [(4)] Clinical studies confirm the correlation between circulating markers of inflammation and the propensity to develop ischemic events and prognosis after acute coronary syndrome (ACS).

Platelets are a source of many inflammatory mediators, platelets activation are known to trigger ACS and play a central role in its progression [5]. Elevated peripheral blood platelet count is associated with the development of major adverse cardiovascular outcomes [6,7].

There are accumulating evidence that lymphocytes play a central role in the modulation of the inflammatory response at every stage of the atherosclerotic process. [8] There is evidence that a low lymphocyte count is associated with worse outcomes in patients with ACS and heart failure. [9,10]

There are many studies evaluating different inflammatory marker in cardiovascular diseases, such as C-reactive protein, fibrinogen [11], interleukin-6 and tumor necrosis factor-alpha. [12] In this study we try to evaluate platelet to lymphocyte ratios (PLR) in patients presenting with ACS.

Aim of the study:

To explore the associations of PLR and NLR with development of major adverse outcomes in patients with ACS.

Patients and Methods:

This study is a prospective cross sectional, in which 218 patients with ACS were enrolled, with a mean age of (59.4 ± 12.2 years), 151(69.3%) patients were males, and they were admitted to cardiac care unit of Albasrah General Hospital, in period from September 2014 to September 2015. The mean follow up period was 7 days.

Patients with the following criteria were considered as AMI: [13]

- Detection of a rise and/or fall of cardiac biomarker values (preferably cTn) with at least one value above the 99th percentile upper reference limit and with at least one of the following:
  a) Symptoms of ischemia (>20 min)

b) Development of pathologic Q waves in the ECG
c) New or presumed new significant ST segment T wave (ST-T) changes or new left bundle branch block (LBBB).
d) Imaging evidence of new or presumed new regional wall motion abnormality.

Unstable angina was defined as :[13]

1. Prolonged (>20 min) anginal pain at rest;

2. New onset (de novo) angina (class II or more of the Canadian Cardiovascular Society classification) ;[14]

3. Recent destabilization of previously stable angina with at least Canadian Cardiovascular Society Class III angina characteristics (crescendo angina);

4. Post-MI angina.

All patients were received standard care for ACS, thrombolytic therapy was used rather than percutaneous coronary intervention for patients with STEMI.

Population criteria:

Inclusion criteria were: patients with ACS aged >18 years.

Any patients with: ischemic symptoms >12 hours before admission, hematological disease, autoimmune disease, CKD with GFR <60 ml/min/1.73m^2 , chronic liver disease, severe valvular heart disease, history or imaging evidence of heart failure previously, ischemic heart diseases within 1 month, malignancy, active infections, history of corticosteroid or cytotoxic drugs intake within 6

months, blood product transfusion in past 6 weeks, premature discharging from the hospital and patients who did not receive standard ACS care, were excluded from the study.

Definitions:

Cardiovascular events during the in-hospital period were recorded. Ventricular tachycardia or ventricular fibrillation were defined at >24 h of onset of ischemic symptoms, atrial fibrillation as a new in-hospital documented ECG showing atrial fibrillation when the baseline ECG was sinus rhythm. Advanced heart failure was defined as Killip classification ≥2 [15], and was confirmed by transthoracic echocardiography, cardiovascular death was defined as death due to AMI, heart failure, or arrhythmia and recurrent ischemia as ≥2 anginal episodes during in hospital stay with or without ECG changes.

Hypertension was defined as either basic BP more than 140/90 or patients already on anti-hypertension medications [16], diabetes as HbA1C > 6.5 or already on diabetic medications [17], dyslipidemia was defined according to American Association of Clinical Endocrinologists' guidelines [18] or patients taking statin.

Sample collection:

In emergency department, a 2.5 ml of blood were drawn from every patient who presumed to have ACS under aseptic technique from peripheral veins, blood then directly was put in an automated hematology analyzer (SFRI medical diagnostic, France). Biochemical parameters were done with a standard way.

PLR and NLR was calculated as the ratio of platelet count, neutrophil count, to lymphocyte count respectively.

Statistical Analyses:

The data obtained from this study was analyzed using the statistical package for social sciences (SPSS) software version 22.0 Clinical characteristics of subjects were analyzed using descriptive statistics. Continuous variables were defined as means ± standard deviation; categorical variables were given as percentages. Data were analyzed by mean with standard deviation, t-test, the chi-square and the receiver operator characteristic (ROC) curve. Statistical significance was defined as $P<0.05$.

Results:

Two hundred and twenty five patients with acute coronary syndrome were enrolled in this study, 7 patients were excluded from the study (either discharged on their responsibility prematurely or referred to other hospitals), their mean age was (59.4±12.2) years, 151 (69.3%) were males, 32 (14.7%) of patients had UA, 52 (24.3%) patients had NSTEMI and 134 (61.0%) had STEMI.

Table 1 shows clinical characteristics of the study populations, there were significant high mean PLR in patients with previous IHD (148.93 ± 78.98 vs 109.39 ± 45.31 P value <0.001), while no significant difference in mean PLR in relation to patient's gender, DM status, HTN status, current smoking or their lipid profile.

The receiver operator characteristic (ROC) curve was constructed to find out best cut-off value of PLR when used as a test to predict cases with ACS at higher risk for mortality, LV failure and serious arrhythmia (figure 1), optimum cut-off

value was a point with best sensitivity and specificity combination, In the ROC analysis, PLR >125 had 67% sensitivity and 79% specificity, (ROC area under curve: 0.758, 95% CI: 0.686-0.829, p<0.0001) and NLR >4.0 had 65% sensitivity and 78% specificity in predicting a mortality, LV failure and serious arrhythmia (ROC area under curve: 0.781, 95% CI: 0.714-0.849, p<0.0001).

Table 2 shows that patients group with PLR ≥ 125 "84 patients" who had developed LV failure, serious arrhythmia and death was higher than those patients having their PLR < 125 "134 patients" (38 {77.6%} vs 11 {22.4%}, 11 {73.3%} vs 4 {26.7%}, 0 {0.0%} vs 5 {100%} p value < 0.001, 0.004, 0.004 respectively).

Table 3 demonstrates the baseline demographic, clinical and laboratory parameters of patients with and without ACS in hospital complications, patients who had developed in hospital complications were older, had a higher rate of previous IHD, DM, HTN and significantly higher serum creatinine level.

Platelet count, neutrophil count and WBC count were significantly higher while lymphocyte count was lower in patients who developed ACS with complications.

Mean PLR and NLR were significantly higher in patients with ACS who had developed complications as compared to those with no complications (167.7± 86.8 vs 99.3±35.1 p <0.001, 7.3±5.4 vs 2.8±1.8 P <0.001 respectively) table 4.

Discussion:

Acute coronary syndromes (ACS) represents the most common cause of death in many part of the world. [(1)]. Different presenting characteristics have become

important factors in deciding on the level of care and choice of interventional and medical therapies. Current guidelines recommend that certain pharmacological and interventional strategies are most appropriate for higher-risk groups. [13] Although individual demographic and clinical characteristics may be associated with an increased risk for adverse outcomes, one must take multiple factors into account simultaneously to optimize the ability to assess risk accurately. For that reason this study aimed to demonstrate any role for PLR in predicting ACS complications.

This study demonstrated that patients who had developed in hospital adverse outcome had significantly higher mean PLR than those patients with no complications. This was consistent with other studies [19-24]. Temiz A *et al* showed that group of patients with PLR >144 had higher rate of LV failure and mortality, but no significant association with post MI angina, and that was consistent with this study. Also they were concluded that there are no significant difference in PLR among those patients who develop serious LV arrhythmia [19] and that was disagreed with this study.

Patients with ACS who developed adverse outcome had higher platelet count in contrast to patients not had any complications (mean 252.0 ± 64.0 vs 221.9 ± 49.7, P value 0.001). This result was consistent with studies done by Nikolsky E *et al*, [5] and Braunwald E et al [6], but was disagree with Ranjith MP *et al*. study. [25]

These observation are explained by the key role of platelet in the pathogenesis of ACS. Platelets interact with endothelial cells and leukocytes and precipitate the release of inflammatory substances that lead to adhesion and transmigration of monocytes. [26] These monocytes are also reported to propagate inflammatory processes in the vessel wall, promoting atherosclerotic lesions [27]. High platelet

counts may indicate a higher degree of antiplatelet drug resistance [28], and a higher tendency to form platelet rich thrombi in atherosclerotic plaques, resulting in poor outcomes. Moreover, higher platelet counts may result from underlying inflammation, as several inflammatory mediators stimulate megakaryocyte proliferation and lead to relative thrombocytosis [29].

On the other hand this study found that patients who developed adverse outcome had lower lymphocyte count, (1.8±0.8 vs 2.4±0.8, P value < 0.001), and this was consistent with Zouridakis EG *et al* study. [30] The relative lymphopenia seen in ischemia might attributed to increased cortisol levels as a result of physiological stress [31], It has been proposed that in response to physiologic stress during myocardial ischemia/infarction, there is a release of cortisol. High cortisol leads to lymphopenia. [32] In ACS lymphocytes infiltrate to the ischemic and reperfused myocardium and express interleukin-10, which may play a significant role in transmigration of mononuclear cells, and induce the expression of tissue inhibitor metalloproteinase-1 [33], metalloproteinase that cause plaque destabilization in atherosclerotic plaque [34]

A statistically significant association was found between the occurrence of adverse out come in patients with ACS and high neutrophil count and high NLR as compared to patients who had no complications ((10.3±4.9)$\times 10^3$/µl vs (6.1 ± 2.9) $\times 10^3$/µl, 7.3 ± 5.4 vs 2.8±1.8, P value <0.0001 respectively) and this was consistent with other studies [35-39].

The potential detrimental role of neutrophils in participating in myocardial injury after ischemia and reperfusion has been suggested years ago, and a growing body of evidence indicates that these cells may act directly to determine myocardial tissue damage besides being part of the acute inflammatory response to

tissue injury [40]. In ACS these cells are functionally activated [41], and local neutrophil infiltration has been documented in culprit plaque lesions suggesting that neutrophils play a role in mediating destabilization of atherosclerotic plaques [42]. A cross-talk between neutrophils and platelets has been recognized and neutrophils are recruited to the injury sites both through the classical recruitment cascade and by adhering to platelets which are attached to the endothelial cells [43]. Moreover, micro particles derived from stimulated polymorph nuclear leukocytes may enhance coagulation and perpetuate thrombus formation because they can activate platelets and enhance platelet P selectin expression [44].

A statistically significant relation between high total leukocyte count and development of ACS adverse outcome ((13.4 ± 5.1) $\times 10^3$/µl vs (9.5 ± 3.2) $\times 10^3$/µl) was found, and that this was consistent with studies of Madjid M. *et al,* [45] and Taglieri N *et al,* [46].

Patients with ACS related complication were older than patients with no complications. This was agreed with Ahmed *et al*. study, who showed the prevalence of ACS was increased and prognosis worsened with aging. [47]

This study demonstrate that patients with higher serum creatinine had worse adverse outcome (0.8 ± 0.2 mg/dl vs 0.7 ± 0.4 mg/dl P value <0.001) which was consistent with study done by Santopinto JJ, *et al*. [48]

Conclusion:

Patients with ACS who have high PLR and NLR have significantly higher mortality rate, significant LV failure and serious arrhythmia in comparison to ACS patients with lower PLR and NLR.

Recommendation:

Complete blood count is a simple laboratory investigation that can be obtained easily; early in the management of patients with ACS. A high PLR, NLR and Leukocyte count, may be used to identify patients at increased risk for development of ACS complications.

Study limitations:

This study had some limitations.

1. Small number of patients had developed complications.
2. It would be better if we had followed the patients and explored the association between adverse long-term cardiac events and PLR.
3. The use of a single blood sample at admission does not anticipate the persistence of PLR over time.

Variables	No.	(%)	PLR	P value

Table 1: Clinical characteristics of the study population in relation to PLR:

				Mean	Std. deviation	
Gender	Male	151	69.3%	123.45	61.77	0.826
	Female	67	30.7%	125.49	65.75	
DM	Yes	87	39.9%	130.65	71.43	0.210
	No	131	60.1%	119.73	56.36	
IHD	Yes	81	37.2%	148.93	78.98	<0.001
	No	137	62.8%	109.39	45.31	
HTN	Yes	94	43.1%	129.63	63.80	0.257
	No	124	56.9%	119.87	62.09	
Smoking	Yes	102	46.8%	132.24	68.52	0.072
	No	116	53.2%	116.91	56.79	
Dyslipidemia	Yes	158	72.5%	121.27	59.30	0.286
	No	60	27.5%	131.47	71.46	

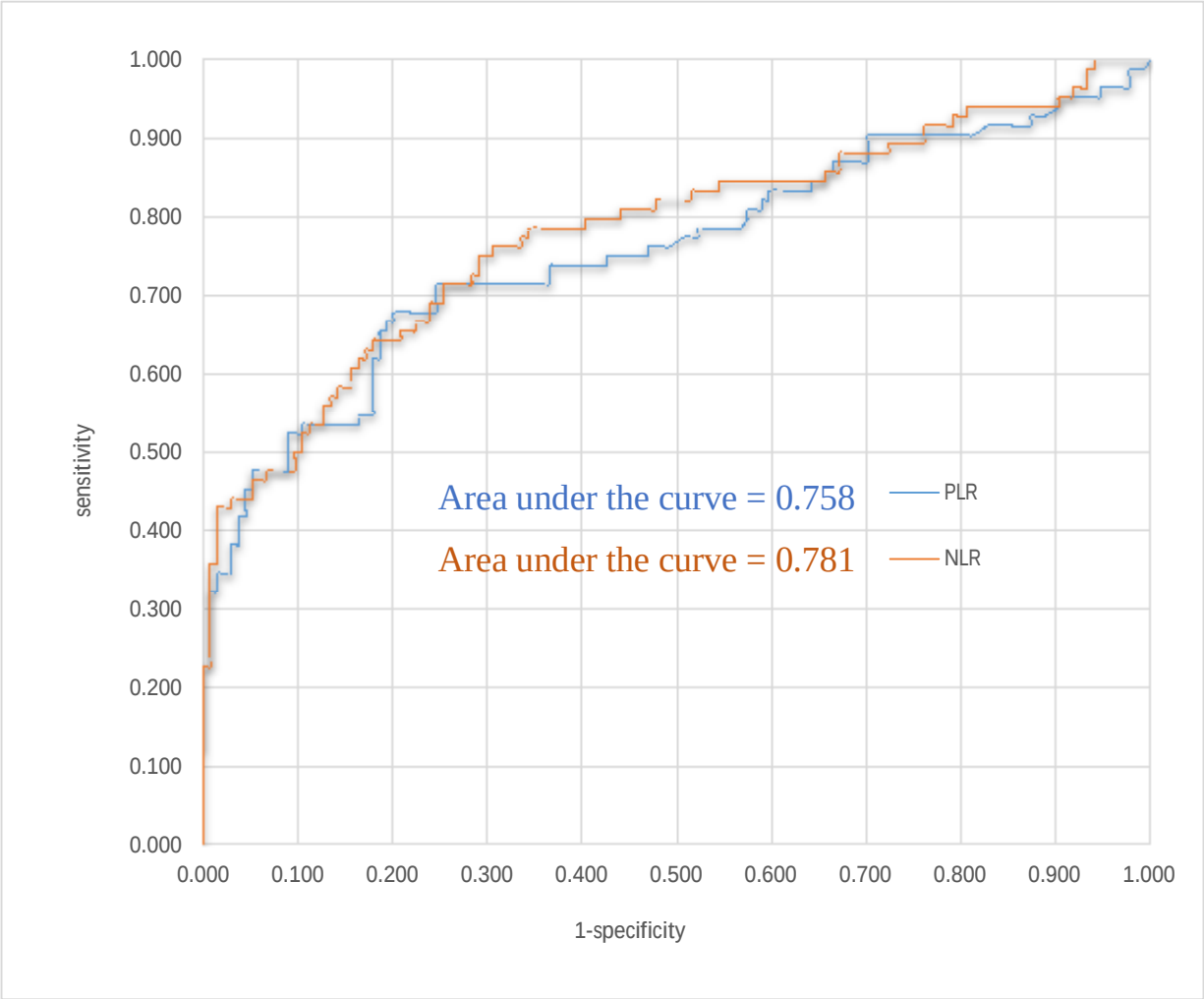

Figure 1: Receiver operating characteristics curve of platelet lymphocyte ratio and neutrophil lymphocyte ratio association with in hospital LV failure, serious arrhythmia and mortality in patients suffering ACS:

Table 2: Association between ACS complications and PLR best cut-off value

ACS Complications	PLR			
	<125 N:134	≥125 N:84	total	P value
LV dysfunction	11 (22.4%)	38 (77.6%)	49 (100%)	<0.001
Recurrent ischemia	12 (80.0%)	3 (20.0%)	15 (100%)	0.126
Arrhythmia	4 (26.7%)	11 (73.3%)	15 (100%)	0.004
Death	0.0 (0%)	5 (100%)	5 (100%)	0.004

Table 3: Demographics and clinical characteristics of patient with ACS in relation to development complications:

		Complications		Total	P value
		Yes (*n*:84)	No (*n*:134)		
Age	Mean	62.5	57.9	-	0.002
	Std. deviation	±12.1	±11.9		
gender	Male *n*(%)	97 (64.2%)	54 (35.8%)	151	0.207
	Female *n*(%)	30 (44.8%)	37 (55.0%)	67	
IHD	Yes *n*(%)	47 (58.0%)	34 (42.0%)	81	<0.001
	No *n*(%)	37 (27.0%)	100 (73.0%)	137	
Smoking	Yes *n*(%)	39 (38.2%)	63 (61.8%)	102	0.933
	No *n*(%)	45 (38.8%)	71 (61.2%)	116	
DM	Yes *n*(%)	41 (47.1%)	46 (52.9%)	87	0.034
	No *n*(%)	43 (32.8%)	88 (67.2%)	131	
HTN	Yes *n*(%)	45 (47.9%)	49 (52.1%)	94	0.014
	No *n*(%)	39 (31.5%)	85 (68.5%)	124	
dyslipidemia	Yes *n*(%)	56 (39.2%)	87 (62.8%)	143	0.792
	No *n*(%)	28 (37.3%)	47 (62.7%)	75	
ACS TYPE	UA *n*(%)	7 (21.9%)	25 (78.1%)	32	0.055
	NSTEMI *n*(%)	18 (34.6%)	34 (65.4%)	52	
	STEMI *n*(%)	59 (44.0%)	75 (56.0%)	134	

Table 4: Some hematological characteristics of patient with ACS in relation to development complications:

Variables		Complications		P value
		Yes (*n*:84)	No (*n*:134)	
Platelet 10³/µL	Mean	252.0	221.9	0.001
	Std. deviation	64.0	49.7	
Lymphocyte 10³/µL	Mean	1.8	2.4	<0.001
	Std. deviation	0.8	0.8	
PLR	Mean	167.7	99.3	<0.001
	Std. deviation	86.8	35.1	
WBC 10³/µL	Mean	13.4	9.5	<0.001
	Std. deviation	5.1	3.2	
Neutrophil 10³/µL	Mean	10.3	6.1	<0.001
	Std. deviation	4.9	2.9	
NLR	Mean	7.3	2.8	<0.001
	Std. deviation	5.4	1.8	
Hb mg/dl	Mean	13.6	13.5	0.479
	Std. deviation	1.3	1.2	
Serum creatinine mg/dl	Mean	0.8	0.7	<0.001
	Std. deviation	0.2	0.4	

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