



Correlation between Inflammatory and Hematologic Biomarkers and Cardiovascular Outcomes Among CCU and Post-CCU Patients Diagnosed with Acute Coronary Syndrome: A Retrospective Study

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Abstract

Background: Deaths associated with the Acute Coronary Syndrome (ACS) remain high among Cardiac/Coronary Care Unit (CCU) and post-CCU patients. Recently, researchers have looked for inexpensive and reliable prognostic indicators as alternatives to the expensive pro-Brain Natriuretic Peptide (proBNP) in ACS patients to predict adverse outcomes.

Methods: We retrieved the Complete Blood Count (CBC) records of ACS patients and calculated values for plateletcrit (PCT), Mean Platelet Volume (MPV), and Neutrophil-to-Lymphocyte Ratio (NLR). We also recorded ACS diagnostic methods, duration of hospital stays (CCU and post-CCU), and therapeutic modalities. We considered outcomes such as death, positive or negative troponin, ST-elevation, ejection fraction <45, and history of arrhythmia.

Results: The multivariate model using forward stepwise logistic regression showed that the history of arrhythmia (OR=124.052, p=0.001), positive troponin (OR=47.545, p=0.002), hospitalization period (OR=2.376, p=0.001), C-reactive protein (CRP) (OR=1.359, p=0.001), and PCT (OR=2.018, p=0.001) are independent predictors of mortality.

Conclusion: CRP and PCT are considered independent predictors of mortality among CCU and post-CCU patients diagnosed with ACS. However, the prognostic significance of NLR and MPV needs to be confirmed by further investigations.

Keywords: Acute coronary syndrome, C-Reactive protein, Humans, Neutrophils, Pro-brain natriuretic peptide (1-76), Prognosis, Troponin

Introduction

Among all known fatal medical conditions, Acute Coronary Syndrome (ACS) has always been the centre of focus for all clinical researchers, prompting them to discover the best possible management strategies encompassing diagnostic, therapeutic, and prognostic strategies. As readers are fully aware, deaths associated with ACS complications remain high among Cardiac/Coronary Care Unit (CCU) and post-CCU patients. This has led to many clinical researchers in recent years to look for inexpensive and reliable prognostic indicators in ACS patients to predict or possibly avoid such adverse outcomes in the most effective way. To the best of our knowledge, pro-Brain Natriuretic Peptide (proBNP) remains the most powerful but expensive prognostic indicator for all-cause morbidity and mortality among ACS patients (1-3). Recently, several studies have evaluated a number of promising predictive biomarkers other than proBNP, including Plateletcrit (PCT), which reflects the total platelet mass in the blood, Mean Platelet Volume (MPV), which is the average platelet size in the blood, Neutrophil to Lymphocyte Ratio (NLR), and quantitative C-Reactive Protein (CRP). In this single-centre retrospective study, we have tried to find out whether these prognostic biomarkers could be a possible alternative to the expensive proBNP factor to predict ACS cardiovascular outcomes, given the fact that they are readily measurable by a simple Complete Blood Count (CBC). A concise review of similar studies in the literature is also considered.

Materials and Methods

This cross-sectional study was conducted at Firoozgar Hospital, a tertiary care university hospital in Tehran, Iran, in the department of internal medicine. The initial CBC records at the time of ACS diagnosis were retrieved, and values for PCT, MPV, and NLR were calculated and recorded by two trained physicians. Information regarding the diagnostic methods for ACS, number of involved coronary arteries, duration of hospital stays (in CCU and post-CCU), and therapeutic modalities (percutaneous intervention, coronary artery bypass grafting, or pharmacological) was all extracted from the files by a cardiologist. Different cardiovascular outcomes during CCU admission or post-CCU hospital care were considered,

including death, positive or negative troponin, any ST-elevation, Ejection Fraction (EF) less than 45, and history of arrhythmia. All patients diagnosed with ACS in 2020 at Firoozgar Hospital were included in the study. The exclusion criteria were an EF less than 45 or congestive heart failure prior to admission, and any forms of autoimmune disease or malignancies.

This research was conducted in accordance with institutional and national policies, and patient records were obtained anonymously. All stages of the project were approved by the Research Ethics Committee of Iran University of Medical Sciences, Tehran, Iran (Code: IR.IUMS.FMD.REC.1400.580).

Descriptive analysis was performed, and the results were reported as mean and median for quantitative data and frequency and percentage for qualitative data in both groups. The Kolmogorov-Smirnov test was used to assess data normality. The t-test and non-parametric Mann-Whitney U test were used to compare normally distributed and non-normally distributed data, respectively. The chi-square test was used to compare quantitative data between the groups. Significance was reported using Odds Ratios (OR) and a 95% Confidence Interval (CI). Logistic regression was performed to determine the most important risk factors for the cardiovascular outcomes. The statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software version 22 (SPSS Corp., Armonk, New York, USA). Values less than 0.05 were considered statistically significant.

Results

The study included a total of 317 patients admitted to CCU and post-CCU wards. The mean age of patients in the CCU group (N=117) and the post-CCU group (N=200) was 68.2 ± 12.8 and 56.1 ± 16 , respectively. Moreover, 74 (63.2%) and 128 (64%) patients were male in the CCU and post-CCU groups, respectively. Furthermore, the mean length of patients' stay in the hospital was 5.9 ± 2.5 and 5.7 ± 2.1 days for the CCU and post-CCU groups, respectively. Overall, 144 (45.1%) patients had a smoking history, and the frequencies of positive troponin (TPN), ST-elevation, EF reduction, and arrhythmia were 111 (34.8%), 49 (15.4%), 30 (9.4%), and 34 (10.7%), respectively. The therapeutic modalities consisted of PCI for 90 (28.4%), fibrinolysis for 210 (66.2%), and Coronary

Artery Bypass Grafting (CABG) for 17 (5.4%) cases. The treatment outcome resulted in the death of 105 (89.7%) and 184 (92%) patients in the CCU and post-CCU groups, respectively. The detailed information on patients' clinical and demographic characteristics is shown in table 1.

Using all-cause mortality as the primary outcome, univariate analysis was performed to determine which variables predicted mortality. The history of arrhythmia, elevation of ST segment in ECG, positive troponin test, duration of hospitalization, CRP level,

NLR, PCT, MPV, and history of Chronic Obstructive Pulmonary Disease (COPD) were all associated with an elevated risk of mortality (Table 2). When these variables were included in a multivariate model using forward stepwise logistic regression, the history of arrhythmia (OR=124.052, p=0.001), positive TPN (OR=47.545, p=0.002), hospitalization period (OR=2.376, p=0.001), CRP (OR=1.359, p=0.001), and PCT (OR=2.018, p=0.001) remained as independent predictors of mortality, as illustrated in table 3.

Table 1. Clinical and demographic characteristics of patients admitted in CCU and post-CCU diagnosed with ACS

No.		Total (n=317)	CCU (n=117)	Post-CCU (n=200)	p-value
Age (mean±SD)		60.6±16	68.2±12.8	56.1±16	0.004
Sex, n(%)	Male	202 (63.3)	74 (63.2)	128 (64)	0.494
	Female	115 (36.7)	43 (36.8)	72 (36)	0.576
Smoking, n(%)		144 (45.1)	50 (42.7)	94 (47)	0.268
Hospitalization [day, (mean±SD)]		5.8±2.2	5.9±2.5	5.7±2.1	0.317
Medical Hx, n(%)	HTN	118 (37)	49 (41.9)	69 (34.5)	0.117
	DM	127 (39.8)	48 (41)	79 (39.5)	0.44
	IHD	162 (50.8)	67 (57.3)	95 (47.5)	0.06
	CHF	28 (8.8)	12 (10.3)	16 (8)	0.541
	CVA	31 (9.7)	20 (17.1)	11 (5.5)	0.001
	CKD	48 (15)	21 (17.9)	27 (13.5)	0.33
	ILD	15 (4.7)	8 (6.8)	7 (3.5)	0.183
	COPD	58 (18.2)	25 (21.4)	33 (16.5)	0.295
Clinical significance, n(%)	Asthma	26 (8.2)	12 (10.3)	14 (7)	0.396
	TPN	111 (34.8)	96 (82.1)	15 (7.5)	0.001
	ST elevation	49 (15.4)	32 (27.4)	17 (8.5)	0.001
	EF reduction	30 (9.4)	19 (16.2)	11 (5.5)	0.002
Modality, n(%)	Arrhythmia	34 (10.7)	11 (9.4)	23 (11.5)	0.351
	PCI	90 (28.4)	40 (34.2)	50 (25)	0.717
	Fibrinolysis	210 (66.2)	66 (56.4)	144 (72)	0.009
Death, n(%)	CABG	17 (5.4)	11 (9.4)	6	0.01
		289 (91.7)	105 (89.7)	184 (92)	0.541

CCU: Cardiac/coronary Care Unit, ACS: Acute Coronary Syndrome, HTN: Hypertension, DM: Diabetes Mellitus, IHD: Ischemic Heart Disease, CHF: Congestive Heart Failure, CVA: Cerebrovascular Accident, CKD: Chronic Kidney Disease, ILD: Interstitial Lung Disease, COPD: Chronic Obstructive Pulmonary Disease, TPN: Troponin, EF: Ejection Fraction, PCI: Percutaneous Coronary Intervention, CABG: Coronary Artery Bypass Grafting.

Table 2. Comparisons of the different variables using univariate analysis

Variable	Odds	95%CI		p-value
		Lower	Upper	
History of arrhythmia	20.074	8.263	48.765	0.001
Positive TPN	31.2	7.244	134.387	0.002
Duration of hospitalization	2.257	1.695	3.004	0.001
NLR	5.318	9.04	3.129	0.001
MPV	1.732	1.345	2.229	0.001
CRP	1.192	1.137	1.250	0.001
PCT	1361.207	34.725	53358.772	0.001

CI: Confidence Interval, TPN: Troponin, CRP: C-reactive Protein, PCT: Plateletcrit, ECG: Electrocardiogram, NLR: Neutrophil to Lymphocyte Ratio, MPV: Mean Platelet Volume.

Table 3. Comparisons of the different variables in a multivariate model, using forward stepwise logistic regression analysis

Variable	Odds	95%CI		p-value
		Lower	Upper	
History of arrhythmia	124.052	4.120	3735.185	0.001
Positive TPN	47.545	1.771	1276.236	0.002
Duration of hospitalization	2.376	1.326	4.258	0.001
CRP	1.359	1.128	1.637	0.001
PCT	2.018	6.638	4.57	0.001

CI: Confidence Interval, TPN: Troponin, CRP: C-reactive Protein, PCT: Plateletcrit.

Discussion

ACS is characterized by a ruptured atherosclerotic plaque that results in thrombus formation in the arterial lumen, blockage of coronary flow, and consequently, a possible Myocardial Infarction (MI). This, in turn, would stimulate the sympathetic nervous system, which induces an inflammatory response to release haematopoietic stem cells from bone marrow spaces, namely white blood cells and platelets 4. This inflammatory process will further lead to systemic atherosclerotic plaque formation, exacerbating the patient's condition (4).

Several studies in the literature have evaluated haematological biomarkers as prognostic indicators in Cardiovascular Diseases (CVD). Most of the available studies focus on Red cell Distribution Width (RDW), MPV, and NLR indices together. Others investigate PCT independently as a novel indicator for ACS risk assessment. The present study combined PCT, NLR, MPV, and CRP indices and evaluated them together.

Although all the mentioned biomarkers demonstrated a significant relationship with higher mortality rates in the univariate analysis, multivariate regression analysis only verified PCT and CRP as significant prognostic indicators among CCU and post-CCU patients.

In a retrospective study conducted by Apkinar *et al* (5) they compared the PCT level as a prognostic index in two groups of patients: those with patent saphenous vein grafts and those with Saphenous Vein Graft Disease (SVG D). The authors concluded that the higher the PCT and MPV readings are, the higher the risk to develop SVG D, with sensitivity and specificity being 80.65 and 81.1%, respectively (5). Another study concluded that elevated PCT levels could be used as an indicator for stricter antiplatelet treatment (6).

Several acute vascular conditions are attributed to high PCT as it was comprehensively investigated by Uğur *et al* (7). In this study, the authors evaluated

2572 hospital records of patients who had undergone Percutaneous Intervention (PCI). They believed that acute vascular conditions following PCI, like shock and reduced left ventricular ejection fraction, were more frequent among patients with high PCT values compared to those patients with lower values. In our study, elevated PCT at the time of ACS diagnosis was significantly associated with a higher mortality rate ($p=0.001$).

The major function of platelets is to prevent bleeding by the formation of a thrombus. However, any dysfunction in the thrombotic activity of platelets can lead to vessel occlusion and ischemia (8). Given the direct relationship between platelet size and activity (9) many researchers have started to investigate the parameter of MPV as an indicator of cardiovascular diseases and the possible prognostic role it might play in assessing CVD outcomes following a major thrombotic event like ACS (8). Several studies have shown that high MPV levels are associated with MI and unstable angina, and increased platelet volumes could increase the risk of mortality among CVD patients (9,10). The steep rise in MPV levels during the first hours of a CVD event and its persistence for several days following the CVD event highlight the MPV's importance as a reliable prognostic index for CVD outcomes (8).

It is now widely accepted that inflammation plays a crucial role in atherosclerotic plaque formation (11). Specifically, the NLR is both a biomarker of systemic inflammation and a prognostic indicator for patients who are planned for Percutaneous Coronary Intervention (PCI) (12,13). In several studies, NLR is correlated with in-hospital mortality as well as long-term mortality among patients with ST-Elevation Myocardial Infarction (STEMI) (14,15). A meta-analysis of 14 studies from the literature yielded

similar results (16).

The correlation between CRP and CVD outcomes has been a controversial subject among researchers. Although the present study illustrated a statistically significant association between high CRP readings and ACS-related mortality ($p=0.001$), researchers are still not convinced about CRP as an accepted prognostic index in CVD-related clinical settings. In a meta-analysis published in 2011, evidence supported long-term prognostic value for CRP, while short-term values remained controversial (17). In a prospective cohort study, a positive association was found between CRP and in-hospital CVD outcomes. However, the indecisive evidence of its incremental prognostic value cast doubt on CRP's usefulness as a prognostic marker in clinical practice (18). Another meta-analysis published in 2020 presented similar results. The study argued that although evidence supports the fact that inflammation has a role in atherosclerotic plaque destabilization, it does not necessitate the use of the CRP test as a predictive biomarker in a clinical context (19).

Conclusion

CRP and PCT are considered to be independent predictors of mortality among CCU and post-CCU patients diagnosed with ACS. However, the prognostic significance of NLR and MPV is yet to be confirmed by further investigations.

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Conflict of Interest

Non-declared.

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