Usefulness of Immature Granulocytes to Predict High Coronary SYNTAX Score in Acute Coronary Syndrome; a Cross-sectional Study

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Abstract: Introduction: Immature granulocytes (IG) in peripheral blood indicate increased bone marrow activation and inflammation, and SYNTAX score (SS) is an anatomical scoring system based on coronary angiogram. This study, aimed to evaluate the relationship between IG and SS, as a new inflammatory marker in patients with acute coronary syndrome (ACS). Methods: Patients aged >18 years who were diagnosed with ACS in the emergency department were included in this study, which was planned as a cross-sectional study. Patients were divided into two groups of patients with high and low SSs according to coronary angiography results. Demographic and laboratory parameters were compared between the groups. Results: Our study consisted of 78 patients diagnosed with ACS, who met the inclusion criteria. The average age of the study group was 59 years, and 67.9% of the patients were male. 21 patients (26.9%) had high SSs and 57 patients (73.1%) had low SSs. Mean IG% was significantly higher in high SS group compared to low SS group (0.71 ± 0.25 vs 0.44 ± 0.21 mg/dl, p<0.001). IG% can present a high SS with 76.2% sensitivity and 75.4% specificity at a cut-off value of 0.7. Conclusion: IG was significantly higher in ACS patients with high SSs. It seems that IG can be used as a parameter, which is quickly accessible and cheap, in order to predict high SS in ACS patients in daily clinical practice.

Keywords: Inflammation; Acute coronary syndrome; Granulocytes; percutaneous coronary intervention; Emergency Medicine; Atherosclerosis

1. Introduction

Acute coronary syndrome (ACS) is one of the main reasons for admission to the emergency department and hospitalization. ACS is usually characterized by atherosclerotic plaque rupture and complete or incomplete thrombosis of the coronary arteries, which is one of the most significant causes of mortality and morbidity [1, 2]. Many pathophysiological factors influence this atherosclerotic process, and inflammation is one of these factors. Inflammation plays a significant role in initiating atherosclerosis and facilitating its progression.

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disease and making revascularization decisions [8]. Previously, many studies have examined the relationship between WBC, CRP, Neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR) and SS; however, there are no studies evaluating the relationship between IG and SS in the literature. Therefore, this study aimed to evaluate the relationship between IG and SS, as a new inflammatory marker in patients with ACS.

2. Methods

Patients aged >18, who had presented to the emergency department with pain in the chest and been admitted to the department of cardiology with a diagnosis of ACS (unstable angina pectoris/myocardial infarction without ST-segment elevation (NSTEMI)/myocardial infarction with ST-segment elevation (STEMI)), were included in this study, which was planned as a prospective cross-sectional study and performed during the period between December 01, 2019, and February 01, 2020. The diagnosis of ACS was defined as having electrocardiographic (ECG) change and/or increase of cardiac markers along with chest pain, which was assumed to be typical chest pain. In compliance with American College of Cardiology and European Society of Cardiology (ACC/ESC) criteria, STEMI was defined as ST-segment elevation in ECG and increase in all the derivations by $\Delta E \geq 0.1mV$ in two consecutive derivations. Necessary approval was received from the Clinical Research Ethics Committee for the study (No: IRB-2019-355). Written informed consent was obtained from all the patients, who agreed to participate in the study.

2.1. Participants

Exclusion Criteria were determined as being <18 years old, being pregnant, having a myeloproliferative disease (it may change hematological parameters), malignancy, having trauma or surgery history within the past 1 week, arrhythmia causing hemodynamic instability, heart failure, inflammatory bowel disease, granulocyte-colony stimulating factor, and using immunosuppressive agents or steroids.

2.2. Data gathering

ACS patients’ age, gender, history of hyperlipidemia, history of hypertension (HT), history of diabetes mellitus (DM), family history, drugs, systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rates (HR) (pulse/min) were recorded. The minimum sample size with a two-sided alpha value of 5%, a statistical power of 80% was estimated to be 50 patients. We planned to enrol a total of 80 patients, taking into account the 20% expected failure rate.

2.3. SYNTAX Score and Angiographic Analysis

In the study, coronary angiography (CAG) was carried out for all the patients using the Judkins technique. In order to grade the stenosis of the coronary vessels, stenoses over 50% in vessels with a size of $\geq 1.5mm$ were taken into consideration. SS was prospectively calculated by two experienced cardiologists using an algorithm based on the diagnostic angiogram. The final score was calculated using individual lesion scores by analysts who were blind to operational data and clinical outcomes. Items such as whether the stenosis was total, the level and the size of the stenosis, presence of collateral flow, presence of bifurcation or trifurcation lesion, severe folds, and severe calcification were evaluated [9, 10].

2.4. Blood Samples

Venous blood samples of the patients were taken within the first hour of admission to the emergency department before the primary CAG. In the samples taken during admission, WBC, neutrophil count, lymphocyte count, and IG% IG count (IGC) were measured using an automated blood analysis system (CoulterÂ® LH 780 Hematologic Analyzer, Beckman Coulter Inc. Brea, USA). Absolute cell numbers were used in the analyses. CRP, haemoglobin, glucose values, and cardiac Troponin T levels, which were measured during the admission, were recorded. The levels of total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides were recorded during admission to the coronary intensive care. The left ventricular ejection fraction (LVEF) of the patients was measured using Vivid S5 (GE Healthcare, Inc. Chicago, IL, USA) device connected to 2-4 MHz transducer via Simpson's method according to the recommendations of the American Society of Echocardiography [11]. According to CAG results, patients with high SSs ($>22$) and patients with low SSs ($\leq 22$) were separated into two groups, and all the parameters were compared.

2.5. Statistical Analysis

Statistical analyses were conducted using SPSS 21.0 package program (SPSS Inc., Chicago, IL). Continuous variables were expressed as mean ± standard deviation, and categorical variables were given as number and percentage. An independent t-test was used for comparing the distribution of the parameters with normal distribution, and the Mann-Whitney U test was applied for those that did not have a normal distribution. In categorical data, the evaluation was made using the chi-square test. Logistic regression was conducted for factors associated with high SS. The optimum cut off value of IG in predicting high SS was assessed through Receiver operating characteristic (ROC) analysis. Statistical significance was defined as a p-value less than 0.05.
Table 1: Comparing the baseline characteristics of patients with high (> 22) and low (≤ 22) SYNTAX score

| Variables                        | SYNTAX Score | P     |
|----------------------------------|--------------|-------|
|                                  | High (n=21)  | Low (n =57)  |
| **Age (years)**                  |              |       |
| Mean ± SD                        | 66.00 ± 16.67| 57.57 ± 14.15| 0.057 |
| **Gender n (%)**                 |              |       |
| Male                             | 15 (68.2)    | 38 (66.6) | 0.789 |
| Female                           | 6 (31.8)     | 19 (33.4) |       |
| **Underlying comorbidity**       |              |       |
| Yes                              | 25.55        | 34.19  | 13.62 |
| No                               | 8.71         | 11.49  | 5.84  |
| **Vital signs**                  |              |       |
| SBP, mm Hg                       | 131.57 ± 14.92| 144.14 ± 27.01| 0.071 |
| DBP, mm Hg                       | 83.19 ± 8.04 | 91.47 ± 15.26| 0.006 |
| Heart rate, beats/min            | 83.07 ± 15.26| 84.33 ± 15.26| 0.283 |
| Ejection fraction, %             | 45.95 ± 12.57| 55.7 ± 12.93 | 0.002 |
| SYNTAX score                     | 27.78 ± 4.79 | 7.38 ± 6.24 | <0.001|
| **Previous history**             |              |       |
| Current smoker                   | 12 (57.1)    | 29 (50.9) | 0.799 |
| Hypertension                     | 11 (52.4)    | 28 (49.1) | 0.500 |
| Diabetes mellitus                | 7 (33.3)     | 22 (38.6) | 0.794 |
| Dyslipidemia                     | 9 (42.9)     | 21 (36.8) | 0.409 |
| History of CAD                   | 8 (38.1)     | 6 (10.5)  | 0.009 |
| **Laboratory findings**          |              |       |
| WBC count (×10³/mm³)             | 13.03 ± 3.05 | 10.68 ± 4.15 | 0.003 |
| Neutrophil, (×10³/mm³)           | 8.77 ± 2.84  | 6.84 ± 3.4 | 0.005 |
| Lymphocyte, (×10³/mm³)           | 3.67 ± 3.20  | 2.97 ± 2.41 | 0.318 |
| NLR                              | 4.09 ± 3.91  | 3.14 ± 2.71 | 0.367 |
| PLR                              | 112.14 ± 59.08| 120.51 ± 57.22| 0.499 |
| Hemoglobin, mg/dL                | 13.89 ± 1.97 | 13.55 ± 1.97 | 0.355 |
| Glucose (mg/dl)                  | 163.33 ± 71.52| 140.36 ± 69.22| 0.017 |
| IGC(×10³/mm³)                    | 0.08 ± 0.09  | 0.07 ± 0.01 | 0.004 |
| IG%                              | 0.71 ± 0.25  | 0.44 ± 0.21 | <0.001|
| CRP (mg/dL)                      | 35.37 ± 17.12| 3.92 ± 0.54  | 0.021 |
| Troponin T (ng L)                | 502.00 ± 157.07| 426.08 ± 157.74| 0.012 |
| **Lipid profiles (mg/dL)**       |              |       |
| Triglycerides                    | 162.72 ± 92.30| 212.33 ± 134.39| 0.188 |
| Total cholesterol                | 211.27 ± 65.80| 220.64 ± 56.83| 0.304 |
| High-density lipoprotein         | 44.00 ± 9.01 | 46.28 ± 10.97 | 0.354 |
| Low-density lipoprotein          | 135.50 ± 57.34| 134.66 ± 45.95 | 0.650 |
| **Previous medication n (%)**    |              |       |
| RAS blocker                      | 2 (9.5)      | 5 (8.8) | 0.611 |
| ACE-I                            | 2 (9.5)      | 14 (24.6) | 0.210 |
| Beta blocker                     | 3 (14.3)     | 15 (26.3) | 0.368 |
| Diuretic                         | 4 (19)       | 9 (15.8) | 0.740 |
| Calcium channel blocker          | 6 (28.6)     | 8 (14)  | 0.184 |
| Statin                           | 10 (47.6)    | 22 (38.6) | 0.605 |
| Antiaggregant                    | 5 (23.8)     | 12 (21.1) | 0.766 |
| Oral antidiabetic drug           | 4 (19)       | 16 (28.1) | 0.562 |
| **Mortality**                    |              |       |
| Number (%)                       | 3 (14.3)     | 0 (0)  | 0.017 |

Data are presented as mean ± standard deviation or frequency (%). SYNTAX score: Synergy between percutaneous coronary intervention with taxus and cardiac surgery; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; CAD: Coronary artery disease; WBC: white blood cell; NLR: neutrophil lymphocyte ratio; PLR: platelet lymphocyte ratio; IGC: Immature granulocyte count; IG%: Immature granulocyte percentage; CRP: C-reactive protein; RAS: Renin-angiotensin system; ACE-I: Angiotensin converting enzyme inhibitor.

3. Results

Our study consisted of 78 patients diagnosed with ACS, who met the inclusion criteria. The average age of the study group was 59 ± 15.21 years, and 67.9% of the patients were male. 21 patients (26.9%) had high SSs (>22) and 57 pa-
### Table 2: Comparing the baseline characteristics of patients with high (> 0.6) and low (≤ 0.6) immature granulocyte

| Variables                        | Immature granulocyte | P     |
|----------------------------------|-----------------------|-------|
|                                  | High (n=22)           | Low (n=56) |
| **Age (years)**                  |                       |       |
| Mean ± SD                        | 61.13 ± 20.28         | 59.33 ± 12.92 | 0.807 |
| **Gender n (%)**                 |                       |       |
| Male                             | 15 (68.2)             | 38 (66.6) | 0.601 |
| Female                           | 6 (31.8)              | 19 (33.4) |
| **Vital signs**                  |                       |       |
| SBP, mm Hg                       | 129.45 ± 16.31        | 145.19 ± 26.37 | 0.07 |
| DBP, mm Hg                       | 83.54 ± 9.18          | 91.48 ± 15.15 | 0.024 |
| Heart rate, beats/min            | 84.81 ± 18.21         | 82.85 ± 8.92 | 0.367 |
| Ejection fraction, %             | 50.90 ± 11.51         | 54.01 ± 10.51 | 0.234 |
| SYNTAX score                     | 17.21 ± 14.80         | 10.97 ± 8.31 | 0.024 |
| **Previous history**             |                       |       |
| Current smoker                   | 13 (59.1)             | 28 (50) | 0.615 |
| Hypertension                     | 10 (45.5)             | 29 (51.8) | 0.802 |
| Diabetes mellitus                | 7 (31.8)              | 22 (39.3) | 0.610 |
| Dyslipidemia                     | 5 (22.7)              | 25 (44.6) | 0.120 |
| History of CAD                   | 5 (22.7)              | 9 (16.1) | 0.522 |
| **Laboratory findings**          |                       |       |
| WBC count (×10^3/mm^3)           | 12.88 ± 3.92          | 10.70 ± 3.90 | 0.032 |
| Neutrophil (×10^3/mm^3)          | 9.26 ± 3.78           | 6.61 ± 2.87 | 0.003 |
| Lymphocyte (×10^3/mm^3)          | 3.70 ± 0.82           | 2.97 ± 0.96 | 0.526 |
| NLR                              | 4.22 ± 4.11           | 3.06 ± 2.73 | 0.111 |
| PLR                              | 112.78 ± 61.46        | 119.95 ± 56.66 | 0.560 |
| Hemoglobin, mg/dL                | 12.95 ± 2.25          | 13.89 ± 1.78 | 0.131 |
| Glucose (mg/dL)                  | 114.38 ± 63.50        | 148.07 ± 73.39 | 0.556 |
| CRP (mg/dL)                      | 24.71 ± 14.98         | 7.35 ± 3.01 | 0.693 |
| Troponin T (ng L)                | 519.66 ± 156.17       | 424.96 ± 160.55 | 0.011 |
| **Lipid profiles (mg/dL)**       |                       |       |
| Triglycerides                    | 175.11 ± 107.80       | 208.35 ± 132.05 | 0.381 |
| Total cholesterol                | 189.22 ± 41.90        | 227.73 ± 60.65 | 0.012 |
| High-density lipoprotein         | 42.38 ± 8.90          | 46.80 ± 10.84 | 0.011 |
| Low-density lipoprotein          | 118.77 ± 31.18        | 140.03 ± 52.11 | 0.08 |
| **Previous medication n (%)**    |                       |       |
| RAS blocker                      | 2 (9.1)               | 5 (8.9) | 0.561 |
| ACE-I                            | 3 (13.6)              | 13 (23.2) | 0.535 |
| Beta blocker                     | 4 (18.2)              | 14 (25) | 0.766 |
| Diuretic                         | 4 (18.2)              | 9 (16.1) | 1.000 |
| Calcium channel blocker          | 5 (22.7)              | 9 (16.1) | 0.522 |
| Statin                           | 6 (27.3)              | 26 (46.4) | 0.135 |
| Antiaggregant                    | 5 (22.7)              | 12 (21.4) | 1.000 |
| Oral antidiabetic drug           | 2 (9.1)               | 18 (32.1) | 0.45 |
| **Mortality**                    |                       |       |
| Number (%)                       | 3 (13.6)              | 0 (0) | 0.02 |

Data are presented as mean ± standard deviation (SD) or frequency (%). SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; SYNTAX score: Synergy between percutaneous coronary intervention with taxing and cardiac surgery; WBC: white blood cell; NLR: neutrophil lymphocyte ratio; PLR: platelet lymphocyte ratio; IGC: Immature granulocyte count; CAD: Coronary artery disease; WBC: white blood cell; NLR: neutrophil lymphocyte ratio; PLR: platelet lymphocyte ratio; IG%: Immature granulocyte percentage; CRP: C-reactive protein; RAS: Renin–angiotensin system; ACE-I: Angiotensin converting enzyme inhibitor.

Patients (73.1%) had low SSs (≤22). There was no statistical difference between the groups in terms of age and gender (p>0.05). Patients with high SSs had significantly lower DBP and LVEF (p=0.006, p=0.002, respectively). Patients with high SSs had significantly higher CAD history comorbidity (p=0.009). Mean WBC, neutrophil, glucose, IGC, and CRP and troponin T levels were significantly higher in patients with high SSs. The mean IG% was significantly higher in the high SYNTAX score group compared to the low SYNTAX score group (0.71±0.25 vs 0.44±0.21mg/dl, p<0.001) (Figure 1). Be-
Table 3: Screening performance characteristics of immature granulocyte percentage in predicting the SYNTAX (synergy between percutaneous coronary intervention with taxus and cardiac surgery) score in 0.7 cut off point

| Characters | Value (95% CI) | Characters | Value (95% CI) |
|------------|---------------|------------|---------------|
| Sensitivity | 76.2 (67.21-84.67) | NPV | 76.5 (69.15 – 82.59) |
| Specificity | 75.4 (66.11-83.81) | PLR | 3.17 (2.2 - 4.57) |
| PPV | 76 (68.74 - 82.02) | NLR | 0.31 (0.21 –0.45) |

Data are presented as mean ± standard deviation (SD) or frequency (%). SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; Confidence interval (CI). PPV: Positive predictive value; NPV: Negative predictive value; PLR: Positive likelihood ratio; NLR: Negative likelihood ratio.

Figure 1: Comparison of immature granulocyte levels between low and high syntax score groups.

Figure 2: Receiver operating characteristic (ROC) curve of immature granulocyte percentage for predicting high syntax (synergy between percutaneous coronary intervention with taxus and cardiac surgery) score (p < 0.001).

4. Discussion

To the best of our knowledge, this is the first study in the literature evaluating the relationship between IG and SS in ACS patients. The main findings of this study suggested that SS was independently correlated with IG%.

SS is a scoring system used to evaluate the complexity and prevalence of coronary artery disease based on CAG. It is commonly used by many physicians to specify the optimal cardiovascular treatment strategy [12, 13]. Studies have shown that patients with high SSs may have poorer cardiovascular outcomes, and the score may be an independent predictor for percutaneous interventions. Moreover, high-risk patients can be identified using this scoring system, and appropriate treatment methods can be selected [14, 15].

Inflammation is critically important for the initiation and progression of coronary atherosclerosis. Inflammation affects many conditions, such as endothelial dysfunction, leukocyte recruitment, and platelet activation during the atherosclerosis process [16]. Recently, it has been revealed that many inflammatory markers, such as CRP, platelet/lymphocyte ratio (PLR) and neutrophil/lymphocyte ratio (NLR), WBC, TNF-α, and cytokines can be independent risk factors for atherosclerosis. The increase in these inflammatory markers has been shown to correlate with the degree of mortality.
and severity of CAD [14, 17]. These inflammatory markers have been evaluated as prognostic markers for many cardiovascular diseases, such as coronary artery ectasia, stable CAD, and myocardial infarction [18, 19]. 840 patients, who underwent coronary angiography for CAD evaluation, were included in a recent study by Sahin et al. In this study, NLR was shown to be significantly associated with CAD severity in patients with STEMI, and they also reported that NLR is an independent marker for SS [2]. In a recent study by Altun et al., Troponin T and NLR were significantly associated with the angiographic severity of ACS evaluated with SS [16]. In a study conducted by Kundi et al., it was reported that the ratio of the Monocyte count to HDL could be used as a parameter that would be quickly accessible and cheap in order to predict high SS and it may be used in daily practice as well [13]. In a study conducted by Sivri et al. on 175 patients, the WBC/mean platelet volume ratio was shown to be correlated with increased SS, and thus, short- and long-term mortality [1]. IG in peripheral blood indicates increased bone marrow activation, and it can be easily measured in automated blood analyzers. It has been shown in studies that the presence of immature granulocytes in peripheral blood, which is not normally observed in healthy people, can indicate bone marrow activation and serious infection [20, 21]. Recent studies suggest that IG is correlated with prevalent intravascular coagulation and mortality in critical patients with suspected sepsis [22]. Park et al. reported that high IG levels are a good diagnostic sign for severe sepsis and septic shock within the first 24 hours after admission to the intensive care unit [23]. Mathews et al. discovered that the increase in IG% was significant in appendicitis complications in the pediatric age group and only compared it with an increased CRP level and left shift [24]. In this study, we showed that patients with high IG levels had higher SSs. Besides, mortality was higher at high IG levels.

6. Conclusion

IG was significantly higher in ACS patients with high Syntax scores. It seems that IG can be used as a parameter, which is quickly accessible and cheap, in order to predict the high SYNTAX score in ACS patients in daily clinical practice.

7. Declarations

7.1. Acknowledgements

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7.2. Author contribution

All the authors have a substantial contribution in the study design, data interpretation and writing and reviewing the manuscript.

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7.4. Ethical approval

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7.5. Conflict of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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