ID Design Press, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2019 Aug 15; 7(15):2428-2433.
https://doi.org/10.3889/oamjms.2019.666
eISSN: 1857-9655
Clinical Science

Predictive Value of Hematologic Indices in the Diagnosis of Acute Coronary Syndrome

Kevin Luke[1], Bambang Purwanto[2], Lilik Herawati[2], Makhyan Jibril Al-Farabi[3, 4], Yudi Her Oktaviono[3*]

[1]Faculty of Medicine, Universitas Airlangga, Surabaya, East Java, Indonesia; [2]Department of Physiology, Faculty of Medicine, Universitas Airlangga, Surabaya, East Java, Indonesia; [3]Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, East Java, Indonesia; [4]School of Management, Healthcare Entrepreneurship Division, University College London, Gower St, Bloomsbury, WC1E 6BT, London, UK

Citation: Luke K, Purwanto B, Herawati L, Al-Farabi MJ, Oktaviono YH. Predictive Value of Hematologic Indices in the Diagnosis of Acute Coronary Syndrome. Open Access Maced J Med Sci. 2019 Aug 15; 7(15):2428-2433. https://doi.org/10.3889/oamjms.2019.666

Keywords: Atherosclerosis; Chest Pain; Complete Blood Count; Inflammation

***Correspondence:** Yudi Her Oktaviono. Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, East Java, Indonesia. E-mail: yudi.her@fk.unair.ac.id

Received: 01-Aug-2019; **Revised:** 09-Aug-2019; **Accepted:** 11-Aug-2019; **Online first:** 13-Aug-2019

Funding: This research did not receive any financial support

Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: Distinguishing between Acute Coronary Syndrom (ACS) and SCAD (Stable Coronary Artery Disease) requires advanced laboratory instrument and electrocardiogram. However, their availabilities in primary care settings in developing countries are limited. Hematologic changes usually occur in the ACS patient and might be valuable to distinguish ACS from SCAD.

AIM: This study compares the hematologic indices between ACS and SCAD patients and analyses its predictive value for ACS.

MATERIAL AND METHODS: A total of 191 patients (79 ACS and 112 SCAD) were enrolled in this study based on the inclusion criteria. Patient's characteristic, hematologic indices on admission, and the final diagnosis were obtained from medical records. Statistical analyses were done using SPSS 23.0.

RESULTS: In this research MCHC value (33.40 vs. 32.80 g/dL; $p < 0.05$); WBC (11.16 vs. 7.40 x109/L; $p < 0.001$); NLR (6.29 vs. 2.18; $p < 0.001$); and PLR (173.88 vs 122.46; $p < 0.001$) were significantly higher in ACS compared to SCAD patients. While MPV (6.40 vs. 10.00 fL; $p < 0.001$) was significantly lower in ACS patients. ROC curve analysis showed MPV had the highest AUC (95%) for ACS diagnosis with an optimum cut-off point at ≤ 8.35 fL (sensitivity 93.6% and specificity 97.3%).

CONCLUSION: There was a significant difference between hematologic indices between ACS and SCAD patients. MPV is the best indices to distinguish ACS.

Introduction

Coronary Artery Disease (CAD) is the leading cause of death worldwide, including Indonesia. WHO reported that CAD caused 138.400 deaths of Indonesian in 2012 [1]. Most of CAD is caused by coronary artery narrowing from atherosclerosis [2]. The characteristics of atherosclerosis determine the clinical manifestation of CAD. Vulnerable plaque or unstable plaque will result in atherothrombosis event which is the hallmark of Acute Coronary Syndrome (ACS), while stable plaque consists of poor-lipid core and thick fibrous cap will be manifested as Stable Coronary Artery Disease (SCAD) [2], [3], [4].

Rapid coronary revascularisation is beneficial for ACS patients to reduce adverse events or death [5]. Therefore, early diagnosis of ACS is critical since mortality rates in the ACS patients are up to seven times higher than SCAD [6]. However, due to the limited availability of the electrocardiogram (ECG) and cardiac markers in the primary care setting, diagnosis of the ACS may become a big challenge for primary care physician in developing countries [7]. The previous study even showed that the availability of ECG in the rural primary care setting was only 63.3% [8]. Hence, easy and accessible screening approach for diagnosis of ACS in primary care settings is urgently needed.

Pathogenesis of atherosclerosis is related to the inflammation and hematologic responses. Various inflammatory substance and hematologic cells are involved in the pathogenesis of atherosclerotic lesion [9], [10], [11]. Leukocyte and platelets play major roles in the foam cell generation, cytokines secretion,

including Reactive Oxygen Species (ROS), and cardiomyocytes death, which contribute to the atherosclerosis progression [12]. The lesion in ACS exhibits acute condition and activates neutrophil as pro-inflammatory cells [4], [13]. ACS also usually followed by inflammation regulation by anti-inflammatory cells such as lymphocyte cells [14], [15]. Platelets also play a role in the ACS by inducing higher inflammatory activity and thrombogenicity [3], [4], [16]. Contrary, the lesion in SCAD exhibits chronic and lower grade of inflammation compared to ACS. Previous studies showed that white blood cell count and inflammatory markers are significantly higher in the ACS group compared to SCAD [9], [10], [11]. However, the comparison of other hematologic indices between ACS and SCAD is yet to be investigated.

Thus, this study compares hematologic indices between ACS and SCAD patients and analyse its predictive value to distinguish ACS.

Material and Methods

Study design, Sampling, and Participants

This retrospective cross-sectional study was conducted in Dr Soetomo General Hospital, Surabaya, Indonesia. Total sampling was done from all medical records of the patient diagnosed with ACS or SCAD from January to December 2017. Patients with kidney and liver abnormalities, active infection, cancer, haematological diseases, corticosteroid therapy, and chemotherapy are excluded. Dr Soetomo General Hospital Surabaya Ethical Committee in Health Research has approved this study (approval number 0485/KEPK/VIII/2018). Privacy and confidentiality of the information were guaranteed, as data did not include patient personal identities

Data Collection

Age, Sex, CAD type (ACS or SCAD), erythrocyte indices (MCHC, Hgb, Hct), leukocytes indices (WBC, Neutrophil Percentage, Lymphocyte Percentage) and platelet indices (MPV, PLT) were obtained from medical records. Diagnosis of ACS is defined by ICD10 diagnosis code I20.0 as Unstable Angina Pectoris (UAP), I21.0 and I21.1 as ST-Elevation Myocardial Infarction (STEMI), and I21.4 as Non-ST-Elevation Myocardial Infarction (NSTEMI). Diagnosis of SCAD is defined by ICD10 diagnosis code I25.0 with no history of ACS or myocardial infarction. Neutrophil to Lymphocyte Ratio (NLR) was calculated by dividing Neutrophil Percentage to Lymphocyte Percentage, while Platelet to Lymphocyte ratio (PLR) was calculated by dividing PLT to the multiplication of Lymphocyte Percentage with WBC.

Statistical Analysis

Statistical analyses were performed using SPSS Statistics 23.0. Continuous variables, presented as mean±SD, was compared using Independent T-test or Mann Whitney test based on the normality test. Specificity and sensitivity were obtained from the ROC curve and cut-off point analysis.

Results

Baseline Characteristics

Total of 191 medical records consisting of 79 ACS patient (9 UAP, 10 NSTEMI, and 60 STEMI) and 112 SCAD 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 = 79)	SCAD (n = 112)	*p*-value
Sex, n (%)			
Male	64 (81.0%)	94 (83.9%)	0.741
Female	15 (19.0%)	18 (16.1%)	
Age (years)	56.82 ± 9.532	57.78 ± 9.300	0.490

Comparison of Erythrocyte Indices

This study focuses on comparing MCHC values between two groups, Hgb and Hct values are used to analyse the component of MCHC value since MCHC is the ratio between Hgb and Hct. MCHC values were significantly higher in ACS than SCAD (p = 0.019), while Hgb and Hct were not significantly different (Table 2).

Comparison of Leukocyte Indices

This study compares the WBC values between two groups: the percentage of Neutrophil and Lymphocyte values are used to calculate NLR and PLR value. WBC and percentage of Neutrophil were significantly higher, while the percentage of Lymphocyte was significantly lower in ACS than SCAD with all p-value less than 0.001, respectively (Table 2).

Comparison of Platelet Indices

This study compares the MPV values between two groups; PLT values are used to calculate PLR value. MPV was significantly lower in ACS than SCAD with p-value less than 0.001, while PLT was not significantly different (Table 2).

Comparison of Other Indices

Both NLR and PLR values were significantly higher in ACS than SCAD with the p-value of less than 0.001 (Table 2).

Table 2: Comparison of hematological indices between ACS and SCAD patients

Indices	ACS (n = 79)	SCAD (n = 112)	*p*-value
Erythrocyte			
Hgb (g/dL)[1]	13.94 ± 1.51	13.72 ± 1.41	0.303
Hct (%)[1]	41.79 ± 4.91	41.69 ± 4,04	0.877
MCHC (g/dL)	33.44 ± 1.85	32.92 ± 1.09	0.019*
Leukocyte			
WBC (x 10^9 /L)	11.72 ± 3.41	8.07 ± 5.31	< 0.001*
Neu% (%)	77.27 ± 11.03	59.94 ± 8.11	< 0.001*
Lymp% (%)	14.92 ± 8.51	27.58 ± 7.06	< 0.001*
Platelet			
PLT (x 10^9 /L)[1]	267.95 ± 75.57	257.91 ± 59.70	0.307
MPV (fL)	6.64 ± 1.29	10.04 ± 0.94	< 0.001*
Other			
NLR	7.45 ± 5.31	2.48 ± 1.58	< 0.001*
PLR	203.84 ± 111.72	136.38 ± 56.200	< 0.001*

[1]Data were normally distributed; *P < 0.05 was considered statistically significant; 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.

Cut-off Point

ROC Curve of MCHC, WBC, NLR, and PLR is set to indicate ACS if its value is increasing (Figure 1A), while ROC Curve of MPV is set to indicate ACS if its value is decreasing (Figure 1B). MPV has highest AUC (95.0%) followed by WBC and NLR (88.4%), PLR (71.7%), and MCHC (60.0%) respectively (Table 3).

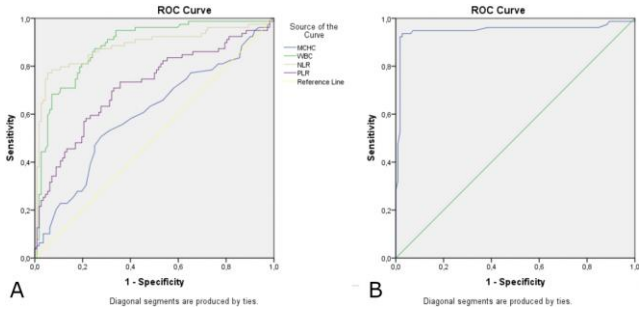

Figure 1: Receiving Operating Characteristics Curve of A) MCHC, WBC, NLR, and PLR; B) MPV

The cut-off point for MPV to distinguish ACS was 8.35 fL with very high sensitivity (93.6%) and specificity (97.3%). This section may be divided by subheadings. It should provide a concise and precise description of the experimental results, their interpretation as well as the experimental conclusions that can be drawn.

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

Indices	AUC (%)	95% CI		Cut-Off	Sensitivity (%)	Specificity (%)
		Lower Bound	Upper Bound			
MCHC	60.0	0.517	0.683	33.050	58.2	59.8
WBC	88.4	0.835	0.933	9.170	81.0	80.4
MPV	95.0	0.907	0.992	8.350	93.6	97.3
NLR	88.4	0.828	0.939	3.187	81.0	85.7
PLR	71.7	0.641	0.793	147.087	69.6	67.9

Discussion

To our knowledge, this is the first study comparing various haematological indices simultaneously between ACS and SCAD patient, especially in Indonesia. Baseline characteristics for both ACS and SCAD are similar, which dominated by male and majority aged below sixty. This result is relatively similar to the previous study in Makassar, Indonesia [17]. Southeast Asian countries indeed have younger morbidity and mortality due to non-communicable disease, primarily cardiovascular disease compared to another region such as European. This difference may be due to a rapid epidemiological transition in Southeast Asian countries [17], [18].

Based on this study, MCHC value is significantly higher in the ACS group. This result is similar to previous studies, which showed MCHC value is significantly higher in CAD patients compared to healthy control [19], [20]. However, a study showed MCHC is lower in acute myocardial infarction compared to SCAD patients, yet it is not statistically significant (32.09 ± 1.34 vs 32.70 ± 1.45, p = 0.071) [20]. The previous theory stated there is a complex interaction between inflammation, iron metabolism, and anaemia, which affect MCHC value. During inflammation, the body will decrease iron serum levels by duodenal absorption and macrophage regulation [21]. Low iron serum levels will lead to iron-deficiency anaemia and decrease MCHC value [22]. Despite a few studies explaining these results; we hypothesise that high grade of inflammation in ACS leads to higher oxidative stress resulting in hemolysis and increasing MCHC value. Oxidative stress impairs erythrocyte metabolism and causes hemolysis [23]. Hemolysis will lead to increased haemoglobin production, followed by increased MCHC value as the ratio between haemoglobin and hematocrit. Other than a high grade of inflammation, risk factor such as smoking also contributes to oxidative stress [23]. Study in Indonesia has shown that ACS patients have a higher number of smoker compared to SCAD patient [17].

The result of WBC is similar to the previous study, which showed WBC of ACS patients is significantly higher compared to SCAD patients [10], [11]. Based on the previous study, WBC of ACS patients ranging from 7.07 ± 2.02 to 9.40 ± 3.30 x 10^9/L, while SCAD patients are ranging from 6.63 ± 1.57 to 6.60 ± 1.40 x 10^9/L [10], [11]. In this study, WBC for ACS is higher than the previous study (11.72 ± 3.41 x 10^9/L) since the majority of participants in this study were STEMI patient (75.95%), while the previous study was UAP [10]. A study comparing WBC of STEMI and NSTEMI group showed higher WBC in the STEMI group (11.850 vs 8.460 x 10^9/L, p = 0.01). Elevation of WBC is related to the complex and dynamic inflammation response in local and systemic level. Leukocyte has major role in

pathogenesis and progression of the atherosclerotic lesion. Local low-grade inflammation during early lesion, endothelial dysfunction, and foam cell production is related to leukocytes activities [3]. Leukocytes activities are also responsible for plaque stability. During various atherosclerosis phases, there is continuous activation and infiltration of neutrophils resulting in plaque instability via myeloperoxidase (MPO) and metalloproteinase (MMP) release [13]. Myocardial damage from the atherosclerosis occlusion can also increase the neutrophil and macrophage numbers via cytokines, chemokine, and other substance stimulation [24].

Previous studies showed that ACS patients have higher MPV compared to SCAD patients [25], [26], [27]. Higher MPV is correlated to various cardiovascular risks and higher thrombogenicity due to platelet metabolic and enzymatic activity [28], [29]. Interestingly, our study showed a different result, which showed that ACS patients had significantly lower MPV compared to SCAD patients. We hypothesise there was dynamic and complex platelet regulation during ACS, including production and consumption of platelet. During inflammation, larger platelet was produced. However, atherothrombotic lesion exhibits high consumption of large and hyperactive platelet [28].

Furthermore, high-grade inflammation diseases such as rheumatoid arthritis and inflammatory bowel disease also showed lower MPV due to local active and large platelet consumption [28]. This theory is supported by the fact that activated platelet is six times more potent to adhere to polymorphonuclear cells and monocytes compared to inactive platelet [30]. Other theories suggest that during ACS, there is acute and general activation of platelet without followed by increased MPV [31].

In this research, both NLR and PLR are higher in ACS compared to SCAD. Similarly, the previous study showed NLR is elevated in both ACS and SCAD compared to healthy controls [32], [33], [34]. Higher NLR in ACS is related to acute and higher-grade inflammation response which neutrophils act as acute phase pro-inflammatory agents and lymphocytes as anti-inflammatory agents. Low lymphocyte level is likely due to the complex interaction between cytokines, neutrophils, and lymphocytes. ACS has the highest levels of circulating IFN-γ, followed by SCAD and healthy control [35]. Neutrophils activated IFN-γ suppresses lymphocyte proliferation through Programmed Death Ligand 1 expression [36].

The previous study also showed PLR is elevated in both ACS and SCAD compared to healthy controls [32], [37], [38]. This study shows that elevated PLR is mainly due to lower lymphocyte count. Low lymphocyte count in ACS condition may be due to cortisol release or lymphocyte migration from blood circulation [37], [38]. Platelet count in ACS and SCAD showed inconsistent results, several studies showed platelet count is higher in ACS group compared to SCAD and healthy control [11], [39], while others showed lower platelet count [32], [40]. A study also showed platelet count in myocardial infarction patient is higher compared to healthy control but lower in unstable angina patient [41]. We hypothesise this inconsistency is due to the complex relation between thrombopoietin and regulation of platelet in inflammation settings. Thrombopoietin, a platelet production regulatory hormone, is elevated in unstable angina patient compared to SCAD and healthy control [42]. This elevation is due to platelet consumption during the acute myocardial attack to stimulate megakaryocytes proliferation [43]. Other theory suggested that interaction between thrombopoietin and its receptor on the platelet surface will decrease thrombopoietin, resulting in the low production of the platelet. Platelet with high MPV will have many receptors which induces inhibitory feedback resulted in lower platelet count [44].

This study analysed the cut-off point for five indices. MPV cut-off point was 8.35 fL, and lower MPV suggests a diagnosis of ACS. This result is different from the previous study, which showed MPV cut-off point was 9.15 fL or higher with sensitivity 72% and specificity 40% [25]. In this research, the cut-off point of NLR was 3.187, which higher NLR is suggestive for ACS diagnosis. The previous study showed that NLR above 2.5 could diagnose ACS with the sensitivity of 63.6% and specificity 80.2% [32]. A meta-analysis also showed that NLR cut-off point from 1.95 to 3.97 could predict severe atherosclerotic lesion [45]. In this research, WBC of more than 9.170 is suggestive for ACS diagnosis. Previously, WBC been reported to have a cut-off point of 6.91; 7.37; and 8.89 x 10^3/μL with each sensitivity and specificity are 86% and 37%; 45% and 54%; 54% and 71% respectively [46]. Overall, our study showed that MPV, NLR, and WBC is not inferior to other inflammation markers such as IL-6 to diagnose ACS. Previously, a study in Indonesia showed IL-6 with cut-off point 4.43 pg/mL can distinguish ACS and SCAD with sensitivity and specificity are 80.95% and 77.42%, respectively [9].

Benefits in Further Clinical Practice: Descriptions of chest pain from CAD patients are often subjective, dependent on communication skills, and different from Diamond and Forrester angina classification [47]. Moreover, the general practitioner ability to diagnose ACS and SCAD based on sign and symptom is considered low [48]. The complete blood count is a simple and accessible examination in the primary care setting. General practitioner with limited resources could consider MPV, NLR, and WBC to distinguish chest pain originated from ACS or SCAD.

Strength and Limitations of the Study: To our knowledge, this is the first study comparing various haematological indices simultaneously between ACS and SCAD patient, especially in Indonesia. Moreover, this study also firstly showed the difference in MCHC,

NLR, and PLR value in ACS and SCAD group. However, this study may yet to be generalised since it only involved single-centre as the source of data. This study also used consecutive samplings from all patients who were admitted for ACS or SCAD diagnosis. Hence, selection bias might occur. In the future, it is suggested to involve more hospital and stratify the sample based on several risk factors such as race and social status to ensure the validity of the hematologic indices among various demographic characteristics.

In conclusion, there was a significant difference in hematologic indices between ACS and SCAD patients. ACS had higher MCHC, WBC, NLR, PLR, and lower MPV compared to SCAD group. MPV had highest AUC (95.0%) with optimum cut-off point was 8.35 fL (sensitivity 93.6% and specificity 97.3%).

Author Contributions

Conceptualisation, Y.H.O. and K.L.; methodology, Y.H.O., K.L., L.H., and B.P.; software, K.L. and M.J.A.; formal analysis, K.L., B.P., M.J.A.; investigation, K.L.; data curation, K.L., L.H.; writing—original draft preparation, K.L., B.P., L.H.; writing—review and editing, L.H., Y.H.O and M.J.A.

References

1. WHO. Indonesia: WHO Statistical Profile [Internet], 2015. [cited 2019 Jun 13]. Available from: https://www.who.int/gho/countries/idn.pdf?ua=1

2. Libby P, Theroux P. Pathophysiology of coronary artery disease. Circulation. 2005; 111(25):3481-8. https://doi.org/10.1161/CIRCULATIONAHA.105.537878 PMid:15983262

3. Cimmino G, Loffredo FS, Morello A, D'Elia S, De Palma R, Cirillo P, et al. Immune-Inflammatory Activation in Acute Coronary Syndromes: A Look into the Heart of Unstable Coronary Plaque. Curr Cardiol Rev. 2016; 13(2):110-7. https://doi.org/10.2174/1573403X12666161014093812 PMid:27758696 PMCid:PMC5452145

4. Acet H, Ertaş F, Akıl MA, Özyurtlu F, Polat N, Bilik MZ, et al. Relationship Between Hematologic Indices and Global Registry of Acute Coronary Events Risk Score in Patients With ST-Segment Elevation Myocardial Infarction. Clin Appl Thromb. 2016; 22(1):60-8. https://doi.org/10.1177/1076029614533145 PMid:24816530

5. Cassar A, Holmes DR, Rihal CS, Gersh BJ. Chronic coronary artery disease: Diagnosis and management. Mayo Clin Proc. 2009; 84(12):1130-46. https://doi.org/10.4065/mcp.2009.0391 PMid:19955250 PMCid:PMC2787400

6. Agewall S. Acute and stable coronary heart disease: Different risk factors. Eur Heart J. 2008; 29(16):1927-9. https://doi.org/10.1093/eurheartj/ehn321 PMid:18621774

7. Bruins Slota MHE, Ruttena FH, van der Heijdena GJMG, Geersinga GJ, Glatzb JFC, Hoesa AW. Diagnosing acute coronary syndrome in primary care: Comparison of the physicians' risk estimation and a clinical decision rule. Fam Pract. 2011; 28(3):323-8. https://doi.org/10.1093/fampra/cmq116 PMid:21239470

8. Oikonomidou E, Anastasiou F, Dervas D, Patri F, Karaklidis D, Moustakas P, Andreadou N, Mantzanas E, Merkouris B. Rural primary care in Greece: working under limited resources. International Journal for Quality in Health Care. 2010; 22(4):333-7. https://doi.org/10.1093/intqhc/mzq032 PMid:20581119

9. Alwi I, Santoso T, Suyono S, Sutrisna B, Kresno SB. The cut-off point of interleukin-6 level in acute coronary syndrome. Acta Med Indones. 2007; 39(4):174-8.

10. Yip HK, Wu CJ, Hang CL, Chang HW, Yang CH, Hsieh YK, et al. Levels and values of inflammatory markers in patients with angina pectoris. Int Heart J. 2005; 46(4):571-81. https://doi.org/10.1536/ihj.46.571 PMid:16157948

11. Hung MJ, Cherng WJ, Cheng CW, Li LF. Comparison of Serum Levels of Inflammatory Markers in Patients With Coronary Vasospasm Without Significant Fixed Coronary Artery Disease Versus Patients With Stable Angina Pectoris and Acute Coronary Syndromes With Significant Fixed Coronary Artery Diseas. Am J Cardiol. 2006; 97(10):1429-34. https://doi.org/10.1016/j.amjcard.2005.12.035 PMid:16679078

12. Bobryshev YV, Ivanova EA, Chistiakov DA, Nikiforov NG, Orekhov AN. Macrophages and Their Role in Atherosclerosis: Pathophysiology and Transcriptome Analysis. Biomed Res Int. 2016; 2016. https://doi.org/10.1155/2016/9582430 PMid:27493969 PMCid:PMC4967433

13. Soehnlein O. Multiple roles for neutrophils in atherosclerosis. Circ Res. 2012; 110(6):875-88. https://doi.org/10.1161/CIRCRESAHA.111.257535 PMid:22427325

14. Hedrick CC. Lymphocytes in Atherosclerosis. Arterioscler Thromb Vasc Biol. 2015; 35(2):253-7. https://doi.org/10.1161/ATVBAHA.114.305144 PMid:25609772 PMCid:PMC4327776

15. Chen C, Cong BL, Wang M, Abdullah M, Wang XL, Zhang YH, et al. Neutrophil to lymphocyte ratio as a predictor of myocardial damage and cardiac dysfunction in acute coronary syndrome patients. Integr Med Res. 2018; 7(2):192-9. https://doi.org/10.1016/j.imr.2018.02.006 PMid:29984180 PMCid:PMC6026362

16. Budzianowski J, Pieszko K, Burchardt P, Rzeźniczak J, Hiczkiewicz J. The Role of Hematological Indices in Patients with Acute Coronary Syndrome. Dis Markers. 2017; 2017. https://doi.org/10.1155/2017/3041565 PMid:29109595 PMCid:PMC5646322

17. Qanitha A, Uiterwaal CSPM, Henriques JPS, Alkatiri AH, Mappangara I, Mappahya AA, et al. Characteristics and the average 30-day and 6-month clinical outcomes of patients hospitalised with coronary artery disease in a poor South-East Asian setting : the first cohort from Makassar Cardiac Center , Indonesia. BMJ Open. 2018; (8):1-11. https://doi.org/10.1136/bmjopen-2018-021996 PMid:29950477 PMCid:PMC6020938

18. WHO. Noncommunicable Diseases in the South-East Asia Region, 2011.

19. Nagula P, Karumuri S, Otikunta AN, Yerrabandi SRV. Correlation of red blood cell distribution width with the severity of coronary artery disease-A single center study. Indian Heart J. 2017; 69(6):757-61. https://doi.org/10.1016/j.ihj.2017.04.007 PMid:29174254 PMCid:PMC5717282

20. Khode V, Ruikar K, Nallulwar S, Sindhur J, Kanabur D. Association of red cell distribution width, haematocrit and other RBC indices with coronay artery disease: A case control study. Niger J Cardiol. 2014; 11(2):88. https://doi.org/10.4103/0189-7969.142088

21. Koorts AM, Levay PF, Becker PJ, Viljoen M. Pro- and Anti-Inflammatory Cytokines during Immune Stimulation: Modulation of Iron Status and Red Blood Cell Profile. 2011; 2011. https://doi.org/10.1155/2011/716301 PMid:21547258 PMCid:PMC3086355

22. Huang Y, Hu Z. Lower mean corpuscular hemoglobin concentration is associated with poorer outcomes in intensive care unit admitted patients with acute myocardial infarction. 2016; 4(5):1-8. https://doi.org/10.21037/atm.2016.03.42 PMid:27294086 PMCid:PMC4885905

23. Metta S, Uppala S, Basalingappa D, Gunti S, Badeti S. Impact of smoking on erythrocyte indices and oxidative stress in acute myocardial infarction. J Dr NTR Univ Heal Sci. 2015; 4(3):159. https://doi.org/10.4103/2277-8632.165400

24. Fang L, Moore XL, Dart AM, Wang LM. Systemic inflammatory response following acute myocardial infarction. J Geriatr Cardiol. 2015; 12(3):305-12.

25. Dehghani MR, Taghipour-Sani L, Rezaei Y, Rostami R. Diagnostic importance of admission platelet volume indices in patients with acute chest pain suggesting acute coronary syndrome. Indian Heart J. 2014; 66(6):622-8. https://doi.org/10.1016/j.ihj.2014.10.415 PMid:25634396 PMCid:PMC4310955

26. Khandekar MM, Khurana AS, Deshmukh SD, Kakrani AL, Katdare AD, Inamdar AK. Platelet volume indices in patients with coronary artery disease and acute myocardial infarction: An Indian scenario. J Clin Pathol. 2006; 59(2):146-9. https://doi.org/10.1136/jcp.2004.025387 PMid:16443728 PMCid:PMC1860313

27. Abef NK-çamur, B RD, Def CK. Could mean platelet volume be a predictive marker for acute myocardial infarction ? Med Sci Monit. 2005; 11(8):387-93.

28. Gasparyan AY, Ayvazyan L, Mikhailidis DP, Kitas GD. Mean platelet volume: a link between thrombosis and inflammation? Curr Pharm Des. 2011; 17(1):47-58. https://doi.org/10.2174/138161211795049804 PMid:21247392

29. Chu S, Becker R, Berger P, Bhatt D, Eikelboom J, Konkle B, et al. Mean platelet volume as a predictor of cardiovascular risk: a systematic review and meta-analysis. J Thromb Haemost. 2010; 8(1):148-56. https://doi.org/10.1111/j.1538-7836.2009.03584.x PMid:19691485 PMCid:PMC3755496

30. Rinder HM, Bonan JL, Rinder CS, Ault KA, Smith BR. Activated and Unactivated Platelet Adhesion to Monocytes and Neutrophils. Blood. 1991; 78(7):1760-9.

31. Mathur A, Robinson MSC, Cotton J, Martin JF, Erusalimsky JD. Platelet reactivity in acute coronary syndromes: Evidence for differences in platelet behaviour between unstable angina and myocardial infarction. Thromb Haemost. 2001; 85(6):989-94. https://doi.org/10.1055/s-0037-1615952 PMid:11434707

32. Ertürk M, Turhan Caglar FN, Bıyık İ. Correlations between hematological indicators and other known markers in acute coronary syndromes. E J Cardiovasc Med. 2018; 5(4):67-74. https://doi.org/10.15511/ejcm.17.00467

33. Bhuiyan M, Sultana S, Hasan A, Barua D, Ahmed M, Aa C. Neutrophil Lymphocyte Ratio (NLR) is an Indicator of Coronary Artery Disease (Cad) in Type 2 Diabetes Mellitus Patients. 2018; 76:1-6.

34. Tabrez S, Alama MN, Jabir NR, Firoz CK. Neutrophils to Lymphocyte Ratio as a Biomarker of Coronary Artery Disease. Acta Medica Mediterr. 2016; 32:1637-42.

35. Min X, Lu M, Tu S, Wang X, Zhou C, Wang S, et al. Serum Cytokine Profile in Relation to the Severity of Coronary Artery Disease. Biomed Res Int. 2017; 2017. https://doi.org/10.1155/2017/4013685 PMid:28349060 PMCid:PMC5352875

36. de Kleijn S, Langereis JD, Leentjens J, Kox M, Netea MG, Koenderman L, et al. IFN-γ-Stimulated Neutrophils Suppress Lymphocyte Proliferation through Expression of PD-L1. PLoS One. 2013; 8(8). https://doi.org/10.1371/journal.pone.0072249 PMid:24015224 PMCid:PMC3756078

37. Harun H, Bahrun U, Darmawaty E. Platelet-Lymphocyte Ratio (PLR) Markers in Acute Coronary Syndrome. Indones J Clin Pathol Med Lab. 2016; 23(1):7-11. https://doi.org/10.24293/ijcpml.v23i1.1176

38. Akboga MK, Canpolat U, Yayla C, Ozcan F, Ozeke O, Topaloglu S, et al. Association of Platelet to Lymphocyte Ratio with Inflammation and Severity of Coronary Atherosclerosis in Patients with Stable Coronary Artery Disease. Angiology. 2016; 67(1):89-95. https://doi.org/10.1177/0003319715583186 PMid:25922197

39. Turk U, Tengiz I, Ozpelit E, Celebiler A, Pekel N, Ozyurtlu F, et al. The relationship between platelet indices and clinical features of coronary artery disease. Kardiol Pol. 2013; 71(11):1129-34. https://doi.org/10.5603/KP.2013.0293 PMid:24297710

40. Ranjani G, Manikandan S, Rohini I, Kalaiselvi S. A study on platelet volume indices in acute coronary syndrome. Int Arch Integr Med IAIM. 2016; 3(38):146-52.

41. Assiri AS, Jamil AM, Mahfouz AA, Mahmoud ZS, Ghallab M. Diagnostic importance of platelet parameters in patients with acute coronary syndrome admitted to a tertiary care hospital in southwest region, Saudi Arabia. J Saudi Hear Assoc. 2012; 24(1):17-21. https://doi.org/10.1016/j.jsha.2011.08.004 PMid:23960663 PMCid:PMC3727553

42. Lupia E, Bosco O, Bergerone S, Dondi AE, Goffi A, Oliaro E, et al. Thrombopoietin Contributes to Enhanced Platelet Activation in Patients With Unstable Angina. J Am Coll Cardiol. 2006; 48(11):2195-203. https://doi.org/10.1016/j.jacc.2006.04.106 PMid:17161245

43. Amraotkar AR, Song DD, Otero D, Trainor PJ, Ismail I, Kothari V, et al. Platelet Count and Mean Platelet Volume at the Time of and after Acute Myocardial Infarction. Clin Appl Thromb. 2017; 23(8):1052-9. https://doi.org/10.1177/1076029616683804 PMid:28294633 PMCid:PMC5572529

44. Loo B van der, Martin JF. A Role for Changes in Platelet Production in the Cause of Acute Coronary Syndromes. Arterioscler Thromb Vasc Biol. 1999; 19:672-9. https://doi.org/10.1161/01.ATV.19.3.672 PMid:10073972

45. Li X, Ji Y, Kang J, Fang N. Association between blood neutrophil-to- lymphocyte ratio and severity of coronary artery disease. Medicine (Baltimore). 2018; 97(39):1-9. https://doi.org/10.1097/MD.0000000000012432 PMid:30278521 PMCid:PMC6181556

46. Meissner J, Irfan A, Twerenbold R, Mueller S, Reiter M, Haaf P, et al. Use of neutrophil count in early diagnosis and risk stratification of AMI. Am J Med. 2011; 124(6):534-42. https://doi.org/10.1016/j.amjmed.2010.10.023 PMid:21507368

47. Jones MM, Somerville C, Feder G, Foster G. Patients ' descriptions of angina symptoms : a qualitative study of primary care patients. 2010; (October 2009):735-41. https://doi.org/10.3399/bjgp10X532378 PMid:20883622 PMCid:PMC2944932

48. Bösner S, Hani A, Keller H, Sönnichsen AC, Karatolios K, Schaefer JR, et al. Accuracy of General Practitioners ' Assessment of Chest Pain Patients for Coronary Heart Disease in Primary Care : Cross-sectional Study with Follow-up. 2010; 243-9. https://doi.org/10.3325//cmj.2010.51.243 PMid:20564768 PMCid:PMC2897083