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Research Article

RELATIONSHIP BETWEEN WHITE BLOOD CELL (WBC) COUNT AND C-REACTIVE PROTEIN (CRP) WITH ANGIOGRAPHIC SEVERITY OF CORONARY ARTERY DISEASE IN PATIENTS WITH ACUTE CORONARY SYNDROME

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ABSTRACTS

Background: Inflammation plays an important role in the initiation and progression of atherosclerosis and systemic blood markers of inflammation like white blood cell count and C-reactive protein have emerged as powerful predictor of coronary events. This study was carried out to evaluate the relationship between baseline white blood cell count and C-reactive protein 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 strategy.

Method: A total of 100 patients with acute coronary syndrome including unstable angina, non-ST elevation myocardial infarction and ST elevation myocardial infarction (not thrombolysed) were evaluated in Department of Cardiology, Sawai Man Singh Medical College & Hospital, Jaipur , Rajasthan, India with a aim to correlate baseline white blood cell count and C-reactive protein with angiographic severity of coronary artery disease.

Results: This study observed that raised white blood cell count and raised C-reactive protein independently and combination of both raised white blood cell count and CRP were significantly associated with angiographic more severe coronary artery disease in form of multi vessel disease ,high stenosis score, more complex lesions and reduced TIMI flow grading.

Conclusion: Raised white blood cell count and C- recactive protein in patient with acute coronary syndrome are associated with angiographic features of severe coronary artery disease. Both these markers can be used as a simpler tool for risk stratification patients with acute coronary syndrome.

KEYWORDS: White Blood Cell Count, C -Reactive Protein, Angiographic Severity, Acute Coronary Syndrome

INTRODUCTION

Among the cardiovascular diseases acute coronary syndrome is the leading cause of death in 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 a complex inflammatory fibro-proliferative response to retention of plasma derived atherogenic lipoproteins in 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] Freidman et al.[5] 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 post- MI mortality.[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.

It is now appreciated that inflammation plays a central role in atherosclerosis and acute coronary syndrome.[8]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.[9] Ferreiros et al.[10] 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.[11] 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). Current knowledge, however, suggests that the CRP concentration might reflect the vulnerability of the artheromatous lesion and likelihood of a plaque rupture.[8],[12],[13],[14]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[9],[15],[16] have been demonstrated. Zerbrack et al.[17] demonstrated such association between plasma hs-CRP and the severity of coronary artery stenosis. C-reactive protein and CAD score 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%). Thus WBC count and CRP may be both a marker of 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. Baseline WBC count and CRP level are considered as significant predictors of CAD and risk of ACS.

The aim of this study was establishing a potential relationship between levels of Total white blood cell count and CRP with the extent of angiographically documented coronary artery disease in Acute Coronary Syndrome patients.

METHODS

Study Method

This was a prospective, observational study and conducted in SMS Medical College and Hospital, Jaipur, Rajasthan, India, 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 130 patients diagnosed as a case of acute coronary syndrome including unstable angina, non- ST elevated myocardial infarction and ST elevated myocardial infarction who were not thrombolysed. 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 in 100 patients among them within 2 weeks of index event. So that finally a total of 100 patients fulfilled inclusion and exclusion criteria(Patients was on statins for more than one month, Any systemic infection, Collagen vascular disease, Recent trauma ,Patients with documented extra-cardiac atherosclerosis, Prior PCI, Ac STEMI (Thrombolysed), Neoplastic disease, Pt who are taking anti-inflammatory drugs ,Immuno supressive drugs ,Anti neoplastic drugs, Women receiving HRT)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 countnormal (4000-11000/cmm) & CRP- normal < 2mg/ L, Group II included WBC count- raised (>11000/ cmm) & CRP- normal < 2mg/L, Group III included WBC count- normal (4000-11000/cmm) & CRP raised >2mg/L, Group IV included WBC countraised (>11000/cmm) & CRP- raised > 2mg/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:[18] Score ranged from 0 to 4, depending on the number vessels involved with a significant stenosis.(50% or greater luminal stenosis).

Stenosis score:[18] 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:[19] Type A, Type B and Type C lesion established by a joint ACC/AHA task force.

Culprit artery TIMI flow:[19] 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 18.

RESULTS

Out of 100 patients 84 (84%) were male & 16 (16%) were female. The mean age of the study population was 52 ± 6.97 years ranging 38 to 72 years. Among the important risk factors of CAD, 55% patients were smoker, 28% patients were hypertensive, 24% patients were diabetic, 18% patients were dyslipidaemic and 7% having family history of IHD. There distribution in the study groups was not statistically significant. (Table 1)

Table 1: *Baseline characteristics distribution among the study groups*

Characteristics	Group I	Group II	Group III	Group IV	p value
Age(years)	52.21±5.09	53.30±4.88	52.75±7.02	52.47±6.97	.93
Male	15	21	20	28	.68
Female	4	5	4	3	
Smoking	10	13	10	22	.15
Hypertension	6	7	5	10	.79
Diabetes	4	6	5	9	.88
Dyslipidaemia	3	4	4	7	.84
Family history of IHD	1	3	1	2	.75

Table 2: *Clinical pattern of presentation among study groups*

Clinical pattern	Group I	Group II	Group III	Group IV	p value
Unstable Angina	13	10	8	3	.03
NSTEMI	2	9	7	7	.29
STEMI	3	8	9	21	.001

Among the distributions of clinical pattern of acute coronary syndrome, Unstable angina was significantly higher among the study I group ($p < 0.05$) and ST elevation MI was significantly higher among the study group IV ($p<.05$). (Table 2)

Table 3: *Distribution of Angiographic severity among study groups*

Character	Group I	Group II	Group III	Group IV	p value
Vessel Score	1.18±0.42	1.90±0.28	1.58±0.21	2.81±0.18	<0.05
Stenosis Score	18.76±3.19	28.80±9.3	24.3±8.98	40.2±18.4	< 0.05
Lesion morphology Simple	89%	82.2%	78.8%	64.12%	

Lesion morphology Complex	11%	17.8%	21.2%	35.88%	<0.05
TIMI flow grading TIMI 0 – 2	13%	20.12%	24.18%	42.3%	
TIMI flow grading TIMI 3	87%	79.88%	75.82%	57.7%	<0.05

Vessel score in Group I, Group II, Group III & Group IV were 1.18 ± 0.42, 1.70 ± 0.28, 1.98 ± 0.21, 2.81 ± 0.18 respectively which was statistically significant ($p < 0.05$). Stenosis score in group- I, group- II, group- III & group- IV were 18.76 ± 3.19, 21.8 ± 9.3, 28.30 ± 8.98 & 40.2 ± 18.4 respectively which was statistically significant ($p < 0.05$). Regarding morphology of the lesions, 89% were simple lesion and 11% were complex lesion in Group I, 82.2% were simple lesion and 17.8% were complex lesion in Group II, 78.8% were simple lesion and 21.2% were complex lesion in Group III, 64.12% were simple lesion and 35.88% were complex lesion in Group IV. The patients in Group IV had significantly higher number of complex lesions (35.88%) in comparison to patients in Group I (11%) and Group II and Group II & Group III had also higher than Group I which were statistically significant ($p < 0.05$). TIMI flow grading in culprit lesion,TIMI 0-2 in Group I,Group II, Group III and Group IV were 13%,20.12%,24.18% ,42.3% respectively and TIMI 3 in Group I,Group II, Group III and Group IV were 87%,79.88%,75.82%,57.7% respectively which was statistically significant ($p<.05$). (Table 3)

Multivariate analysis (Table 4, Table 5) for predicting angiographic severity of coronary artery disease in form of vessel score and stenosis score showed that raised total WBC count and CRP level were the independent predictors of severe coronary artery disease. Other risk factors like smoking, hypertension, diabetes, dyslipidaemia, and family history of IHD were not found independent predictors of severe coronary artery disease.

Table 4a *: Prediction of stenosis score in relation to white blood cell count (WBC count) and other risk factors multivariate analysis*

Variable		**Observed power**	**p value**
Fixed Variable		0.999	.001
WBC Count Co-Variables	Smoking	.38	.16
	Hypertension	.54	.40
	Diabetes	.26	.34
	Dyslipidaemia	.17	.26
	Family history of IHD	.05	.72

Table-*4b:* *Prediction of stenosis score in relation to white blood cell count (WBC count) and other risk factors multivariate analysis*

Variable	**Observed power**	**p value**
Fixed Variable	0.999	.001

WBC Count Co-Variables	Smoking	.57	.078
	Hypertension	.42	.070
	Diabetes	.38	.097
	Dyslipidaemia	.24	.21
	Family history of IHD	.03	.92

Table 5a: *Prediction of stenosis score in relation to CRP and other risk factors multivariate analysis*

Variable		**Observed power**	**p value**
Fixed Variable		0.997	.001
CRP level Co-variables	Smoking	.22	.10
	Hypertension	.14	.38
	Diabetes	.35	.28
	Dyslipidaemia	.21	.19
	Family history of IHD	.06	.88

Table 5b: *Prediction of stenosis score in relation to CRP and other risk factors multivariate analysis*

Variable		**Observed power**	**p value**
Fixed Variable		0.999	.001
CRP level Co-variables	Smoking	.12	.56
	Hypertension	.36	.11
	Diabetes	.34	.19
	Dyslipidaemia	.27	.24
	Family history of IHD	.07	.98

DISCUSSION

This was a prospective, observational study and conducted in Department of Cardiology, SMS Medical College and Hospital, jaipur, Rajasthan, India 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 of raised WBC count & CRP level were significant predictor of multivessel disease and high stenosis score. In our study, we observed angiographic severity in relation to WBC count and found that raised WBC count group was associated with high stenosis score, (28.8 ±9.3 vs 18.76 ±3.19, p value < 0.05) and high vessel score (1.90 ± 0.28 vs 1.18 ± 0.42, p value < 0.05) were also statistically

significant. This was consistent with findings of Sabatine et al,[11] 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). Angiographic severity in relation to isolated to CRP was also observed in our study. Raised CRP group was associated with high stenosis score (24.3 ±8.98 vs 18.76 ±3.19, p value < 0.05) and high vessel score (1.58 ±0.21 vs 1.18 ± 0.42, p value < 0.05) which were statistically significant. This was consistent with findings of Nyandak et al.[20] in that study they observed that higher hs- CRP levels were associated with higher stenosis in CAD patients.

In our study, regarding morphology of the lesion we also observed higher WBC count and CRP level were associated with more complex lesion (Type B & Type C lesion). We found 35.88% complex lesion in Group IV and 11 % complex lesion in Group I, which was statistically significant (p< 0.05). Avanzas et al.[21] correlated CRP level with the number of complex stenosis . Zairis et al.[22]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. We have demonstrated that elevated WBC count and CRP level were associated with reduced TIMI flow of culprit vessel in the setting of acute coronary syndrome. In our study we observed that in patients having normal WBC count and normal CRP level 87% of patients were having TIMI-3 flow grading and those having raised WBC count and CRP level, 57.7% of patients were having TIMI -3 flow grading which was statistically significant (p<.05). This is consistent with the findings of Sabatine et al[11] 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 (p = 0.01) .Sabatine et al.[11] observed that the baseline WBC count was higher in patients with worse culprit artery TIMI flow grading (P = 0.007). Moukarbel GV et al.[23] also found that elevated CRP level on admission was a marker for anatomic complexity of culprit lesion and worse perfusion grading in patients with elevated CRP (p = 0.007) and cTnT levels (p = 0.027).

Limitations

a. Number of study population was limited.
b. 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 this study that either raised WBC count or raised CRP level independently and combination of both were significantly associated with angiographic feature of more severe coronary artery disease in form of multi vessel disease, high stenosis score, complex lesions and worse TIMI flow gradings. Thus WBC count and CRP can be used as a simpler tool for risk stratification in patients with acute coronary syndrome.

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