

The Association of Neutrophil to Lymphocyte Ratio and Other Complete Blood Count Parameters with Global Registry of Acute Coronary Events Risk Score in Patients with Non-ST Segment Elevation – Acute Coronary Syndrome: A Single-Center Study

Ali Safaa Abduljabbar^{1*} , Muataz Fawzi Hussein¹

Received: 15 May 2024

Published: 23 Sep 2024

Abstract

Background: The involvement of inflammation in the start and advancement of atherosclerotic plaques in acute coronary syndrome has been clarified. White blood cell count and its differential are key inflammatory markers in cardiovascular disease, with the neutrophil-to-lymphocyte ratio (NLR) emerging as a marker of inflammation and a predictor of mortality in patients with acute coronary syndrome. The study aims to investigate the utility of neutrophil to lymphocyte ratio and other complete blood count parameters as a risk stratification tool and independent predictor of Global Registry for Acute Coronary Events (GRACE) risk score in Non-ST segment elevation acute coronary syndrome (NSTEMI-ACS).

Methods: This was a cross-sectional retrospective single-center study conducted in Baghdad Teaching Hospital. A total of 110 patients diagnosed with NSTEMI-ACS were enrolled in this study. Demographic data and components that determine the GRACE risk score were recorded at admission to the emergency department alongside risk factors for coronary artery disease. Venous blood for relevant laboratory analysis was obtained from all patients. Patients were categorized into three risk groups according to the GRACE risk score. The study results were statistically analyzed using the one-way Analysis of Variance (ANOVA) test and the Kruskal Wallis test. Spearman test and multiple linear regression analysis were used for correlation and identification of independent predictors respectively.

Results: The mean age of patients was 59.4 years with a standard deviation of 21.1 years. The majority of them were males (61.8%). The predominant portion (102) had non-ST elevation myocardial infarction (NSTEMI). The mean total white blood cell count, absolute neutrophil count, absolute lymphocyte count, and neutrophil to lymphocyte ratio of the patients were $11.1 \times 10^3/\text{ml}$, $8.7 \times 10^3/\text{ml}$, $1.7 \times 10^3/\text{ml}$, and 5.9 respectively. The mean admission left ventricle ejection fraction (LV EF) of the patients was 52.5 % with a standard deviation of 9.6 %. There is a significant positive correlation between NLR and GRACE risk score ($r = 0.339$, $P < 0.001$) and a statistically significant negative correlation between NLR and LV EF ($r = -0.385$, $P = 0.005$).

Conclusion: This study showed a statistically significant association and positive correlation between neutrophil-to-lymphocyte ratio (NLR) and Global Registry of Acute Coronary Events (GRACE) risk score, so neutrophil-to-lymphocyte ratio (NLR) is a valuable marker for risk stratification and prognosis in NSTEMI-ACS patients, serving as an independent predictor of the GRACE risk score.

Keywords: Acute Coronary Syndrome, Neutrophil to Lymphocyte Ratio, Risk Score, Inflammation

Conflicts of Interest: None declared

Funding: None

***This work has been published under CC BY-NC-SA 4.0 license.**

Copyright© Iran University of Medical Sciences

Cite this article as: Abduljabbar AS, Hussein MF. The Association of Neutrophil to Lymphocyte Ratio and Other Complete Blood Count Parameters with Global Registry of Acute Coronary Events Risk Score in Patients with Non-ST Segment Elevation – Acute Coronary Syndrome: A Single-Center

Corresponding author: Dr Ali Safaa Abduljabbar, ali.s.543@comed.uobaghdad.edu.iq

¹ College of Medicine, University of Baghdad, Baghdad, Iraq

↑What is “already known” in this topic:

The neutrophils are regarded as an indicator of ongoing inflammation, while lymphocytes are considered as a marker of regulatory pathways. The relationship between neutrophil-to-lymphocyte ratio (NLR) and STEMI has been identified in multiple studies but what is known about its relationship with NSTEMI-ACS is less than expected.

→What this article adds:

The significance of neutrophil-to-lymphocyte ratio (NLR) in enhancing risk stratification and prognostication for NSTEMI-ACS patients, advising for its inclusion in routine clinical assessments to improve patient outcomes. NLR and left ventricle ejection fraction (LV EF) might be independent predictors of the GRACE risk score and, consequently, independent predictors of admission to 6-month mortality.

Introduction

Atherosclerosis is the main reason for cardiovascular disease, which is responsible for the majority of deaths globally (1). Inflammation is a critical factor in initiating and advancing atherosclerosis (2). The formation of plaque and subsequent rupture is significantly influenced by the inflammatory process at the atherosclerotic lesion (3). The combination of this and the formation of a thrombus leads to the blockage of the impacted coronary artery, which is then followed by the death of the supplied myocardial tissue. These pathological processes are clinically known as acute coronary syndrome (ACS). This term encompasses ST-segment elevation myocardial infarction (STEMI), non-STEMI, and unstable angina pectoris (4). The latter two are collectively referred to as Non-ST segment elevation ACS.

Neutrophils are identified as a marker of ongoing inflammation, and lymphocytes as a marker of regulatory pathways. The neutrophil-to-lymphocyte ratio (NLR) as an indicator of systemic inflammation is associated with poor prognosis in numerous cardiovascular diseases, including acute coronary syndrome. Recent evidence highlights that high NLR values are significantly and independently associated with a higher risk of complications and mortality post-acute myocardial infarction (MI) (5-12).

The clinical presentation of NSTEMI-ACS has been well explained in 2020 European Society of Cardiology (ESC) Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation which is defined as patients with acute chest discomfort but no persistent ST-segment elevation exhibit ECG changes that may include transient ST-segment elevation, persistent or transient ST-segment depression, T-

wave inversion, flat T waves, or pseudo-normalization of T waves; or a normal ECG (13).

Several prognostic models have been created to predict the future likelihood of all-cause mortality or the combined risk of all-cause mortality or MI. These models have been translated into clinical risk scores, with the GRACE risk score demonstrating the most superior discriminatory performance (14-16).

The GRACE risk score has been shown to predict clinical outcomes, offering superior risk assessment for death or myocardial infarction compared to subjective physician assessment (17, 18).

Objective risk assessment using the GRACE risk score can help identify patients with NSTEMI-ACS who would benefit the most from risk-determined care interventions (19, 20).

In essence, all GRACE risk score models calculated at presentation to the hospital use eight variables: age, systolic blood pressure (SBP), pulse rate, and serum creatinine; cardiac arrest at admission, elevated cardiac biomarkers, and ST-segment deviation; and Killip class at presentation for risk prediction. GRACE risk score predicts the probability of in-hospital death as well as the probability of death from admission up to 6 months. GRACE risk score parameters and their values are illustrated in Figure 1 (21).

Based on this score, patients with NSTEMI-ACS are stratified into three risk groups: Low risk (<109), intermediate risk (109-140), and high risk (>140). Provided that the patient has no indication for immediate invasive strategy (refractory angina, recurrent angina, ventricular arrhythmia, signs or symptoms of heart failure, or hemodynamic instability) within two hours, the GRACE score can be used to

1. Find points for each predictive factor:

Killip Class	Points	SBP, mm Hg	Points	Heart Rate, Beats/min	Points	Age, y	Points	Creatinine Level, mg/dL	Points
I	0	≤80	58	≤50	0	≤30	0	0-0.39	1
II	20	80-99	53	50-69	3	30-39	8	0.40-0.79	4
III	39	100-119	43	70-89	9	40-49	25	0.80-1.19	7
IV	59	120-139	34	90-109	15	50-59	41	1.20-1.59	10
		140-159	24	110-149	24	60-69	58	1.60-1.99	13
		160-199	10	150-199	38	70-79	75	2.00-3.99	21
		≥200	0	≥200	46	80-89	91	>4.0	28
						≥90	100		

Other Risk Factors	Points
Cardiac Arrest at Admission	39
ST-Segment Deviation	28
Elevated Cardiac Enzyme Levels	14

2. Sum points for all predictive factors:

Killip Class	+	SBP	+	Heart Rate	+	Age	+	Creatinine Level	+	Cardiac Arrest at Admission	+	ST-Segment Deviation	+	Elevated Cardiac Enzyme Levels	=	Total Points
--------------	---	-----	---	------------	---	-----	---	------------------	---	-----------------------------	---	----------------------	---	--------------------------------	---	--------------

3. Look up risk corresponding to total points:

Total Points	≤60	70	80	90	100	110	120	130	140	150	160	170	180	190	200	210	220	230	240	≥250
Probability of In-Hospital Death, %	≤0.2	0.3	0.4	0.6	0.8	1.1	1.6	2.1	2.9	3.9	5.4	7.3	9.8	13	18	23	29	36	44	≥52

Figure 1. GRACE score for risk assessment (21)

Table 1. Treatment strategy of NSTE-ACS according to GRACE risk score (22)

GRACE score	Treatment strategy
GRACE score > 140	Early invasive strategy (within 24 hours)
GRACE score 109-140	Delayed invasive strategy (25-72 hours)
GRACE score < 109	Ischemia-guided strategy using optimal medical therapy

guide the choice of invasive strategy or ischemia –guided strategy using optimal medical therapy as illustrated in [Table 1](#) (22).

The statistical link between NLR and STEMI has been demonstrated in numerous studies, although there is limited data on the association between NLR levels and the GRACE risk score in patients with NSTE-ACS.

Given the easy access to measuring complete blood count in routine blood tests, the study's aim was to examine the association of the concomitant hematological indices such as neutrophil to lymphocyte ratio and mean platelet volume (which could provide cost-effective risk stratification tools) with GRACE risk score in patients with NSTE-ACS.

Methods

Study design and settings

This was a cross-sectional retrospective single-center study conducted at Baghdad Teaching Hospital – Coronary Care Unit (CCU). 110 patients enrolled in the study who were admitted and managed at the CCU during the period from January 2022 to September 2022. These patients met the criteria of NSTE-ACS created by the European Society of Cardiology and the American College of Cardiology.

Inclusion criteria

All adult patients diagnosed with NSTE-ACS according to the ESC and American Heart Association AHA: Patients with elevated troponin level (myocardial necrosis) have Non-ST segment elevation myocardial infarction (NSTEMI) while those possessing normal troponin level (myocardial ischemia without necrosis) have unstable angina (UA).

Exclusion criteria

1. Patients with clinical evidence of active infection.
2. Patients with positive polymerase chain reaction (PCR) for COVID-19 (confirmed) or who have clinical and radiological evidence of COVID-19 (suspected).
3. Patients with ST elevation MI, stable angina, acute myocarditis, or acute pericarditis.
4. Patients with leukemia, lymphoma, solid tumors, or benign hematological diseases that affect white blood cell (WBC) count like aplastic anemia or megaloblastic anemia.
5. Patients with a known history of active systemic inflammatory conditions, chronic liver disease, heart failure, or renal failure.
6. Patients on steroids or marrow suppressive medications.
7. Patients who refuse to participate in the study.

Ethical consideration

Once the aim of the study was explained to each patient,

verbal consent was obtained before data collection. The patients also signed a consent form following the Declaration of Helsinki, which is included in the hospital admission documents. The data confidentiality was ensured and the patients were reassured that data would only be utilized for research purposes.

Data collection

Demographic data and components that determine the GRACE risk score (Age, Heart rate, Systolic blood pressure, Serum creatinine, cardiac arrest at admission, ST segment deviation on Electrocardiograph (ECG), Troponin level, and Killip class of heart failure) were recorded at admission to the emergency department. The GRACE risk score and the estimated admission to 6-month mortality were obtained by MDCalc application.

Risk factors for coronary artery disease (diabetes mellitus, dyslipidemia, hypertension, and smoking) were recorded by direct interview with the patient in the coronary care unit. Electrocardiography was recorded at the emergency department.

Venous blood was obtained from all patients diagnosed with Non-ST segment elevation acute coronary syndrome on admission to the emergency department. Complete blood count, serum troponin, and serum creatinine were analyzed by an automated blood counter in the emergency department. Lipid profile, HbA1C, and fasting blood glucose were obtained from patients at the coronary care unit.

Laboratory investigations were then retrospectively collected from patients' admission files in the coronary care unit, and Echocardiography to estimate LV EF was done by the cardiologist on admission to the coronary care unit. GRACE score was calculated for each patient and three risk groups were made according to this score.

The presence of hypertension was determined by a Systolic Blood Pressure (SBP) of 140 mm Hg or higher and/or a Diastolic Blood Pressure (DBP) of 90 mm Hg or higher, in addition to receiving antihypertensive treatment. The definition of diabetes mellitus included having a Fasting Blood Glucose (FBG) level of 126 mg/dl or higher, current use of a healthy diet or medication to control blood glucose, or an HbA1C level of 6.5% or higher. Hyperlipidemia was characterized by having Low-density lipoprotein (LDL) levels exceeding 130 mg/dl, total cholesterol levels surpassing 200 mg/dl, triglyceride levels exceeding 200 mg/dl, or current use of antihyperlipidemic medications. Smoking was considered to be positive if active smoking in the last 6 months.

Statistical analysis

Analysis and presentation of data using statistical analysis with Statistical Product and Service Solution (SPSS) version 23.0 for Windows software. The quantitative data

were presented as mean \pm standard deviation while the binomial ones were presented as frequency and percentages. Analysis of data was done after testing for normal distribution. The study results were statistically analyzed using the one-way Analysis of Variance (ANOVA) test if the data were normally distributed and the Kruskal Wallis test if the data were not normally distributed. Spearman test was employed for correlation analysis between NLR and GRACE risk score and between NLR and LV EF. Multiple linear regression analysis was done on five important parameters to determine independent predictors of the GRACE risk score. P value ≤ 0.05 was deemed to be statistically significant.

Results

The study population consisted of 110 patients diagnosed with NSTEMI-ACS. The patients were divided into 3 groups according to the GRACE risk score: Low risk (<109), intermediate risk (109-140), and high risk (>140) 44 (40%) were included in the low-risk group, 36 (33%) were included in the intermediate-risk group, and 30 (27%) were included in the high-risk group. Only 8 (7.2%) had unstable angina, while the majority ($n=102$, 92.8%) had NSTEMI.

Demographic characteristics and risk factors of patients

The mean age of patients was 59.4 ± 12.1 years. About

61.8% of the patients were male. In all, 53 (48%) patients were hypertensive, 50 (45.5%) patients were diabetic, 38 (34.5%) patients had dyslipidemia, and 45 (41%) patients were smokers.

Patients who have hypertension and dyslipidemia were more likely to have intermediate and high GRACE risk scores, while those who are active smokers were more likely to have low and intermediate GRACE risk scores.

Demographic characteristics and risk factors of patients according to GRACE risk score groups are demonstrated in Table 2.

Clinical characteristics and Left Ventricle Ejection Fraction (LV EF) of the patients

Patients with low SBP were more likely to have high GRACE risk scores. 12 (10.9%) of the patients developed cardiac arrest in the form of pulseless ventricular tachycardia or ventricular fibrillation at admission. All of them received a synchronized DC shock and survived. 53 (48%) of the patients had no signs of heart failure (Killip class 1), 41 (37%) of the patients had fine basal crackles (Killip class 2), 12 (11%) of the patients had frank pulmonary edema (Killip class 3), and 4 (4%) of the patients had cardiogenic shock (Killip class 4). All patients who had cardiogenic shock were in the high-risk group.

Patients who had reduced LV EF were more likely to

Table 2. Demographics and risk factors of the patients

Variable	Total (N=110) X \pm SD	Low risk (N=44) X \pm SD	Intermediate risk (N=36) X \pm SD	High risk (N=30) X \pm SD	P value
Age, years	59.5 \pm 12.1	51.6 \pm 11.1	61.4 \pm 8.9	68.6 \pm 9.4	<0.001
Male, n (%)	68 (61.8%)	28 (64%)	24 (66.7%)	16 (53.3%)	0.710
HTN, n (%)	53 (48%)	14 (31.8%)	19 (53%)	20 (66.7%)	0.027
DM, n (%)	50 (45.5%)	19 (43%)	14 (38.9%)	17 (57%)	0.379
Dyslipidemia, n (%)	38 (34.5%)	8 (18.2%)	14 (38.9%)	16 (53.3%)	0.028
Smokers, n (%)	45 (41%)	27 (61%)	13 (36%)	5 (17%)	0.006
Estimated admission to 6 month mortality, %	12.1 \pm 14.2	2.8 \pm 1.2	9.9 \pm 3.1	28.4 \pm 18.5	

HTN; Hypertension, DM: Diabetes Mellitus

Table 3. Clinical characteristics and LV EF of the patients

Variable	Total (N=110) X \pm SD	Low risk (N=44) X \pm SD	Intermediate risk (N=36) X \pm SD	High risk (N=30) X \pm SD	P value
SBP, mmHg	125.7 \pm 27.8	141.2 \pm 29.5	121.4 \pm 16.9	109.3 \pm 24.8	< 0.001
Cardiac arrest, n (%)	12 (10.9%)		4 (11.1%)	8 (26.7%)	
Killip 1, n (%)	53 (48%)	34 (77%)	17 (47%)	2 (7%)	
Killip 2, n (%)	41 (37%)	9 (21%)	16 (44%)	16 (53%)	
Killip 3, n (%)	12 (11%)	1 (2%)	3 (8%)	8 (27%)	
Killip 4, n (%)	4 (4%)			4 (13%)	
LV EF, %	52.5 \pm 9.6	57.6 \pm 6.4	54 \pm 6.2	43.2 \pm 10.2	< 0.001

SBP: Systolic Blood Pressure, LV EF: Left Ventricle Ejection Fraction

Table 4. Laboratory parameters of the patients

Variable	Total (N=110) X \pm SD	Low risk (N=44) X \pm SD	Intermediate risk (N=36) X \pm SD	High risk (N=30) X \pm SD	P value
WBC, cells $\times 10^3$ /ml	11.1 \pm 4.1	10.2 \pm 3.2	11.4 \pm 4.9	12.1 \pm 4.0	0.126
ANC, cells $\times 10^3$ /ml	8.7 \pm 4.0	7.6 \pm 2.9	9.1 \pm 4.9	9.9 \pm 3.8	0.036
ALC, cells $\times 10^3$ /ml	1.7 \pm 0.7	1.9 \pm 0.7	1.8 \pm 0.7	1.5 \pm 0.8	0.074
NLR	5.9 \pm 3.4	4.4 \pm 2.0	6.0 \pm 3.8	7.9 \pm 3.8	<0.001
MPV, fL	9.5 \pm 0.8	9.4 \pm 0.7	9.6 \pm 0.7	9.7 \pm 1.1	0.230
Troponin I, μ g/L	0.95 \pm 0.89	0.91 \pm 0.89	0.99 \pm 0.89	0.95 \pm 0.9	0.738
Creatinine, mg/dL	1.0 \pm 0.4	0.8 \pm 0.2	1 \pm 0.3	1.3 \pm 0.5	< 0.001

WBC: White blood cells, ANC: Absolute neutrophil count, ALC: Absolute lymphocyte count, MPV: Mean platelet volume

have a high GRACE risk score.

The systolic blood pressure, development of cardiac arrest, cardiac function classification (Killip class), and admission LV EF according to GRACE risk score groups are demonstrated in Table 3.

Laboratory parameters of the patients

Patients who had high absolute neutrophil count (ANC) and neutrophil to lymphocyte ratio (NLR) were more likely to have intermediate and high GRACE risk scores. Patients who had high serum creatinine were more likely to have high GRACE risk scores.

The laboratory parameters according to the GRACE risk score group are demonstrated in Table 4.

Correlation analysis

In this cross-sectional retrospective study, the Spearman correlation test was done to analyze the correlation between NLR and GRACE risk score. The result showed that there is a significant positive correlation between NLR and GRACE risk score ($r = 0.339$, $P < 0.001$), as shown in Figure 2.

Spearman correlation test was done again to analyze the correlation between NLR and LV EF. The result showed that there is a statistically significant negative correlation between NLR and LV EF ($r = -0.385$, $P = 0.005$), as shown in Figure 3.

Multiple analysis

Multiple linear regression analysis was conducted to identify independent predictors of GRACE risk score. It revealed that age, NLR, and LV EF were independent predictors of GRACE risk score. Aging ($b = 1.8708$, $P < 0.001$), higher NLR values ($b = 1.4955$, $p\text{-value} = 0.0092$), and LV

EF ($b = -1.5968$, $P < 0.001$) were significantly associated with GRACE risk score as shown in Table 5.

Discussion

In this study, the mean patient's age was 59.4 ± 12.1 years. Among all, the majority were males (61.8%). Similarly, Adam et al. identified that the mean age of ACS is 55.4 years (23). In a similar study, Oncel et al. identified that ACS prevalence was higher in males (80.2%) (24). The protective effect of estrogen hormone in premenopausal females on blood vessel endothelium plays a role (25).

This study revealed a statistically significant association between smoking and GRACE risk score ($p = 0.006$). Another study by Acet et al. reported similar results with a significant association between smoking and GRACE risk score ($P < 0.001$) (26). Smoking results in endothelial injury and chronic inflammation of the coronary and peripheral arteries, adds to the process of atherosclerosis, and acts as a powerful predictor of cardiovascular events. Smoking induces collateral vessel formation and was associated with lower and intermediate GRACE risk scores (27).

This study also showed a significant association between SBP and GRACE risk score ($P < 0.0001$). Those with higher GRACE scores had lower SBP and vice versa. Acet et al. found similar results with a significant association between SBP and GRACE risk score ($P < 0.001$). Those having high GRACE risk scores are more likely to have hemodynamic instability resulting in hypotension (26).

Only 12 (10.9%) of the patients developed cardiac arrest in the form of pulseless ventricular tachycardia or ventricular fibrillation. No one was in the low-risk group, and most of them (66.7%) were in the high-risk group.

Most of the patients with Killip class 1 were in the low-risk group, while most of the patients with Killip class 2

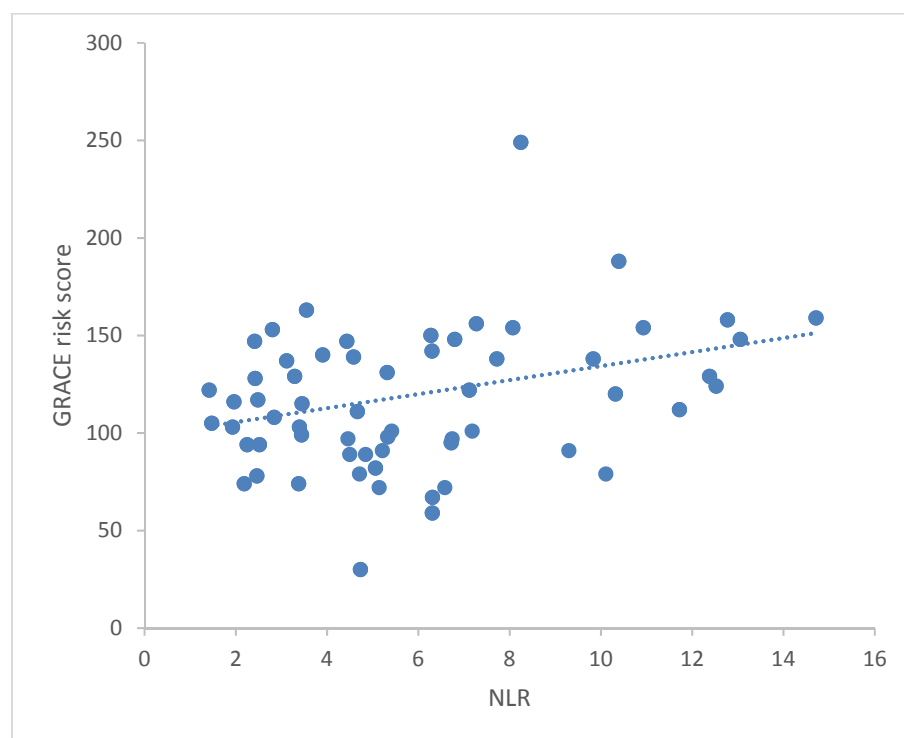


Figure 2. Scatter plot correlation between NLR and GRACE risk score

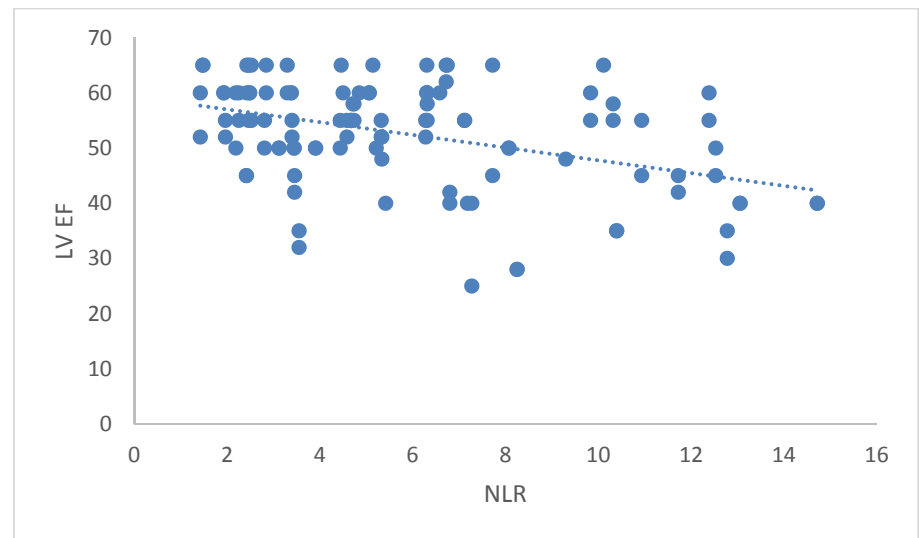


Figure 3. Scatter plot correlation between NLR and LV EF

Table 5. Independent predictors of GRACE risk score by multiple linear regression analysis

Predictor	B coefficient	Standard Error	t-statistic	p-value
Constant	86.0496	28.3607	3.0341	0.003
Age	1.8708	0.1575	11.8806	< 0.001
Gender	4.7633	3.8589	1.2344	0.220
NLR	1.4955	0.5636	2.6536	0.009
MPV	-0.5868	2.2578	-0.2599	0.795
LV EF	-1.5968	0.2087	-7.6503	< 0.001

NLR: Neutrophil to lymphocyte ratio, MPV: Mean platelet volume, LV EF: Left Ventricle Ejection Fraction

were in the intermediate and high-risk groups. All patients who had cardiogenic shock were in the high-risk group. Acet et al. found similar results regarding cardiac function classification using the Killip class (26).

This study demonstrated a statistically significant association between serum creatinine and GRACE risk score ($P < 0.0001$). Higher values were found in the intermediate and high-risk groups. Another study by Baginda et al. found similar results with a significant association between serum creatinine and GRACE risk score ($P = 0.001$). Patients with high GRACE risk scores are more likely to have hemodynamic instability resulting in renal impairment (28).

This study also showed a statistically significant association between LV EF and GRACE risk score ($P < 0.0001$). Declining LV function was found in the high-risk group. Acet et al. found similar results with a significant association between admission LV EF and GRACE risk score ($P < 0.001$) (26).

Among the five complete blood count (CBC) parameters (WBC, ANC, ALC, NLR, and MPV), this study showed a statistically significant association between ANC and GRACE risk score ($P = 0.036$) and an even stronger statistically significant association between NLR and GRACE risk score ($P < 0.0001$). No statistically significant association was identified between the other 3 parameters (WBC, ALC, and MPV) and the GRACE risk score.

Inflammation plays a crucial role throughout the stages of ACS, affecting the development and rupture of atherosclerotic plaque (24). Neutrophils make the formed plaque more fragile by releasing arachidonic acid and superoxide

radicals by proteolytic enzymes (29). Plaque destabilization causes injury to blood vessel endothelium. Neutrophils adhere to capillary endothelium and inhibit reperfusion of ischemic capillaries (30).

Lymphocytes play a role in controlling the immune responses throughout all stages of the development of atherosclerosis. The systemic inflammatory response is characterized by a low lymphocyte count (26, 31). Systemic inflammation secondary to myocardial ischemia leads to increased cortisol levels, which results in decreased lymphocyte count (32).

The combination of neutrophils as inflammatory markers and lymphocytes as regulatory markers in the form of neutrophil to lymphocyte ratio (NLR) is an important predictor of systemic inflammation in ACS (32).

This study showed a statistically significant association between NLR and GRACE risk score ($P < 0.0001$). Higher NLR values were found in the high-risk group compared with lower values in the low and intermediate-risk groups. Similar to the results of this study, Oncel et al. identified that the increment in NLR values was significantly associated with the GRACE risk score ($p < 0.001$) (24). Another study by Acet et al. showed similar results with a statistically significant association between the increase in NLR values and the GRACE risk score ($p = 0.008$) (26). In previous research, high neutrophil count has been independently linked to greater infarct size, mechanical complications, and mortality in patients with acute MI (33, 34).

In this study, the Spearman correlation test was done to analyze the correlation between NLR and GRACE risk

score. The result showed that there is a statistically significant positive correlation between NLR and GRACE risk score ($r = 0.339$, $P < 0.001$). Acet et al. found similar results with a statistically significant positive correlation between NLR values and GRACE risk scores ($r = 0.172$; $P < 0.001$) (26).

Multiple linear regression analysis was conducted to find independent predictors of GRACE risk score. Age, gender, two CBC parameters (NLR and MPV), and LV EF were included in the analysis. It revealed that age, NLR, and LV EF were independent predictors of GRACE risk score. Aging ($b = 1.8708$, $P < 0.0001$), higher NLR values ($b = 1.4955$, $P = 0.0092$), and LV EF ($b = -1.5968$, $P < 0.0001$) were statistically significantly associated with GRACE risk score. Similar results were demonstrated by Acet et al. where age ($b = 1.759$, $P < 0.001$), NLR ($b = 1.2$, $P = 0.044$), and LV EF ($b = -0.995$, $P < 0.001$) were found to be an independent predictor of worse GRACE risk score (26).

NLR is a cost-effective and easily accessible marker that adds another level of risk assessment for predicting short-term and long-term outcomes (35). Correia et al. showed that evaluating inflammation enhances risk assessment and offers extra predictive data for the GRACE risk score (36).

Again, the Spearman correlation test was utilized to analyze the correlation between NLR and LV EF. The result showed that there is a statistically significant negative correlation between NLR and LV EF ($r = -0.385$, $P = 0.005$). Higher NLR values were associated with more severe LV dysfunction. Another study by Chen Chen et al. showed similar results with a statistically significant negative correlation between NLR values and LV EF ($r = -0.208$, $P < 0.001$). It is possible that high NLR (which indicated a high degree of systemic inflammation) contributed to greater myocardial damage resulting in LV dysfunction (37).

Study Limitations

1. This was a single-center study with a retrospective design. It included a relatively small sample size. These findings need to be analyzed in a study with a larger sample size.
2. A comparison between NLR and other markers of inflammation could not be made as they were not routinely obtained.
3. Cut-off values of NLR were not determined for low, intermediate, and high-risk groups.
4. The study acknowledges some potential confounders like smoking, which acts as a strong predictor of cardiovascular events, potentially confounding the association between NLR and the GRACE risk score.
5. The retrospective pattern of the study might introduce recall bias and limit the control over data completeness. Age-related differences in immune status and inflammatory response could introduce bias.

Conclusion

- Routine use of GRACE risk score for risk stratification of patients with NSTEMI-ACS. This study showed a statistically significant association and positive correlation between NLR and GRACE risk score, so NLR can provide

additional value about risk stratification and prognosis in patients with NSTEMI-ACS.

- Age, NLR, and LV EF were identified to be independent predictors of GRACE risk score and, therefore, may be independent predictors of admission to 6-month mortality.
- NLR was found to have a statistically significant negative correlation with LV ejection fraction

Recommendations

- NLR needs to be determined routinely for risk stratification of patients with NSTEMI-ACS during hospitalization because it is simple, cost-effective, and it can guide further clinical practice
- Cut-off values of NLR need to be determined in a large prospective study design.
- Comparison of NLR with other markers of inflammation, such as C reactive protein as risk stratification tools in patients with NSTEMI-ACS

Authors' Contributions

Lecturer Dr. Ali Safaa Abduljabbar contributed to collection of data, analysis of data, and writing and reviewing the article. Professor Dr. Muataz Fawzi Hussein contributed to the supervision and review of the analysis of data and editing of the methods and discussion parts of the article.

Ethical Considerations

This research was designed with the approval of the scientific committee of the College of Medicine, University of Baghdad, Iraq.

Acknowledgment

The authors would like to express their gratitude to the team at Baghdad Teaching Hospital/ Coronary Care Unit and Emergency Department for their help and support.

In addition, the authors would like to thank all those who participated and helped in this study.

Conflict of Interests

The authors declare that they have no competing interests.

References

1. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet*. 2006; 367(9524):1747-1757
2. Libby P. Inflammation in atherosclerosis. *Nature*. 2002;420(6917):868-874.
3. Fiechter M, Ghadri JR, Jaguszewski M, Siddique A, Vogt S, Haller RB. Impact of inflammation on adverse cardiovascular events in patients with acute coronary syndromes [published online April 6, 2013]. *J Cardiovasc Med (Hagerstown)*. 2013.
4. Corti R, Hutter R, Badimon JJ, Fuster V. Evolving concepts in the triad of atherosclerosis, inflammation and thrombosis. *J Thromb Thrombolysis*. 2004;17(1):35-44.
5. Erkol A, Oduncu V, Turan B, Kilicgedik A, Karabay CY, Akgun T, et al. Neutrophil to lymphocyte ratio in acute ST-segment elevation myocardial infarction. *Am J Med Sci*. 2014;348:37-42.
6. Arruda-Olson AM, Reeder GS, Bell MR, Weston SA, Roger VL. Neutrophilia predicts death and heart failure after myocardial infarction: a community-based study. *Circ Cardiovasc Qual Outcomes*. 2009;2:656-62.
7. Rudiger A, Burckhardt OA, Harpes P, Muller SA, Follath F. The

- relative lymphocyte count on hospital admission is a risk factor for long-term mortality in patients with acute heart failure. *Am J Emerg Med*. 2006;24:451–4.
8. Ertem AG, Ozcelik F, Kasapkara HA, Koseoglu C, Bastug S, Ayhan H, et al. Neutrophil lymphocyte ratio as a predictor of left ventricular apical thrombus in patients with myocardial infarction. *Korean Circ J*. 2016;46:768–73.
 9. Gul U, Kayani AM, Munir R, Hussain S. Neutrophil lymphocyte ratio: aprognostic marker in acute st elevation myocardial infarction. *J Coll Phys Surg Pakistan*. 2017;27:4–7.
 10. Ghaffari S, Nadiri M, Pourafkari L, Sepehrvand N, Movasagpoor A, Rahmatvand N, et al. The predictive value of total neutrophil count and neutrophil/lymphocyte ratio in predicting in-hospital mortality and complications after STEMI. *J Cardiovasc Thorac Res*. 2014;6:35–41.
 11. Gazi E, Bayram B, Gazi S, Temiz A, Kirilmaz B, Altun B, et al. Prognostic value of the neutrophil–lymphocyte ratio in patients with ST-elevated acute myocardial infarction. *Clin Appl Thromb Hemost*. 2015;21:155–9.
 12. Horne BD, Anderson JL, John JM, Weaver A, Bair TL, Jensen KR, et al. Which white blood cell subtypes predict increased cardiovascular risk? *J Am Coll Cardiol*. 2005;45:1638–43.
 13. Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2021;42(14):1289–1367.
 14. Aragam KG, Tamhane UU, Kline-Rogers E, Li J, Fox KA, Goodman SG, et al. Does simplicity compromise accuracy in ACS risk prediction? A retrospective analysis of the TIMI and GRACE risk scores. *PLoS One*. 2009;4:e7947.
 15. D'Ascenzo F, Biondi-Zoccai G, Moretti C, Bollati M, Omede P, Sciuto F, et al. TIMI, GRACE and alternative risk scores in acute coronary syndromes: a metaanalysis of 40 derivation studies on 216,552 patients and of 42 validation studies on 31,625 patients. *Contemp Clin Trials*. 2012;33:507514.
 16. Gale CP, Manda SO, Weston CF, Birkhead JS, Batin PD, Hall AS. Evaluation of risk scores for risk stratification of acute coronary syndromes in the Myocardial Infarction National Audit Project (MINAP) database. *Heart*. 2009;95:221227.
 17. Bing R, Goodman SG, Yan AT, Fox K, Gale CP, Hyun K, et al. Use of clinical risk stratification in non-ST elevation acute coronary syndromes: an analysis from the CONCORDANCE registry. *Eur Heart J Qual Care Clin Outcomes*. 2018;4:309317.
 18. Chew DP, Junbo G, Parsonage W, Kerker P, Sulimov VA, Horsfall M, et al. Perceived Risk of Ischemic and Bleeding Events in Acute Coronary Syndrome Patients (PREDICT) Study Investigators. Perceived risk of ischemic and bleeding events in acute coronary syndromes. *Circ Cardiovasc Qual Outcomes*. 2013;6:299308.
 19. Fox KA, Anderson FA Jr., Dabbous OH, Steg PG, Lopez-Sendon J, de Werf FC, et al. Intervention in acute coronary syndromes: do patients undergo intervention on the basis of their risk characteristics? The Global Registry of Acute Coronary Events (GRACE). *Heart*. 2007;93:177182.
 20. Saar A, Marandi T, Ainla T, Fischer K, Blondal M, Eha J. The risk-treatment paradox in non-ST-elevation myocardial infarction patients according to their estimated GRACE risk. *Int J Cardiol*. 2018;272:2632
 21. Granger CB, Goldberg RJ, Omar Dabbous, Karen S Pieper, Kim A Eagle, Christopher P Cannon, et al. Global Registry of Acute Coronary Events Investigators. Predictors of hospital mortality in the global registry of acute coronary events. *Arch Intern Med*. 2003;163:23452353.
 22. Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr, et al. *J Am Coll Cardiol*. 2014 Dec 23;64(24):e139–e228.
 23. Adam AM, Rizvi AH, Haq A, Naseem R, Rehan A, Shaikh AT, et al. Prognostic value of blood count parameters in patients with acute coronary syndrome. *Indian Heart J*. 2018;70(2):233–40.
 24. Oncel RC, Ucar M, Karakas MS, Akdemir B, Yanikoglu A, Gulcan AR, et al. Relation of neutrophil-to-lymphocyte ratio with GRACE risk score to in-hospital cardiac events in patients with ST-segment elevated myocardial infarction. *Clin Appl Thromb*. 2015;21(4):383–8.
 25. Darmawan. Peran Rasio Netrofil Limfosit sebagai prediktor major adverse events tujuh hari dalam perawatan pada pasien sindrom koroner akut. Penerbit Fakultas Kedokteran Universitas Indonesia. 2016:8-49.
 26. Acet H, Ertaş F, Akil 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.
 27. Centers for Disease Control and Prevention. How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease. A Report of the Surgeon General. pp. 2010;363-367.
 28. Siregar BY, Hasan R, Isnanta R. Association of Neutrophil Lymphocyte Ratio (NLR) with Global Registry of Acute Coronary Events (GRACE) Scores in Acute Coronary Syndrome. *Journal of Endocrinology, Tropical Medicine, and Infectious Disease (JETROMI)*. 2020;2(3):162-170.
 29. Li Y, Chen X, Huang L, Lu J. Association between neutrophil–lymphocyte ratio and arterial stiffness in patients with acute coronary syndrome. *Biosci Rep*. 2019;39(5):1–7.
 30. Crea F, Libby P. Acute coronary syndromes: The way forward from mechanisms to precision treatment. *Circulation*. 2017;136(12):1155–66.
 31. Núñez J, Miñana G, Bodi V, Núñez E, Sanchis J, Husser O, et al. Low Lymphocyte Count and Cardiovascular Diseases. 2011;18(21):3226-33.
 32. Angkananard T, Anothaisintawee T, McEvoy M, Attia J, Thakkinstian A. Neutrophil Lymphocyte Ratio and Cardiovascular Disease Risk: A Systematic Review and MetaAnalysis. *Biomed Res Int*. 2018.
 33. O'Donoghue M, Morrow DA, Cannon CP, Wei Guo, Murphy SA, Gibson CM, et al. Association between baseline neutrophil count, clopidogrel therapy, and clinical and angiographic outcomes in patients with ST elevation myocardial infarction receiving fibrinolytic therapy. *Eur Heart J*. 2008;29(8):984-991.
 34. Kirtane AJ, Bui A, Murphy SA, Barron HV, Gibson CM. Association of peripheral neutrophilia with adverse angiographic outcomes in ST elevation myocardial infarction. *Am J Cardiol*. 2004;93(5):532-536.
 35. Shen XH, Chen Q, Shi Y, Li HW. Association of neutrophil/lymphocyte ratio with long-term mortality after ST elevation myocardial infarction treated with primary percutaneous coronary intervention. *Chin Med J*. 2010;123(23):3438-3443
 36. Correia LC, Andrade BB, Borges VM, Jorge C, Ana P B, Rafael F, et al. Prognostic value of cytokines and chemokines in addition to the GRACE Score in non-ST-elevation acute coronary syndromes. *Clin Chim Acta*. 2010;411(7-8):540-545.
 37. 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):192–199.