Relationship between Baseline White Blood Cell count and C-reactive protein with Angiographic severity of Coronary Artery Disease in Patients with Acute Coronary Syndrome.

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Key words:
WBC; C-reactive protein; Acute coronary syndrome.

Abstract:

Background: *Inflammation has been shown to play a role in atherosclerosis and acute coronary syndrome. This study was carried out to evaluate the relationship between baseline white blood cell (WBC) count and C-reactive protein (CRP) with angiographic severity of coronary artery disease in patients with acute coronary syndrome and to identify those subsets of patients with acute coronary syndrome who may need to undergo invasive or conservative strategies.*

Method: *A total of 100 patients with acute coronary syndrome including unstable angina, non-ST elevated myocardial infarction & ST elevated myocardial infarction were evaluated in National Institute of Cardiovascular Disease (NICVD), Dhaka with a view to correlate angiographic findings, C-reactive protein and WBC count.*

Results: *This study observed that either raised WBC count or raised CRP independently and combination of both WBC count and CRP elevation were significantly associated with more severe coronary artery disease. Either raised WBC count or raised CRP or combination of raised WBC count and CRP were significant predictor of multivessel disease and high stenosis score.*

Conclusion: *Elevation of WBC count and CRP in patients with acute coronary syndrome are associated with severe coronary disease. WBC count and CRP can be used as a new and even simpler tool for risk stratification in acute coronary syndrome.*

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Introduction:

Among the cardiovascular diseases acute coronary syndrome is the leading cause of death of developed country and second leading cause of death in developing country and by the year 2020, ischemic heart disease will hold first place in the World.[1] Major underlying mechanism of ischemic heart disease is atherosclerosis process in coronary arteries of heart. Atherosclerosis is not a single disease entity rather represents a common response of the artery to numerous potentially different forms of insult. Atherosclerosis is a complex inflammatory fibroproliferative response to retention of plasma derived atherogenic lipoproteinsin the arterial intima.[2] Acute coronary syndrome has commonly been shown to occur as a result of the disruption of atherosclerotic plaque at a site of a high density of inflammatory cells.[3] Inflammation plays an important role in the initiation and progression of atherosclerosis and systemic blood markers of inflammation including leukocyte count, C-reactive protein have emerged as powerful predictors of coronary events.[4] An association between white cell count and cardiovascular disease was first noted more than a quarter century ago.[5] Freidman et al. observed that an increased WBC count was associated with an increased risk of developing acute-MI and Schlant et al. observed that an elevated WBC count was predictor of mortality post- MI.[6] More recently Barron et al.[7] demonstrated that in setting of MI, an elevated WBC count was associated with reduced epicardial and myocardial perfusion and worse clinical outcomes. Cannon et al. [8] also found that an elevated WBC count was associated with increased short term and long term mortality in the full spectrum of ACS.

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It is now appreciated that inflammation plays a central role in atherosclerosis and acute coronary syndrome.[9] This has led to renewed interest in the study of inflammatory markers, including C-reactive protein and more recently WBC count, in acute coronary syndrome. An inflammatory response is often found at the site of plaque rupture and even subtle elevations in CRP predict a higher rate of MI in otherwise healthy persons.[10] Ferreiros et al.[11] demonstrated that elevation of CRP indicates presence of evolving inflammation at the coronary plaque and in unstable angina, CRP is a strong independent marker of increased 90 days risk. In support of this relationship between inflammation and CAD, Sabatine et al.[12] observed that the extent of CAD found at angiography was related to the WBC count, even after adjusting for traditional risk factors. They also demonstrated that patient with a low CRP but an elevated WBC count remained at significantly higher risk of death at six months (p= 0.049) and patient with a high CRP were at even higher risk (p= 0.004). Rahman et al.[13] conducted a study at National Institute of Cardiovascular Diseases, Dhaka and observed that C-reactive protein can be consider as a prognostic marker in patients with unstable angina for development of major coronary events.

Systemic inflammation also plays a pivotal role in atherosclerosis inception and progression.[14] Mononuclear cells, macrophages, and T lymphocyte are prominent in atheromatous plaques in the arterial wall.[15] Furthermore, the shoulder region of a plaque, the most vulnerable site of rupture in acute coronary syndrome is heavily infiltrated with inflammatory cells.[16]Cytokines, which cause the de novo hepatic production of acute phase reactants such as CRP, have been shown to increase in acute coronary syndrome even in the absence of myocardial necrosis.[17] Therefore CRP has been examined as a surrogate marker of other inflammatory mediators such as interleukin-6 and tumor necrosis factor to better understand the inflammatory components of atherosclerosis. Current knowledge, however, suggests that the CRP concentration might reflect the vulnerability of the artheromatous lesion and likelihood of a plaque rupture.[9,14,16,17]This acute phase reactant has been studied over the last several years in a wide variety of atherosclerotic disease. Its prognostic utility in acute coronary syndrome and ability to predict future coronary events in apparently healthy men and women[10,18,19] have been demonstrated.

Zerbrack et al.[20] demonstrated such association between plasma hs-CRP and the severity of coronary artery stenosis. C-reactive protein and CAD independently and additively contributed to the risk prediction: low CRP and lowest CAD score was associated with lowest risk, and high CRP and highest CAD score was associated with the highest risk, with a 10-fold difference between extremes (2.5% vs. 24%). Hasnat MA et al.[21] conducted a study at Dhaka medical college hospital, Bangladesh and showed that high hs-CRP associated with angiographically severe coronary artery disease. Thus WBC count and CRP may be both a marker heightened inflammatory state and more extensive atherosclerosis disease burden and a direct contributor to coronary thrombosis and microvascular injury in the setting of plaque rupture.

So we hypothesized that baseline WBC count or CRP level may be considered as significant predictor of angiographic severity of coronary artery disease in patients with coronary syndrome. We studied the relation of WBC count and CRP level to the presence and severity of coronary artery disease as determined by coronary angiography.

Methods:

Study Method:

This was a prospective, observational study and conducted in National Institute of Cardiovascular Diseases (NICVD), Dhaka during the period of February 2011 to December 2011 in order to observe relationship between baseline WBC count and CRP level with angiographic findings in patients admitted with acute coronary syndrome. At first, total 230 patients diagnosed as a case of acute coronary syndrome including unstable angina, non-ST elevated myocardial infarction and ST elevated myocardial infarction. Blood sample was drawn for WBC count and CRP level within 24 hours of symptoms which was considered as baseline sample. But angiogram was done only 100 patients among them within 2 weeks of index event. So that finally a total of 100 patients fulfilled inclusion and exclusion criteria and underwent coronary

angiogram were selected for the study and classified into four groups – Group I, Group II, Group III & Group IV according to the WBC count and CRP level. Group I included WBC count- normal (4000-11000/cmm) & CRP- normal < 10mg/L, Group II included WBC count- raised (>11000/cmm) & CRP- normal < 10mg/L, Group III included WBC count- normal (4000-11000/cmm) & CRP- raised >10mg/L, Group IV included WBC count- raised (>11000/cmm) & CRP- raised > 10mg/L.

Laboratory Method:
WBC count was done by manual method with use of Haemocytometer. CRP estimation was carried out by sensitive immunochemical quantitative method (Nephelometry system). Interpretation of coronary angiogram was done by one cardiologist to assess severity of coronary artery disease. In this study angiographic severity of coronary artery disease was assessed by vessel score, stenosis score, lesion morphology and TIMI flow grading.

Vessel score [22]: Score ranged from 0 to 4, depending on the number vessels involved with a significant stenosis. (50% or greater luminal stenosis)

Stenosis score: [22] The evaluation of degree of stenosis relates to the percentage reduction in the diameter of the vessel. By Gensini score, the lesions are roughly classified by visual estimation of reduction of luminal diameter.

Lesion morphology: [23] Type A, Type B and Type C lesion established by a joint ACC/AHA task force.

Culprit artery TIMI flow: [23] According to the TIMI grade flow in the culprit artery is defined by American College of Cardiology (TIMI Grade 0-3)

Data Analysis:
Continuous variables were summarized as groups or as mean ± standard deviation (SD) and categorical data as frequencies and percentages. For continuous variables differences among groups were analyzed by Analysis of Variance (Anova) test. The chi- square was applied to compare differences between discrete variables. For multiple comparisons a p value <0.05 was considered statistically significant.

The whole analysis was done with the help of computer using SPSS (Statistical package for social science) program version 10.

Results:
Out of 100 patients 87 (87%) were male & 13 (13%) were female having a male and female ratio 6.69: 1. The mean age of the study population were 51 ± 6.97 ranging 35 to 70 years. Among the important risk factors of CAD, 61.4% patients were smoker, 37% patients were hypertensive, 31% patients were diabetic, 20.7% patients were dyslipidaemic and 11.9% having family history of IHD. There distribution in the study groups was not statistically significant. Distributions of clinical pattern of acute coronary syndrome (Unstable angina, non- STMI, STMI) were significant among the study 4 groups (p < 0.1).

In this study, angiographic severity was assessed by vessel score, stenosis, lesion morphology and TIMI flow grading and tries to find out their

Table-I
Distribution of baseline characteristics among the study group

Characteristics		Group I* No (percent)	Group II* No (percent)	Group III* No (percent)	Group IV* No (percent)	P value*
Age (Mean ± SD)		51 ± 6.93	52 ± 6.74	53 ± 6.23	53 ± 6.04	0.52
Sex	Male	16 (18.39%)	22(25.28%)	17% (85%)	32 (19.54%)	0.12
	Female	6 (26.08 %)	2(8.7%)	3 (13.04%)	2(8.7%)	0.34
Smoking		15(68.2%)	19 (76%)	9(45%)	19(55.9%)	0.14
Diabetes		3(13.6%)	7(28%)	5(25%)	16(47.1%)	0.053
Hypertension		14(63.6%)	9(36%)	2(10%)	14(41.2%)	0.063
Dyslipidaemia		3(4.5%)	5(8%)	5(15%)	8(14.7%)	0.54
Family history of IHD		1(4.5%)	4(16%)	5(25%)	2(5.9%)	0.12
Clinical pattern	UA	16(72.7%)	5(30%)	6(30%)	6(17.6%)	.001
	NSTMI	1(4.5%)	9(36%)	6(30%)	6(17.6%)	.01
	STMI	5(22.7%)	11(44%)	8(40%)	21(64.7%)	.003

*Group I = WBC normal & CRP normal, *Group II = WBC raised & CRP normal
*Group III = WBC normal & CRP raised, *Group IV = WBC raised & CRP raised
*P value in chi-square test

relationship with baseline WBC count and CRP level. Vessel score in Group I, Group II, Group III & Group IV were 1.14 ± 0.56, 2.24 ± 0.83, 2.00 ± 0.58, 3.00 ± 0.65 respectively which was statistically significant ($p < 0.5$). Stenosis score in group- I, group- II, group- III & group- IV were 6.00 ± 4.19, 18.72 ± 10.31, 13.80 ± 4.94 & 32.41 ± 15.75 respectively which was statistically significant ($p < 0.5$).

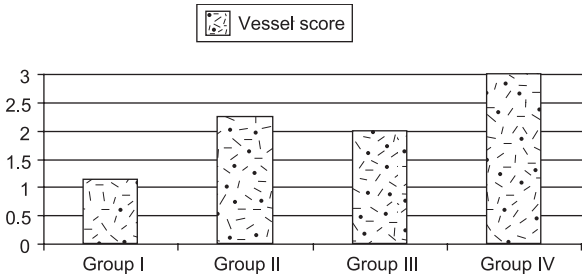

Fig.-1: *Vessel score in relation to study groups.*

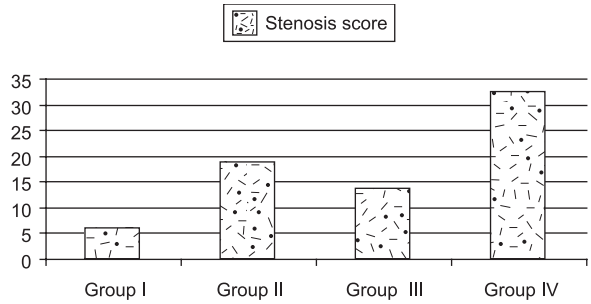

Fig.-2: *Stenosis score in relation to study groups.*

Regarding morphology of the lesions, 88.8% were simple lesion and 11.2% were complex lesion in Group I, 83.3% were simple lesion and 16.7% were complex lesion in Group II, 80.8% were simple lesion and 19.2% were complex lesion in Group III, 63.1% were simple lesion and 36.9% were complex lesion in Group IV. The patients in Group IV had significantly higher number of complex lesions (36.9%) in comparison to patients in Group I (11.2%) and Group II and Group II & Group III had also higher than Group I which were statistically significant ($p < 0.5$). Regarding TIMI flow grading in culprit lesion, TIMI 0-2 in Group I, Group II, Group III & Group IV were 11.1%, 16.7%, 19.2%, 36.9% respectively and TIMI 3 in Group I, Group II, Group III & Group IV were 88.8%, 43.3%, 80.8%, 63.1% respectively which was statistically significant ($p < 0.5$).

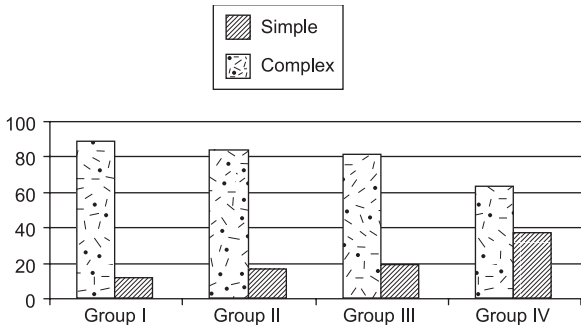

Fig.-3: *Morphology of the lesion in relation to study group.*

Multivariate analysis for predicting angiographic severity of coronary artery disease was also observed in the study. Study observed that WBC count and CRP level, as independent predictors of severe coronary artery disease, were statistically significant (vessel score, $p < 0.5$ & stenosis score, $p < 0.5$) Diabetes mellitus was found independent predictors of severe stenotic lesion ($p < 0.5$) but not multivessel disease in this study. Other risk factors like hypertension, smoking, dyslipidaemia & family history of IHD were not found independent predictors of severe coronary artery disease in this study.

Table IIa

Prediction of vessel score & stenosis score in relation to WBC count and other risk factors.

Variable	Observed power	P value	Variable	Observed power	P value
Fixed Variable	.999	.001	Fixed variable	.999	
WBC count			CRP level		
Co-variable			Co-variable		
Smoking	.32	.13	Smoking	.49	.053
Diabetes	.15	.35	Diabetes	.87	.002
Hypertension	.66	.42	Hypertension	.38	.09
Dyslipidemia	.19	.28	Dyslipidemia	.29	.15
Family history of IHD	.07	.63	Family history of IHD	.05	.99
Vessel score, WBC & other risk factors			Stenosis score, WBC & other risk factors		

Table IIb

Prediction of vessel score and stenosis score in relation to CRP level and other risk factors.

Variable	Observed power	P value	Variable power	Observed	P value
Fixed Variable	.997	.001	Fixed variable	.999	.001
CRP level			CRP level		
Co-variable			Co-variable		
Smoking	.14	.13	Smoking	.08	.61
Diabetes	.43	.35	Diabetes	.57	.03
Hypertension	.05	.42	Hypertension	.43	.07
Dyslipidemia	.31	.28	Dyslipidemia	.29	.15
Family history of IHD	.12	.63	Family history of IHD	.05	.97
Vessel score, CRP & other risk factors			Stenosis score, CRP & other risk factor		

Discussion:

This was a prospective, observational study and conducted in National Institute of Cardiovascular Diseases (NICVD), Dhaka in order to observe relationship between baseline WBC count and CRP level with angiographic findings in patients admitted with acute coronary syndrome. This study observed that either raised WBC count or CRP level or combination raised WBC count & CRP level was significant predictor of multivessel disease and high stenosis score. This was consistent with findings of Sabatine et al;[12] in that study they observed high WBC count was a significant predictor of multivessel disease ($p = 0.018$) and a statistically significant correlation between baseline WBC count and the overall extent of a patient's CAD (Stenosis > 50%) ($p < 0.001$). They observed that those patients having normal WBC count,[multivessel disease (53%) and no vessel disease (20%)] and those having raised WBC count,[multivessel disease (70%) and no vessel disease (9%)].

In our study, we also observed angiographic severity in relation to WBC count and found that raised WBC count group was associated with high stenosis score, (26.87 ± 15.01 vs 11.70 ± 9.99, p value < 0.5) and high vessel score (2.69 ± 0.84 vs 1.62 ± 0.75, p value < 0.5) were statistically significant. Nyandak et al.[24] observed that higher hs- CRP levels were associated with higher stenosis and extent score in CAD patients. They showed in their study that Spearman's correlation coefficient between hs-CRP and angiographic stenosis score was $r = 0.316$ ($p < 0.004$) and hs-CRP with angiographic extent score was $r = 0.338$ ($p < 0.005$).

In our study, regarding morphology of the lesion we also observed higher WBC count and CRP level was associated with more complex lesion (Type B & Type C lesion). We found 36.9% complex lesion in Group IV and 11.2 % complex lesion in Group I, which was statistically significant ($p < 0.5$). We have demonstrated that elevated WBC count and CRP level was associated with reduced TIMI flow of culprit vessel in the setting of acute coronary syndrome. Avanzas et al.[25] correlated CRP level with the number of complex stenosis (irregular border, ulceration or filling defect). Zairis et al.[26] demonstrated that with increasing of CRP tertile a significant increase in either the number of multiple complex lesions or presence of apparently thrombus containing lesions. This is also consistent with the findings of Sabatine et al[12] and Baron et al.[7]. They observed elevations in baseline WBC count are associated with reduced epicardial and myocardial blood flow. Barron et al. observed that patients with a closed infarct related artery at 90 mins (TIMI grade 0 or I flow) had a higher WBC count than did patients with an open artery ($11.7 \pm 5.9 \times 10^9$, n= 186 versus $10.8 \pm 3.5 \times 10^9$, n = 430; p = 0.01) The presence of angiographically apparent thrombus and complex lesion was associated with a higher WBC count ($11.5 \pm 5.2 \times 10^9$/L, n = 290 versus $10.7 \pm 3.5 \times 10^9$/L, n = 648; p = 0.008).There also was association between higher WBC count worse myocardial perfusion as assessed with TIMI myocardial perfusion grading system (P = 0.04). Sabatine et al. observed that the baseline WBC

count was higher in patients with worse culprit artery TIMI flow grading: 8.1 x 10^9/L in patients with TFG 3; 9.3 X 10^9 /L in patients with TFG 1; 10.75 X 10^9/L with TFG 0 (P = 0.007).

In our study we observed that in patients having normal WBC count < 10 x 10^9 /L [TFG 0 (0%), TFG 1-2 (5.26%), TFG 3 (13.95%)] and those having raised WBC count > 10 x 10^9/ L [TFG 0 (13.33%), TFG 1-2 (51.28%), TFG 3 (34.88%)](p = 0.004). Moukarbel GV et al.[27] also found that elevated CRP level on admission was that elevated CRP level on admission was a marker for anatomic complexity of culprit lesion in patients with elevated CRP (p = 0.007) and cTnT levels (p = 0.027). Angiographic severity in relation to isolated to CRP was also observed in our study. Raised CRP group was associated with high stenosis score (25.52 ± 15.67 vs 12.77 ± 10.23, p value < 0.5) and high vessel score (2.64 ± 0.79 vs 1.72 ± 0.9, p value < 0.5) were statistically significant. Zerbrack et al. [20] observed that C-reactive protein correlated with the severity/ extent of CAD for the entire cohort by all measures of CAD (p > 0.008) except for the number of moderate lesions. Espliguero et al.[28] found that hs-CRP was significantly higher in patients with ACS compared to CSA (P = 0:004) and correlated with number of complex angiographic stenoses (r = 0:36, P = 0:01). Hs-CRP was also increased in patients with NYHA functional class III or IV compared to those in class I or II (P < 0:0001).

Angiographic severity in relation to isolated to CRP was also observed in our study. Raised CRP group was associated with high stenosis score (25.52 ± 15.67 vs 12.77 ± 10.23, p value < 0.5) and high vessel score (2.64 ± 0.79 vs 1.72 ± 0.9, p value < 0.5) were statistically significant.

Although the results of this study support the hypothesis, there are some facts to be considered which might affect the results:

- Number of study population was limited.
- Angiography could not be done very early after admission.
- Difference of CAG findings between thrombolytic recipients and non recipients was not compared.
- Angiography was evaluated by visual estimation so there was chance of inter observer and intra observer variation of interpretation of the severity of stenosis.

Conclusion:

We can conclude from the study that either raised WBC count or raised CRP level independently and combination of both was significantly associated with more severe coronary artery disease. The study observed that either raised WBC count or CRP level or combination of both were significant predictor of multivessel disease and high stenosis score. Thus WBC count and CRP can be used as a new and even simpler tool for risk stratification in acute coronary syndrome.

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