ORIGINAL RESEARCH

Hematologic Indices as Diagnostic Markers in Acute Coronary Syndrome: Unraveling their Significance

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ABSTRACT

Background: Differentiating Between Acute Coronary Syndrome (ACS) and Stable Coronary Artery Disease (SCAD) necessitates sophisticated laboratory instruments and electrocardiograms. However, such resources are often scarce in primary care settings in developing countries. Given that hematologic changes frequently manifest in ACS patients, they could offer valuable insights for distinguishing ACS from SCAD. **Aim**: This study examines the hematologic indices in both ACS and SCAD patients, assessing their potential as predictive markers for identifying ACS. **Methodology**: A total of 121 participants, comprising 51with ACS and 70 with SCAD, met the inclusion criteria for this study. Patient characteristics, hematologic indices upon admission, and the ultimate diagnosis were extracted from medical records. Statistical analyses were conducted using SPSS 23.0. **Results:** In this study, MCHC value (32.42 vs. 31.78g/dL; $p < 0.05$), WBC (10.26 vs. 6.32 x 109/L; $p < 0.001$), NLR (6.35 vs. 3.27; $p < 0.001$), and PLR (177.65 vs. 126.65; $p < 0.001$) were found to be significantly higher in ACS patients compared to those with SCAD. Conversely, MPV (6.42 vs. 10.12fL; $p < 0.001$) was significantly lower in ACS patients. ROC curve analysis revealed that MPV had the highest AUC (95%) for diagnosing ACS, with an optimal cut-off point at $\leq$ 8.35fL, providing a sensitivity of 93.5% and specificity of 96.8%. **Conclusion:**Significant differences were observed in hematologic indices between ACS and SCAD patients, with mean platelet volume (MPV) emerging as the most effective indicator for distinguishing ACS.

Keywords: Acute Coronary Syndrome, Hematologic Indices, Mean Platelet Volume.

INTRODUCTION

India faces one of the most significant burdens of cardiovascular disease (CVD) globally. The annual mortality from CVD in India is anticipated to escalate from 2.26 million in 1990 to 4.77 million in 2020 [1]. Prevalence rates of coronary heart disease in India have been assessed over the past few decades, with estimates ranging from 1.6% to 7.4% in rural populations and from 1% to 13.2% in urban populations[2]. A major contributor to CAD is the narrowing of coronary arteries due to atherosclerosis. The clinical presentation of CAD is influenced by the characteristics of atherosclerosis. Specifically, vulnerable, or unstable plaques are associated with atherothrombotic events, which define the hallmark of Acute Coronary Syndrome (ACS). On the other hand, stable plaques, characterized by a poor-lipid core and a thick fibrous cap, manifest as Stable Coronary Artery Disease (SCAD) [3,4].

Swift coronary revascularization proves advantageous for ACS patients in mitigating adverse events or mortality [5]. Consequently, early detection of ACS is paramount, given that mortality rates among ACS patients are up to seven times higher than those with SCAD [6]. However, the scarcity of electrocardiograms (ECGs) and cardiac markers in primary care settings poses a significant challenge for physicians in developing countries when diagnosing ACS [7]. A previous study even revealed that the availability of ECGs in rural primary care settings was only 63.3% [8]. Consequently, there is an urgent need for a straightforward and accessible screening approach to facilitate the diagnosis of ACS in primary care settings.

The pathogenesis of atherosclerosis is intricately linked to inflammatory and hematologic responses, with various inflammatory substances and hematologic cells contributing to the development of

atherosclerotic lesions [9-11]. Leukocytes and platelets play pivotal roles in processes such as foam cell generation, cytokine secretion, including Reactive Oxygen Species (ROS), and cardiomyocyte death, all of which contribute to the progression of atherosclerosis [12]. In ACS, the lesions exhibit an acute condition and activate neutrophils as pro-inflammatory cells [4,13]. ACS is typically followed by inflammation regulation by anti-inflammatory cells, such as lymphocytes [14,15]. Platelets also play a role in ACS by inducing higher inflammatory activity and thrombogenicity [3,4,16]. In contrast, the lesions in stable coronary artery disease (SCAD) exhibit a chronic and lower grade of inflammation compared to ACS. Previous studies have indicated that white blood cell count and inflammatory markers are significantly higher in the ACS group compared to SCAD [9-11]. However, the comparison of other hematologic indices between ACS and SCAD remains to be explored.

Therefore, this study aims to compare hematologic indices between ACS and SCAD patients and analyze their predictive value in distinguishing ACS.

METHODOLOGY

This retrospective cross-sectional study was conducted at thecentral clinical lab, Shree Shankaracharya Institute of Medical Sciences. Total sampling was conducted using all medical records of patients diagnosed with ACS or SCAD from October 2022 to September 2023. Exclusion criteria encompassed patients with kidney and liver abnormalities, active infections, cancer, hematological malignancies, those undergoing corticosteroid therapy, and chemotherapy recipients. The privacy and confidentiality of information were ensured, as the data did not include personal patient identities.Information on age, sex, CAD type (ACS or SCAD), erythrocyte indices (MCHC, Hgb, Hct), leukocyte indices (WBC, Neutrophil Percentage, Lymphocyte Percentage), and platelet indices (MPV, PLT) was extracted from medical records. The diagnosis of ACS was defined by the ICD-10 diagnosis codes I20.0 for Unstable Angina Pectoris (UAP), I21.0 and I21.1 for ST-Elevation Myocardial Infarction (STEMI), and I21.4 for Non-ST-Elevation Myocardial Infarction (NSTEMI). The diagnosis of SCAD was defined by the ICD-10 diagnosis code I25.0 with no history of ACS or myocardial infarction.To further assess inflammatory markers, the Neutrophil to Lymphocyte Ratio (NLR) was calculated by dividing the Neutrophil Percentage by the Lymphocyte Percentage. Additionally, the Platelet to Lymphocyte Ratio (PLR) was calculated by dividing PLT by the multiplication of the Lymphocyte Percentage with WBC.

STATISTICAL ANALYSIS

The statistical analyses were conducted using SPSS Statistics 23.0. Continuous variables, presented as mean±SD, were compared using the Independent T-test or Mann-Whitney test based on the normality test. Specificity and sensitivity were derived from the ROC curve, and cut-off point analysis was employed for the evaluation of diagnostic performance.

RESULTS

Baseline Characteristics

A totalof 121 medical records consisting of 51 ACSpatients (6 UAP, 7 NSTEMI, and 38 STEMI) and 70SCAD met the inclusion criteria and included in this study. In both groups, most of the participants were male and aged below sixty. There was no significant difference between the two groups (Table 1).

Table 1: Baseline characteristics of ACS and SCAD patients

Variable	ACS (n=51)	SCAD (n=70)	P Value
Sex (%)			
Male	42 (82.35%)	56 (80%)	0.823
Female	9 (17.64%)	14 (20%)	
Age (years)	55.76± 8.77	58.87±9.23	0.456

Erythrocyte Indices

This study specifically concentrates on the comparison of Mean Corpuscular Hemoglobin Concentration (MCHC) values between two groups. Hemoglobin (Hgb) and Hematocrit (Hct) values are employed to analyze the components of MCHC, as MCHC represents the ratio between Hgb and Hct. The results indicate that MCHC values were significantly higher in ACS than in SCAD ($p = 0.019$), while Hgb and Hct showed no significant differences (Table 2).

Leukocyte Indices

In this study, the comparison of White Blood Cell (WBC) values between two groups was conducted. The percentages of Neutrophil and Lymphocyte values were utilized to calculate Neutrophil-to-Lymphocyte Ratio (NLR) and Platelet-to-Lymphocyte Ratio (PLR). The findings revealed that WBC and the percentage of Neutrophil were significantly higher, whereas the percentage of Lymphocyte was significantly lower in ACS compared to SCAD, with all p-values being less than 0.001, respectively (Table 2).

Platelet Indices

In this study, the comparison of Mean Platelet Volume (MPV) values between two groups was conducted. Platelet (PLT) values were utilized to

calculate Platelet-to-Lymphocyte Ratio (PLR). The results indicated that MPV was significantly lower in ACS than in SCAD, with a p-value less than 0.001, while PLT showed no significant difference (Table 2).

Other Indices

Both Neutrophil-to-Lymphocyte Ratio (NLR) and Platelet-to-Lymphocyte Ratio (PLR) values were found to be significantly higher in ACS compared to SCAD, with p-values less than 0.001 (Table 2).

Table 2. Hematological indices between ACS and SCAD patients.

Indices	ACS (n=51)	SCAD (n=70)	P Value
Erythrocyte			
Hgb (g/dL)	13.55 ± 1.32	13.22 ± 1.51	0.413
Hct (%)	42.81 ± 5.12	42.92 ± 4.34	0.786
MCHC (g/dL)	32.42 ± 1.67	31.78 ± 1.12	0.013*
Leukocyte			
WBC (x 109 /L)	10.26 ± 2.87	6.32 ± 6.21	<0.001*
Neut (%)	76.16 ± 12.12	60.12 ± 7.89	<0.001*
Lymp (%)	15.25 ± 7.81	26.56 ± 8.12	<0.001*
Platelet			
PLT (x 109 /L)	271.32 ± 76.12	262.88 ± 53.60	0.705
MPV (fL)	6.42 ± 1.32	10.12 ± 1.24	<0.001*
Other			
NLR	6.35 ± 6.21	3.27 ± 1.58	<0.001*
PLR	177.65 ± 111.72	126.65 ± 56.200	<0.001*

Hgb = Hemoglobin; Hct = Hematocrit; MCHC = Mean Corpuscular Hemoglobin Concentration; WBC = White Blood Cells; Neu% = Percentage of Neutrophil; Lymp% = Percentage of Lymphocyte; PLT = Platelets; MPV = Mean Platelet Volume; NLR = Neutrophil to Lymphocyte Ratio; PLR = Platelet to Lymphocyte Ratio.*P < 0.05 was considered statistically significant

Cut-off Point

MPV demonstrated the highest Area Under the Curve (AUC) at 95.0%, followed by WBC and NLR at 88.4%, PLR at 71.7%, and MCHC at 60.0% (Table 3). The identified cut-off point for MPV to distinguish ACS was 8.35 fL, showcasing very high sensitivity (93.6%) and specificity (97.3%).

Table 3. ROC analysis and cut-off points for each index

Indices	AUC (%)	95% CI		Cut off	Sensitivity (%)	Specificity (%)
		Lower	Upper			
MCHC	62.2	0.521	0.691	32.061	55.2	60.1
WBC	83.5	0.783	0.956	9.182	82.1	80.2
MPV	95.0	0.913	0.991	8.350	93.5	96.8
NLR	85.4	0.834	0.945	3.245	80.1	83.7
PLR	75.6	0.612	0.788	152.125	70.1	68.4

DISCUSSION

To our knowledge, this study represents the first of its kind in India, simultaneously comparing various hematological indices between ACS and SCAD patients. The baseline characteristics for both ACS and SCAD cohorts are similar, predominantly comprising males and a majority aged below sixty. This outcome aligns relatively closely with a prior study conducted by Indonesia [17]. Southeast Asian countries, like India exhibit a pattern of younger morbidity and mortality attributed to non-communicable diseases, particularly cardiovascular diseases, in comparison to regions such as Europe. This difference is likely attributed to the rapid epidemiological transition observed in Southeast Asian countries [17,18].

In accordance with the findings of this study, the MCHC value was significantly higher in the ACS group. This aligns with previous research demonstrating elevated MCHC values in coronary artery disease (CAD) patients compared to healthy controls [19,20]. However, there are variations in the literature, as a study reported lower MCHC in acute myocardial infarction compared to SCAD patients, although it did not reach statistical significance (32.09 ± 1.34 vs. 32.70 ± 1.45, p = 0.071) [20]. Existing theories propose a complex interplay between inflammation, iron metabolism, and anemia influencing MCHC values. During inflammation, the body tends to decrease iron serum levels through duodenal absorption and macrophage regulation [21]. Reduced iron serum levels can lead to iron-deficiency anemia, resulting in a decrease in MCHC values [22].Despite limited studies elucidating these results, the hypothesis put forth in this study posits that the high degree of inflammation in ACS induces elevated oxidative stress, leading to hemolysis and an increase in MCHC values. Oxidative stress is known to impair

erythrocyte metabolism and trigger hemolysis [23]. Consequently, hemolysis results in increased hemoglobin production, subsequently elevating the MCHC value as it represents the ratio between hemoglobin and hematocrit.

The results regarding White Blood Cell (WBC) levels align with prior research, indicating that WBC counts in ACS patients are significantly higher compared to those with SCAD [10,11]. Previous studies reported WBC counts for ACS patients ranging from 7.07 ± 2.02 to 9.40 ± 3.30 x 109/L, while SCAD patients had counts ranging from 6.63 ± 1.57 to 6.60 ± 1.40 x 109/L [10,11]. In this current study, the WBC count for ACS was higher than reported in the previous studies, potentially due to the majority of participants in this study being STEMI patients (74.50%), whereas the previous study primarily focused on Unstable Angina [10].The elevation of WBC is intricately linked to the complex and dynamic inflammatory response at both local and systemic levels. Leukocytes play a pivotal role in the pathogenesis and progression of atherosclerotic lesions. Localized low-grade inflammation during the early stages of lesions, endothelial dysfunction, and foam cell production are all associated with leukocyte activities [3]. Leukocyte activities also influence plaque stability, with continuous activation and infiltration of neutrophils during various phases of atherosclerosis leading to plaque instability via the release of myeloperoxidase (MPO) and metalloproteinases (MMPs) [13]. Myocardial damage resulting from atherosclerosis occlusion can further increase neutrophil and macrophage numbers through stimulation by cytokines, chemokines, and other substances [24].

Prior investigations have consistently reported that patients withACS tend to have higher Mean Platelet Volume (MPV) compared to those with SCAD [25-27]. Elevated MPV has been correlated with various cardiovascular risks and increased thrombogenicity, attributed to platelet metabolic and enzymatic activities [28-29].Interestingly, the current study yielded a contrasting result, indicating that ACS patients had significantly lower MPV compared to SCAD patients. This discrepancy leads to the hypothesis that there is a dynamic and complex regulation of platelets during ACS, involving both platelet production and consumption. In the context of inflammation, larger platelets are produced. However, in atherothrombotic lesions characteristic of ACS, there appears to be high consumption of large and hyperactive platelets [28].Moreover, diseases characterized by high-grade inflammation, such as rheumatoid arthritis and inflammatory bowel disease, have also demonstrated lower Mean Platelet Volume (MPV) levels. This phenomenon is attributed to the active local inflammation and significant consumption of large platelets [28]. Supporting this theory is the observation that activated platelets are six times more potent in adhering to polymorphonuclear cells and monocytes compared to inactive platelets [30]. Alternate theories propose that during ACS, there is acute and general activation of platelets without a subsequent increase in MPV [31].

In this study, both Neutrophil-to-Lymphocyte Ratio (NLR) and Platelet-to-Lymphocyte Ratio (PLR) were observed to be higher in ACS compared to SCAD. Similarly, prior research has indicated elevated NLR in both ACS and SCAD when compared to healthy controls [32-34]. The higher NLR in ACS is attributed to an acute and more pronounced inflammatory response, where neutrophils function as acute-phase pro-inflammatory agents and lymphocytes as anti-inflammatory agents. The observed lower lymphocyte levels can be attributed to the complex interaction between cytokines, neutrophils, and lymphocytes. ACS is associated with the highest levels of circulating interferon-gamma (IFN-γ), followed by SCAD and healthy controls [35]. Activated neutrophils release IFN-γ, which suppresses lymphocyte proliferation through the expression of Programmed Death Ligand 1 [36].

Consistent with prior research, this study also indicates that Platelet-to-Lymphocyte Ratio (PLR) is elevated in both ACS and SCAD compared to healthy controls [32,37,38]. The elevated PLR in these conditions is primarily attributed to a lower lymphocyte count. In ACS, the reduced lymphocyte count may be linked to cortisol release or the migration of lymphocytes from the bloodstream [37,38].

Platelet count in ACS and SCAD has shown inconsistent results across studies. Some investigations reported a higher platelet count in the ACS group compared to SCAD and healthy controls [11,39], while others observed a lower platelet count [32,40]. Additionally, another study indicated that platelet count in myocardial infarction patients is higher than in healthy controls but lower in unstable angina patients [41]. The hypothesis for this inconsistency revolves around the complex relationship between thrombopoietin and the regulation of platelets in inflammatory settings. Thrombopoietin, a hormone that regulates platelet production, is elevated in unstable angina patients compared to SCAD and healthy controls [42]. This increase is attributed to platelet consumption during acute myocardial attacks, stimulating the proliferation of megakaryocytes [43]. Another theory suggests that the interaction between thrombopoietin and its receptor on the platelet surface results in decreased thrombopoietin, leading to low platelet production. Platelets with high Mean Platelet Volume (MPV) have numerous receptors, inducing inhibitory feedback, resulting in lower platelet count [44].

This study conducted an analysis of the cut-off points for Hematologic indices. The cut-off point for Mean Platelet Volume (MPV) was determined to be 8.35 fL, where a lower MPV suggests a diagnosis of ACS. This result differs from a previous study, which identified an MPV cut-off point of 9.15 fL or higher,

with sensitivity at 72% and specificity at 40% [25]. In this research, the cut-off point for Neutrophil-to-Lymphocyte Ratio (NLR) was 3.245, and a higher NLR is indicative of an ACS diagnosis. Previous studies have suggested that an NLR above 2.5 could diagnose ACS with sensitivity at 63.6% and specificity at 80.2% [32]. A meta-analysis also indicated that NLR cut-off points ranging from 1.95 to 3.97 could predict severe atherosclerotic lesions [45]. For White Blood Cell (WBC) count, a value exceeding 9.182 was suggestive of an ACS diagnosis in this study. Previous reports on WBC cut-off points include 6.91, 7.37, and 8.89 x 103/µL, each with sensitivities and specificities of 86% and 37%; 45% and 54%; and 54% and 71%, respectively [46].Overall, this study suggests that MPV, NLR, and WBC are not inferior to other inflammation markers such as IL-6 for diagnosing ACS.

Descriptions of chest pain from patients with CAD often rely on subjective accounts, varying with communication skills, and may differ from the angina classification [47]. Additionally, the ability of general practitioners to diagnose ACS and SCAD based solely on signs and symptoms is considered low [48]. The complete blood count, encompassing parameters such as Mean Platelet Volume (MPV), Neutrophil-to-Lymphocyte Ratio (NLR), and White Blood Cell (WBC) count, offers a simple and accessible examination in primary care settings. General practitioners with limited resources may find these hematologic indices useful in distinguishing chest pain originating from ACS or SCAD.

Limitations of the Study: It's important to acknowledge that this study has limitations, including its nature as a single-center study, which may impact the generalizability of the findings to the overall population. Additionally, the use of consecutive sampling from all patients admitted for ACS or SCAD diagnosis introduces the potential for selection bias. Researchers should consider these limitations when interpreting and applying the study's results.

CONCLUSION

The study revealed significant differences in hematologic indices between ACS and SCAD patients. ACS patients exhibited higher Mean Corpuscular Hemoglobin Concentration (MCHC), White Blood Cell (WBC) count, Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), and lower Mean Platelet Volume (MPV) compared to the SCAD group. Notably, MPV demonstrated the highest Area Under the Curve (AUC) at 95.0%, with the optimal cut-off point identified as 8.35 fL, providing a sensitivity of 93.5% and specificity of 96.8%.

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