Original Article

The Role of White Blood Cells in Acute Coronary Syndrome

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Summary:

Background:

Inflammation has been shown to play a role in atherosclerosis and acute coronary syndromes. An elevated total WBC count has been associated with increased cardiovascular risk, but which leukocyte subtypes carry this risk. is uncertain. This study was designed to determine the effect of WBC count and other inflammatory markers on severity and outcome of patients with UA/NSTEMI.

Patients and Methods:

Seventy (70) patients with UA / NSTEMI admitted to CCU at the Iraqi Center for Heart Diseases were subjected to thorough history and physical examination and WBC indices to find their relation to clinical severity and outcome for both in-hospital and/month after discharge. The results were compared with other thirty (30) patients with chronic stable angina and thirty (30) healthy persons as two control groups.

Results:

High total baseline total WBC was more prevalent in patient with UA/NSTEMI than in those with stable angina and normal persons (94.1%, 5.9%. and 0%) respectively. High baseline neutrophil was found only in those with UA./NSTEMI (100%, 0%, and 0%). High baseline Neutrophil/lymphocyte (N/L ratio) and Positive CRP were more prevalent in patients with UA/NSTEMI than in other two groups (92.3%. 7.7%. 0%) and (98.5%, 1 .5%. 0%) respectively.

Higher total baseline WBC count was significantly found in more severe Braunwald's class of those with UA/NSTEMI 6.3%. 31.3%. and 50.5% for patients with class I, II, III respectively. The same was true for baseline high neutrophil count (6.7%. 33.3% to 60%), high Baseline N/L ratio (7.7%, 15%. and 21.6%).

Patient in the UA/NSTEMI group with higher baseline WBC count had higher risk for death as compared to those of low and intermediate WBC count (0.00%. 0.00%. and 100.00%). The same was true for those with higher baseline neutrophil count (0.00%. 1.90%, 20.00%) and those with higher baseline N/L ratio (0.00%. 25.000%. 75.000%) respectively.

Conclusions:

Total baseline WBC and differential count is simple, cheap and widely available bedside test that predicted the severity of CAD and one month survival.

Keywords: WBC count, differential count, CRP, UA/NSTEMI

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Introduction:

Leukocytes are the major cellular counterparts of inflammation and immune response, they include neutrophils, lymphocytes, as well as monocytes, basophils and eosinophils (1). Alterations in the number and proportional variation of circulating leukocytes have long been recognized as measure of reaction of the host to disease process acutely and chronically. Normally, 90% of neutrophils pool is in the marrow and 2-3% in circulation, while the remainder in the tissues (1).

Different physiologic factors can affect WBC count like: age, sex, race, diurnal rhythm, menstruation and pregnancy (2). Many other pathological causes can alter WBC count: Acute infection, inflammatory response like surgery (1st 12-36 hours) or ischemic necrosis like myocardial infarction, it may be useful in distinguishing MI or unstable angina from stable angina as leukocytosis indicate tissue necrosis (3).

Inflammation and Atherosclerosis:

Inflammatory reaction may be blamed in the pathogenesis of coronary atherosclerosis, evolution of acute coronary syndromes and later on in the severity and prognosis following acute events (4). The role of WBCs in atherosclerosis can be assessed simply by the WBCs count in the peripheral blood (5). WBCs might play a pathogenetic role in vascular injury and that the WBCs count provide a rough measure of the intensity of that process.

The deformability of WBCs may be altered in ischemia, delayed its transit through the microcirculation and may contribute to further ischemia. Furthermore, the degree of this impaired deformability correlates with the clinical course of the patients: a more severe abnormality predicts a greater risk of pulmonary edema, cardiogenic shock and death. This deformability impairment is due to ischemia directly and or complement activation. The prognostic significance of altered leukocyte rheology in patients with ischemia suggests a possible vicious circle.

The acute phase reactant CRP, a simple downstream marker of inflammation has now emerged as a major cardiovascular risk factor. Although it is primarily derived from the liver, recent data indicate that cells within human coronary arteries, particularly in the atherosclerotic intima can elaborate CRP (6).

CRP when measured with new high-sensitivity assays (hsCRP) adds important prognostic information. hsCRP level predicts subsequent risk better than LDL cholesterol level (7) and hsCRP levels of less than 1 mg/L, 1-3. mg/L greater than 3 mg/L should be interpreted as low, intermediate and high risk respectively. Because hsCRP levels are stable over long periods of time, have no circadian variation, and are not affected by food intake, screening can easily be done on an outpatient basis at the time of cholesterol evaluation (8).

Cardiac markers such as creatinine kinas-MB and the troponin predict a worse long-term prognosis in those with unstable angina in a linear way (9). WBC count is shown to predict morbidity and mortality in many studies (10, 11), CRP is shown to have direct relationship with death in patients with acute coronary syndrome (9).

This study was designed to emphasize the usefulness of simple, cheep and ready available tests like WBC count and CRP on building stratification of severity and prediction of outcome in patient with UA/NSTEMI.

Patients and Methods:

Seventy (70) patients presented with UA / NSTEMI to the coronary care unit of the Iraqi Center for Heart Disease, from January 1st to August 30th, 2005 were enrolled in this study. The criteria for enrollment include patients presented to CCU with chest pain ischemic in nature associated with electrographic changes in the form of ST-T changes. Patients with ST segment elevation on admission ECG i.e. STEMI and diseases known to effect WBC count like infection, chronic inflammation, surgery, trauma, and hemorrhage were excluded.

Diabetes was diagnosed if the fasting, blood sugar > 126 mg/dl or use of antidiabetes medication. Hypertension was diagnosed on the bases of blood pressure ≥140/90 mmHg, or use of anti-hypertensive agents. Use of cholesterol lowering agents or total cholesterol level after fasting for 12 hours ≥ 200 mg/dl identified those with hypercholesterolemia. Overweight was diagnosed if BMI (weight Kg / height m^2) > 25 Kg/m^2. Family history of

premature coronary heart disease includes coronary heart disease in male first-degree relative < 55 years, and female first-degree relative < 65 years. Comprehensive medical history with proper medical examination was performed on every patient. Those who presented with progressive chest pain, symptoms at rest lasting more than 20 minutes or chest pain with minimal exercise and their ECG accepted by our inclusion criteria were classified in three classes according to Braunwald's clinical classification of UA / NSTEMI (class I, II,III) (12).

Venous blood sample was aspirated at the time of inserting i.v. line i.e. before any medical intervention. The first sample was anticoagulanted with potassium EDTA 2 mg/dl, for WBC counting and differential counts. Second blood sample was taken for CRP, cardiac troponin, blood urea, serum creatinine, and fasting cholesterol level.

WBC counting and differential study was determined by two expert hematologists. Patients were classified into three groups, those with low WBC count < 6 x 10^3 /mm^3, intermediate WBC count 6 x 10^3 /mm^3 - 10 x 10^3 / mm^3 , high WBC count > 10x10^3/ mm^3.

Differential WBC counts include neutrophil, lymphocyte and monocyte (N = 2-7.5 x 10^3 / mm^3, L = 1.5-4.0 x 10^3 / mm^3, M = 0.2 - 0.8 x 10^3 / mm^3). Patients were classified into three group; low, intermediate, and high neutrophil groups according to their normal value. Because there is no cutoff point for each, neutrophil / lymphocyte (N/L) ratio was taken and patients divided into three groups ranging from low group ratio < 10 percentile, intermediate ratio between 10-90 percentile, and high ratio > 90 percentile.

Qualitative CRP study was done (hsCRP was not available), CRP mentioned as positive for abnormal CRP and negative for normal CRP.

Cardiac troponin T. (kit by Roche Diagnostic Corporation) was assessed in CCU as bedside test with a cutoff point of 0.01 ng/ml based on prior work (9). Follow up of patients admitted to CCU was done daily: Echocardiographic study was arranged for all patients. Left ventricular ejection fraction and regional wall motional abnormality were assessed/normal study when ejection fraction (EF) > 55% and no regional motional wall abnormality and abnormal study when EF < 55% and/or regional motional wall abnormalities.

All patients underwent diagnostic coronary angiography during hospitalization which determined the number and severity of coronary artery disease (> 70% stenosis considered significant coronary artery diseases). The patients were followed up daily in hospital and for thirty (30) days after discharge from hospital by follow up visit to the outpatient department or by telephone call.

Control groups:

Tow control groups were found to compare the results with, the first one consisted of thirty (30) patients (age and sex matched) with stable angina aged between 40-60 years who presented for routine follow up to the outpatient clinic in the same center. Second one consists of thirty (30) healthy control persons (age and sex matched) aged between 35-60 years who represent paramedical staff and some relatives of patients in the hospital. Both groups were subjected to the same protocol.

Statistical analysis:

Data were collected and analyzed by using SPSS (statistical package of social science) version 10. Chi-squire test/used to compare between frequency variables. Statistical significance was considered when P-value <0.005.

Results:

The demographic features of patient with UA/NSTEMI and those with stable angina and healthy persons are seen in (table 1).

When we compare UA/NSTEMI patients with other two groups (stable angina and normal Groups) the results were: higher baseline total WBC count is found more in UA/NSTEMI group (94.1%) than in other two groups (5.9% and 0 %) respectively (p=0.0001) (table 2). Higher baseline neutrophil count was also found more among patients with UA/NSTEMI 100% compared to 0% in both other two groups (p=0.0001) (table2). High N/L ratio was found in patient with UA/NSTEMI (92.3%), while only 7.7% and 0% in patients with stable angina and healthy person respectively (p=0.0001) (table2). CRP was positive in 98.5% in patients with UA/NSTEMI while only in 1.5

and 0 % in stable angina and healthy persons respectively (p=0.00001) (Table2).

The total of WBC and neutrophil count was significantly more prevalent in Braiinwald's class III (62.5 % and 60 %) than in class I and II (6.3% and 6.7%) and (31.3% and 33.3 %) respectively (p=0.002) (p=0.008) (table 3). CRP was predictive of more severe presentation 92.3%, 80 %, and 100 % for patients in class I, II and III respectively (p=0.0001) (table 3). The clinical severity can be predicted from the high L/N ratio (7.7%, 15% and 21% in class I, II, and III respectively) (p=0.0001) (table 3).

High baseline WBC count is associated with one month mortality of 25 % compared to 0 % in the intermediate and low WBC count, which is statistically significant (p=0.0001) (table4). This is also true for neutrophil count (20% in high group compare to 1.9 % and 0 % in intermediate and low count respectively)(p=0.0001) (Table 4). All the dead patients were found in those with positive CRP, nobody in other two groups (p-0.0001) (table 4). High N/L ratio is predictive of higher one month mortality for patients with UA/NSTEMI (75%) than 25% and 0% in normal and low ratio respectively (p=0.0001) (table 4).

Discussion:

Finding inexpensive, simple and easily accessible tests in medicine is still fascinating and of paramount importance in the face of limited health economic resources. For this and others this study was made.

In cardiology practice building up risk stratification for severity and prognosis get the mind of the patient and his treating physician equally. Seventy patients with UA/NSTEMI were enrolled in this study to estimate how much it is applicable to rely on simple hematological indices and markers in achieving this.

Although the link between high baseline WBC count and MI was dated back to more than 25 years (13), yet it extends progressively in the last years to involve the whole spectrum of acute coronary syndrome (14, 11). In our study it was seen that high baseline WBC count was associated with more severe clinical presentation as measured by Braunwald's classes (62.5% in class III versus 6.3 % in class I p = 0.002, table 2). This was consistent with many studies that showed the same clinical relation (11), the relation which was proved at angiographic level in others (10). Regardless of Braunwald's classes high baseline WBC count was seen in those with UA/NSTEMI as compared with stable angina or healthy control groups with statistically significant power (table 3). We and others (14, 10, 15) have shown that the high baseline WBC count can be taken as a good predictor of mortality in patient with UA/NSTEMI, although in many of these studies this was true for short (one month) and long (six months) term follow-up. The period of follow up in our study was only 30 days and it was difficult to follow patients up more than this due to our security conditions. Being observational, our study identified only the association between WBC count and acute coronary syndrome but not causality so it will not answer the usually addressed question whether this is adaptive response to ischemia or it is maladaptive processes as circulating leukocyte-platelet aggregates appear in acute coronary syndromes and might facilitate vascular plugging (16, 17).

On reviewing published studies it is still more difficult to reach a final agreement about which WBC subtype can be correlated well with prognosis of acute coronary syndrome and at which level (18). Contradictory results still exist, in the face of Hiroshima and Nagasaki Adult Health Study (19) that found a good correlation between all type of WBC subtype but not lymphocyte, two UK studies (20) that showed the correlation to be found with neutrophils and eosinophils but not with others, and in one study eosinophils was highly correlated with clinical severity of angina and anti-anginal therapy decreased the count to control level (21). In our study we measured the baseline neutrophils count and ratio of neutrophils to lymphocyte (N/L ratio); the results showed that high neutrophils count and high N/L ratio was significantly associated with clinical severity of UA/NSTEMI (table 2), furthermore it predict one month high mortality rate (Table 4). This was contradicted the hypothesis that macrophage/monocyte and lymphocyte transmigrate from the vascular space into subendothelial layers of large and medium-sized arteries and that circulating WBC

fraction increased to maintain equilibrium with plaque fraction (19, 22).

Many studies, in parallel with our result, stress the role of neutrophils in ischemic cardiovascular disease particularly in acute phases. Increased expression of neutrophils adhesion molecules and other markers has been described in patients with acute coronary syndrome and ischemic heart disease (10, 15).

Recently, neutrophil invasion of atherosclerotic plague has been directly visualized in an animal model (23) and has been shown in the culprit clinical plagues in patients with acute coronary syndrome (14).

The study showed that the presence of another inflammatory marker, CRP is also a powerful predictor of severity and mortality in patients with acute coronary syndrome (table 2, 4) this is in agreement with Mar S Sabatine et al (10) study which showed that those with ACS who have had high CRP level had a relatively higher risk of dying at six months (5% to 7%).

Conclusion:

In patients with UA/NSTEMI, elevations of basal total WBC count, high basal neutrophil count, high N/L ratio and positive CRP can predict the clinical severity of the disease as well as outcome after one month.

Recommendation:

Simple bedside tests can be used to replace the more expensive markers (or in their absence) to assess the severity and predict prognosis in patients with ACS.

Limitations:

One of the limitations of this study is that CRP was measured qualitatively because of the unavailability of hsCRP assay in Iraq at time of the study.

Table 1: Demographic chart of patients with acute coronary syndrome, stable angina and healthy control

		Patients		Stable angina		Control	
Number		70		30		30	
Age (years)		30-60 Mean (45)		40-60 Mean (50)		35-60 Mean (47.5)	
Sex	**Female**	40	57.14%	20	66.66%	20	66.6%
	Male	30	42.85%	10	33.33%	10	33.3%
HT		43	61.42%	20	66.66%	0	
DM		18	25.5%	10	33.33%	0	
Smoking		32	45.71%	12	40%	0	
Hypercholesterolemia		35	50%	15	50%	0	
Abnormal echocardiography		32	45%	10	33.33%	0	
BMI > 25 kg/m^2		10	14.2%	10	33.3%	0	
Angiography	**Normal**	8	11.4%	4	13.3%		
	1 vessel	27	38.5%	14	46.6%		
	2 vessel	24	34.7%	7	23.33%		
	3 vessel	11	15.7%	5	16.6%		

Table 2: Relation between WBC indices and CRP with Braunwald's classes

		Braunwald's Classes			Total No. (%)	P Value
		Class I No. (%)	Class II No. (%)	Class III No. (%)		
Total WBC count	**Low**	2 (13.3)	6 (40)	7 (46.7)	15 (100)	0.12
	Intermediate	10 (25.6)	9 (23.1)	20 (51.3)	39 (100)	0.015
	High	1	5	10	16	0.002

		(6.3)	(31.3)	(62.5)	(100)	
Neutrophil Count	**Low**	0 (0)	2 (100)	0 (0)	2 (100)	0.059
	Intermediate	12 (22.6)	13 (24.5)	28 (52.8)	53 (100)	0.001
	High	1 (6.7)	5 (33.3)	9 (60)	15 (100)	0.008
CRP	**Positive**	12 (92.3)	16 (80)	37 (100)	65	0.0001
	Negative	1 (7.7)	4 (20)	0 (0)	5	0.0001
N/L	**Normal**	12 (92.3)	15 (75)	22 (59.5)	49	
	High	1 (7.7)	3 (15)	8 (21.6)	12	0.0001

Table 3: Comparison between UA/NSTEMI, Stable Angina and Control group in regard to WBC indices and CRP and Braunwald's classes

		UA/NSTEMI	**Stable Angina**	**Control**	**P Value**
		No. (%)	**No. (%)**	**No. (%)**	
Total WBC count	**Low**	15 (55.6)	8 (29.6)	4 (14.8)	0.005
	Intermediate	39 (45.3)	21 (24.4)	26 (30.2)	0.01
	High	16 (94.1)	1 (5.9)	0 (0)	0.0001
Neutrophil Count	**Low**	2 (100)	0 (0)	0 (0)	0.049
	Intermediate	53 (46.9)	30 (26.5)	30 (26.5)	0.001
	High	15 (100)	0 (0)	0 (0)	0.0001
CRP	**Positive**	65 (98.5)	1 (1.5)	0 (0)	0.00001
	Negative	5 (7.8)	29 (45.3)	30 (46.9)	0.00002
N/L	**Low**	9 (81.8)	2 (18.2)	0 (0)	0.0001
	Normal	49 (46.2)	27 (25.5)	30 (28.3)	0.005
	High	12 (92.3)	1 (7.7)	0 (0)	0.0001

Table 4: WBC indices with survival rate

		UA/NSTEMI	**Stable Angina**	**Control**	**P Value**
		Survive No. (%)	**Death No. (%)**	**Total No.**	
Total WBC count	**Low**	15 (100)	0 (0)	15	0.0001
	Intermediate	39 (100)	0 (0)	39	0.0001
	High	12 (75)	4 (25)	16	0.0004
Neutrophil Count	**Low**	2 (100)	0 (0)	2	0.045
	Intermediate	52 (98.1)	1 (1.9)	53	0.0002
	High	12 (80)	3 (20)	15	0.0001
CRP	**Positive**	61 (92.4)	4 (100)	65	0.0001
	Negative	5 (7.6)	0 (0)	5	0.0001
N/L	**Low**	9 (13.6)	0 (0)	9	0.072
	Normal	48 (72.2)	1 (25)	49	
	High	9 (13.6)	3 (75)	12	0.0001

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