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Original Research Article

Prognostics Role of Inflammatory and Platelet Biomarkers in the Patients Presented with Acute Coronary Syndrome: A Cross Sectional Study

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Abstract

Background: Acute myocardial infarction is characterized by elevated levels of inflammatory cytokines, platelet activity, and leukocytosis. Platelets and inflammatory markers are the important regulatory players in the complicated mechanism involved in myocardial infarction. Our study aimed to evaluate the inflammation markers concentrations, and platelet biomarkers parameters in the group of ACS patients (STEMI, NSTEMI, and UA) as compared to the control group.

Methodology: This was a cross-sectional study conducted at Pathology department, NSCB Medical college, Jabalpur from January 2021 to June 2022. Total of 230 patients, 180 cases and 50 controls were taken for this study. Data was collected after taking informed written consent. All patients underwent a standard 12 lead ECG examination, which was interpreted by an expert cardiologist regarding the standard ischemic ECG changes. Data analysis was done through IBM SPSS software version 21. Ethical permission was been taken before commencement of the study.

Result: In our study out of 230 study subjects, 180 were cases and 50 controls. Out of 180 cases of ACS includes three main clinical categories, i.e., STEMI (ST-elevation myocardial infarction) includes 23 cases (41.1%), NSTEMI (non-ST-elevation MI) includes 74 cases (133%), and unstable angina includes 83 cases (149%). It was found that inflammatory markers like CRP, was found to be statistically significant with ACS ($p<0.001$), mean value of CRP ACS cases was 31.56 ± 23.14 and controls mean CRP value was 5.92 + 2.04. The area under the curve for PLT was 0.95 with SE = 0.014 and 95% CI ranging from 0.921 to 0.975 ($P<0.05$); for CRP was 0.98 with SE=0.008 and 95% CI ranging from 0.959 to 0.991 ($P<0.05$); and for D-DIMER was 0.91 with SE = 0.020 and 95% CI ranging from 0.867 to 0.947 ($P<0.05$). In our study, CRP cut off 8.85 mg/L predicted ACS the best with both sensitivity and specificity being (93%) and (88%).

Conclusion: We would like to conclude in our study that platelet parameters mainly MPV, PLT, LPLT and PTC were significantly raised in the patients admitted with ACS to the tertiary care hospital. We also conclude that the inflammatory markers mainly, CRP and D-DIMER have good predictive power with AUC = 0.900.

Keywords: Acute coronary syndrome, CRP, D-DIMER, Platelets.

Introduction

The term "CVDs" refers to a set of disorders that affect the blood vessels and heart and include rheumatic heart disease, coronary heart disease, and cerebrovascular disease. Heart attacks and strokes account for more than four out of every five CVD deaths, and one third of these deaths happen before the age of 70. [1]

According to WHO, 17.9 million deaths worldwide or 32% of all fatalities in 2019

were attributable to CVDs. In 2019, non-communicable illnesses caused 17 million premature deaths (before the age of 70), and 38% of those fatalities were attributable to CVDs. Early detection of cardiovascular disease is crucial in order to start treatment with counselling and medication. [1] In India, 2.59 million CVD-related deaths were reported in 2016. Due to deaths from CVD in adults between the ages of 35 and 64, India experiences the biggest loss in years of life that could have been spent being productive. According to reports, the prevalence of CVD is two to three times higher in urban than in rural areas. [2]

The broad term used to describe the myocardial ischemia-related clinical signs and symptoms is “acute coronary syndrome” (ACS), which is the first indicator of coronary artery disease. The classifications of ACS include unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI). Unfavorable cardiovascular outcomes, like sudden cardiac death, can result from ACS. Therefore, preventing acute coronary events is one of the most crucial public health objectives, and finding those who are more likely to develop ACS and would benefit from preventative measures is now a very difficult task. [3] Acute myocardial infarction is characterized by elevated levels of inflammatory cytokines, platelet activity, and leukocytosis. Platelets are important regulatory players in the complicated mechanism that repairs vascular injury and maintains the patency of small capillaries. [3] Excessive platelet activation brought on by the interaction of platelets with endothelial cells causes a reduction in platelet half-life and an increase in platelet turnover. It may have an impact on the mean platelet volume (MPV), the percentage of large platelets (LPLT), and the platelet count (PLT).

Additionally, platelets within the atherosclerotic plaque may continue to be activated for an extended period of time, allowing the generation of proinflammatory cytokines like IL-6. Numerous biomarkers of inflammation have thus far been used as markers of ACS. The majority of the investigations focused on IL-6, fibrinogen, and C-reactive protein. Due to their high sensitivity, these inflammatory biomarkers are recommended as reliable prognostic and evolution-monitoring markers. [3] It has been suggested that both inflammatory and thrombotic mechanisms contribute significantly to the onset of ACS. The key factor in platelet activation and thrombotic consequences in ACS is inflammation. By the time cardiac cell necrosis begins, platelet activation parameters and markers

of inflammation may be helpful indicators of disease activity. [3] Therefore, conducting this study enables to evaluate the inflammation markers (white blood cells count/WBC, lymphocyte/ platelet ratio, C-reactive protein/CRP, interleukin6/IL-6) concentrations, and platelet biomarkers parameters (platelet count/PLT, mean platelet volume/MPV, large platelet/LPLT activity) in the group of ACS patients (STEMI, NSTEMI, and UA) as compared to the control group without coronary artery disease.

Methodology

Study Area:

- Department of Pathology N.S.C.B. Medical College & Hospital, Jabalpur (M.P.)

Duration of Study-

- January 2021 to June 2022

Study design:

Cross-sectional study.

Inclusion criteria:

- All cases presenting the clinical characteristic with ACS, diagnosed and hospitalized at the Department of Cardiology Intensive Care unit and for the control none cardiac patients come for routine health check-up, after matching according to age.
- The criteria of ACS diagnosis included the detection of rise of cardiac troponin I (cTnI) with at least one value above 99th percentile URL, and at least one of the following: clinical symptoms of ischemia, new or presumed new significant ST segment-T wave changes or new Left Bundle Branch Block (LBBB), development of pathological Q waves, imaging evidence of new loss of viable myocardium, a new regional wall motion abnormality.

Exclusion criteria:

- Active inflammation,
- Cancer
- Chronic circulatory insufficiency
- Severe renal failure,
- Acute coronary syndrome in medical history,
- Antiplatelet drugs (acetylsalicylic acid, clopidogrel, ticagrelor),
- Anticoagulant treatment (acenocoumarin, warfarin, dabigatran, rivaroxaban).

According to the clinical and biochemical criteria of the European Society of Cardiology ACS patients were divided into three sub-groups:

- Patients with STEMI
- Patients with NSTEMI
- Patients with UA

Controls

The control group had 50 healthy volunteers (matched for age of cases). The potential subjects underwent their periodical check-ups at the Department of Cardiology, Super specialty hospital, NSCB Medical College, Jabalpur. Those who did not revealed any medical history of any cardiovascular problems, hypertension, neoplasia or diabetes with normal routinely performed electrocardiogram (ECG), were selected as controls.

Clinical Data Collection

Clinical data was collected after taking informed written consent. All patients underwent a standard 12 lead ECG examination, which was interpreted by an expert cardiologist regarding the standard ischemic ECG changes. Diagnosis of ACS was confirmed with typical symptoms, ECG changes, laboratory tests and/or coronary angiograph.

Samples Handling and Storage

Blood samples from all subjects included to the study were drawn immediately after the diagnosis of ACS. Samples collected into EDTA-K2 tubes were analyzed within 2 hours of venipuncture. Tubes with the blood collected without anticoagulant were

allowed to clot for 30 min before centrifugation (15 min at 1000 RPM); obtained serum were stored at -75°C until further analysis.

Evaluation of Inflammation and Platelet Biomarkers

The platelet count (PLT), mean platelet volume (MPV), the percentage of large platelet (LPLT), and white blood cells count (WBC) was determined in the whole blood collected into EDTA-K2 tubes with the use of Mindray hematological analyzer according to the manufacturer's instruction.

Ethical issues:

Written and oral consent was taken from patient after explaining advantages and steps of examination and need for follow up.

Sample Size:

Based on previous year experience, expected number of CAS where around 720 annually so 25% cases were selected randomly thus 180 cases were included in the study from Department of Cardiology Intensive Care unit which were diagnosed and hospitalized cases of CAS disease.

Around 180 cases [Group-A] with ACS, diagnosed and hospitalized at the Department of Cardiology Intensive Care unit and 50 control [Group-B] s (the control group without coronary artery disease).

Data Analysis:

All the records were recorded by using structured schedule (Case Report Form) and entered in Microsoft Excel Sheet. The obtained results were analyzed with the use of the SPSS 25.0 statistical software IBM, Chicago. The data that followed the normal distribution in the preliminary statistical analysis (X^2-test), were analyzed using nonparametric statistical analysis. The Mann–Whitney test and Kołmogorov–Smir nov test were used in order to compare two independent samples and ANOVA rank Kruskal–Walli‟s test was used for the comparison of three samples. The post hoc Dwass–Steele–Crit chlow–Fligner test was also be conducted to assess which groups is different, if significant differences were found. The values for each given measured variable were also represented as medians and interquartile ranges. Differences were considered statistically significant for $p<0.05$. Correlation coefficients were obtained by applying Spearman's rank method. The relation between the sensitivity and specificity was obtained using a receiver operator characteristic (ROC) curve. The ROC curve is a line graph that plots the probability of true positive results or the sensitivity of the test – against the probability of false positive results for a range of different cut-off points. ROC curves to calculate the areas under the ROC curves (AUCs), positive predictive values (PPV), negative predictive values (NPV), diagnostic accuracy (ACC), as well as standard errors (SE) was generated.

Results

Table 1: A-Distribution of study subjects (ACS) according to their various parameters under study

Parameters		Frequency	Percentage
Sex	Female	64	35.56%
	Male	116	64.44%
Present history	ACS, HTN	1	.56%
	ACS	48	26.67%
	ACS, AWMI	68	37.78%
	ACS, AWMI, ST+	2	1.11%
	ACS, CAG	1	.56%
	ACS, HB	1	.56%

	ACS, IWMI	17	9.44%
	ACS, MR	1	.56%
	ACS, OLDMI	21	11.67%
	ACS, RHD	6	3.33%
	ACS, ST ELEV	3	1.67%
	ACS, USA	5	2.78%
	ACS.IWMI	1	.56%
	ACS, AWMI	1	.56%
	ACS, OLDMI	3	1.67%
	ACS	1	.56%
Angiography	Double Veesel Disease	50	27.78%
	Multi Vessel Disease	7	3.89%
	Singl Veesel Disease	97	53.89%
	Triple Vessel Disease	26	14.44%
Final Diagnosis	USA	83	0.461
	STEMI	23	0.128
	NSTEMI	74	0.411

In current study, Cases present with majority of males (64.4%) as compared to females (35.5%). In the present history of the study isolates, maximum (37.8%) was came-up with the ACS, AWMI. With the intervention of angiography, 53.89% had single vessel disease with the final diagnosis of USA (46%).

Table 1: B-Distribution of control subjects according to their various parameters under study controls had majority of males (58%) with only marginal percent of females i.e. 42%.

Gender	Frequency	Percentage
Female	21	42%
Male	29	58%

Table 2 : A- Descriptive statistics of study subjects (ACS) according to their various parameters under study.

Variables	Mean	SD
Age (Yrs.)	53.639	11.5834
SBP mm of Hg	124.456	11.2956
DBP mm of Hg	78.12	6.550
Pulse beats per min	84.372	7.4833
Resp. rate per min,	20.472	1.5261
min So2 saturation	.9708	.00780
Echocardiography	.8074	4.43824
Hb gm/dl	12.5056	1.82036
TLC 10^3/uL	8.5528	2.31291
ANC	5.7813	2.22278
ALC	1.7537	.92282
PLT 10^3/uL	279.7278	73.39621
MPV fL	9.4733	1.75673
PTC %	.2450	.06781

PDW %	16.0972	1.18936
LPLT	28.3539	9.40549
CRP mg/l	31.5611	23.13508
DIMER ug/ml	12.3397	5.3768

Group 1 had a mean age (± SD) of 53 ± 11.5, with mean systolic blood pressure of 124 ± 11.29, mean Hb range of 12.5 ± 1.82, mean platelet counts of 279.728 ± 73.39.

Table 2: B-descriptive statistics of control subjects according to their various parameters under study

Variables	Mean	Std. Deviation
Age (Yrs.)	41.40	10.70
SBP mm of Hg	118.44	5.59
DBP mm of Hg	76.52	4.08
Pulse beats per min	79.44	3.81
Resp. rate per min,	18.68	1.25
min So2 saturation	0.98	0.01
Hb gm/dl	12.38	1.75
TLC 10^3/uL	7.86	1.73
ANC	5.22	1.63
ALC	1.91	0.84
PLT 10^3/uL	172.18	29.17
MPV fL	8.86	0.81
PTC %	0.54	1.92
PDW %	16.21	1.31
LPLT	24.96	6.38
CRP mg/l	5.92	2.04
DIMER ug/ml	3.54	2.17

Group 2 had a mean age (± SD) of 41 ± 10.7, with mean systolic blood pressure of 118 ± 5.59, mean Hb range of 12.38 ± 1.75, mean platelet counts of 172.18 ± 29.17.

Table 3: Association between study subjects and various inflammatory markers

Parameters	Group	Mean	SD	t value	p value
CRP mg/l	Case	31.56	23.14	7.81	**0.001**
	Control	5.92	2.04		
DIMER ug/ml	Case	12.34	5.38	10.37	**0.001**
	Control	3.54	2.17		

From above table it is evident that inflammatory markers like CRP, D-DIMER was found to be statistically significant with ACS ($p<0.05$).

Table 4: Association between study subjects and various inflammatory markers

Angiography			Group			p value
		Case	Control		Total	
	N	%	N	%	N	%	
Double Veesel Disease	50	100.00%	0	0.00%	50	100.00%	**0.001**
Multi vessel Disease	7	100.00%	0	0.00%	7	100.00%	

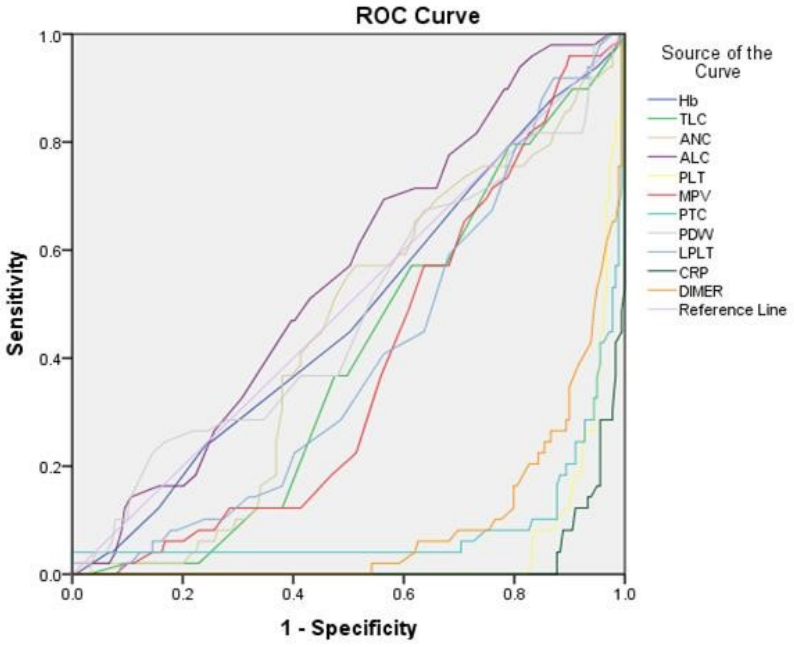
Na	0	0.00%	50	100.00%	50	100.00%	
Singl veesel Disease	97	100.00%	0	0.00%	97	100.00%	
Triple vessel Disease	26	100.00%	0	0.00%	26	100.00%	

From above table it is evident that angiography finding was found to be statistically significant with ACS. It is evident that maximum angiography finding was single wall disease which is highly significant. ($p<0.05$).

Table 5: Association between angiography findings of study subjects and various in flammatory markers.

Variables	Angiography	N	Mean	Std. Deviation	F value	p value
CRP mg/l	**Single**	97	33.41	23.00	1.78	0.15
	Double	50	31.07	23.49		
	Triple	26	30.66	24.53		
	Multiple	7	12.80	3.86		
	Total	180	31.56	23.14		
DIMER ug/ml	**Single**	97	12.83	5.41	2.24	0.09
	Double	50	12.58	5.47		
	Triple	26	11.19	4.88		
	Multiple	7	8.04	4.40		
	Total	180	12.34	5.38		

From above table it is evident that the one-way Annova test when applied between angiography findings and inflammatory markers was found to be statistically non- significant with CRP ($p>0.05$), with maximum frequency of Single angiography (97) and similarly with D-DIMER the association was nonsignificant. ($p>0.05$).



Graph 1: ROC curve between control and pathological findings

Among control ROC curve none of the AUC findings are above 0.554, which is of ALC, having non-significant finding (p-0.243).

Discussion

ACS is an extensive term accounting for any condition causing sudden reduced blood flow to the heart, the common feature of which is chest pain. In our study, total number of patients is 230, in which cases are 180 in number and controls are 50 in numbers. Out of 180 cases of ACS includes three main clinical categories, i.e., STEMI (ST-elevation myocardial infarction) includes 23 cases (41.1%), NSTEMI (non-ST-elevation MI) includes 74 cases (133%), and unstable angina includes 83 cases (149%). Main role in the development of ACS played by both the inflammatory as well as thrombotic processes. Inflammatory markers together with platelet activation parameters may be useful indicators of disease activity, by the time myocardial-cell necrosis occurs.

In the present study, the group of cases comprised majority of males (64.4%) as compared to females (35.5%). Similarly, among the control‟s majority were males (58%) and females constituted 42%. In a study by Saif et al. (2012) conducted in Saudi, majority population i.e., 77% were males, similar to our study. Kamińska J et al. (2016) observed the male predominance (59 males out of 93 participants). [3,4]

In our study, the cases had a mean age (± SD) of 53 ± 11.5 years while controls had a mean age (± SD) of 41 ± 10.7 years. In the study by Patil et al. (2017) the mean age was found to be 60.37±13.87 years varying between 30-93 years, with majority i.e., 44% in the age group of 61-75 years. [5] Kamińska et al. (2016) observed the mean age to be 63 years. From the present study, it is evident that parameters like age found to be statistically significant with ACS ($p<0.05$). In a study by Saif et al. (2012) the mean age in their study was 58.01±12.92 years and also reported that NSTEMI increased with age. [3-4] Only 25% of patients aged ⩽40 years reported NSTEMI compared to 49% of patients aged >70 years ($p < 0.001$). This study revealed about age and relationship to acute coronary syndrome in a large Saudi population and found that older patients have higher hospital mortality as they are treated less aggressively. [5] The cases had mean systolic blood pressure highly significant compared to control ($P<0.001$) that is 124 ± 11.29mm/Hg while controls had mean of systolic blood pressure of 118 ± 5.59. Among the cases mean SBP STEMI, NSTEMI and UA patients to be 124 + 8.44, 123 + 10.73 and 125 + 12.49 mmHg respectively. From the present study, it is evident that parameters like systolic blood pressure, pulse, respiratory rate, saturation found to be statistically significant with ACS ($p<0.05$). However diastolic BP was nonsignificant. Kamińska et al. (2016) reported the mean SBP among STEMI, NSTEMI and UA patients to be 130, 150 and 130 mmHg respectively; and DBP was 80, 87 and 80 mmHg respectively with a non-significant association. [3]

In the present study parameters like PLTs, MPV, PTC and LPLT were found to be statistically significant with ACS ($p<0.05$). However other parameters like Hb, TLC, ANC and PDW were non-significant. The mean platelet counts of cases 279.728 ± 73.39 while controls had mean platelet counts of 172.18 ± 29.17. The study done by Harikumar et al (2018), the platelet count was 217 $x10^3$/microliter and 233 $x10^3$/microliter in ACS and controls respectively. Due to small study population contrast result seen. [6]

In the present study, it was found that inflammatory markers like CRP, was found to be statistically significant with ACS ($p<0.001$), mean value of CRP ACS cases was 31.56 ± 23.14 and controls mean CRP value was 5.92 + 2.04. Among the cases 5mean CRP in STEMI, NSTEMI and UA patients to be 42.37 + 28.89, 28.99 + 20.99 and 30.86 + 22.65 respectively. Kamińska

et al. (2016) found a significant association between CRP and ACS with a p-value of 0.000 and the mean value of CRP was 2.1 ± 2.14. [3] D-DIMER was found to be statistically significant with ACS (p<0.001), mean value of D-DIMER ACS cases was 12.3397 ± 5.37 and controls DDIMER mean value was 3.54 + 2.17. Among the cases mean D-DIMER in STEMI, NSTEMI and UA patients to be 12.97 + 6.22, 12.23 + 6.06 and 12.26 + 4.47 respectively. Study done by Mansour et al. (2020) found a significant association between D-Dimer and ACS with a p-value of 0.001 and the mean value of D-Dimer was 2.46 ± 1.98. [7] Another Study done by Yukichi et al. (2008), found a significant association between D-Dimer and ACS with a p-value of <0.05.[8]

The areas under the receiver operating characteristic (ROC) curve for assessing the predictive values of PTC, CRP and D-DIMER in predicting the occurrence of acute coronary syndromes were constructed by plotting the sensitivities for all individual cut-off values versus the corresponding (1specificity). A P value < 0.05 was considered statistically significant. The area under the curve for PLT was 0.95 with SE = 0.014 and 95% CI ranging from 0.921 to 0.975 (P<0.05); for CRP was 0.98 with SE=0.008 and 95% CI ranging from 0.959 to 0.991 (P<0.05); and for D-DIMER was 0.91 with SE = 0.020 and 95% CI ranging from 0.867 to 0.947 (P<0.05). In our study, CRP cut off 8.85 mg/L predicted ACS the best with both sensitivity and specificity being (93%) and (88%). Study done by Kamińska et al. (2016), found that CRP cut off 0.41 mg/L with SE = 0.040 predicted ACS the best with both sensitivity and specificity being (96%) and (20%), AUC was 0.798. D-DIMER cut off 6.05 mg/L predicted ACS the best with both sensitivity and specificity being (86%) and (78%). [3]

D-DIMER cut off 6.05 mg/L predicted ACS the best with both sensitivity and specificity being (86%) and (78%). Study done by Mansour et al. (2020), found that D-DIMER cut off 0.5 mg/L predicted ACS the best with both sensitivity and specificity being (84%) and (95%), in this cutoff value of d dimer less than our study might be due to small sampled size. Study done by Yokkaichi et al. (2008), found that D-DIMER cut off 0.7 mg/L predicted ACS the best with both sensitivity and specificity being (75%) and (55%), AUC was 0.702.[7-9]

Conclusion

We would like to conclude in our study that platelet parameters mainly MPV, PLT, LPLT and PTC in readily available, relatively inexpensive and useful markers which are significantly raised in the patients admitted with ACS to the tertiary care hospital. We also include inflammatory markers mainly, CRP and D-DIMER have good predictive power with AUC = 0.900. These parameters we can used to predict high risk patients of ACS to early diagnosis and intervention, if need timely referral to higher center to save valuable life especially resource limited area.

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