Neutrophil Lymphocyte Ratio and its Relationship to Global Registry of Acute Coronary Events (GRACE) Score in patients admitted with Acute Coronary Syndrome

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Abstract
Background: Neutrophil to lymphocyte ratio (NLR) as an indicator of systemic inflammation has been linked to morbidity and mortality in Acute coronary syndrome (ACS). Global Registry of Acute Coronary Events (GRACE) score is recommended by recent guidelines for risk stratification and prognosis of ACS cases. This research aimed to study NLR and its relationship to GRACE Score in ACS cases.
Methods: This cross-sectional study was performed on 120 cases, aged ≥ 18 years, with ACS either ST elevation acute myocardial infarction (STEMI), non-ST elevation acute myocardial infarction (NSTEMI), or unstable angina (UA), clinically confirmed through ischemic symptoms and electrocardiography (ECG) changes. Cases underwent further subdivision into three equal groups: STEMI group, NSTEMI group, and UA group. All cases underwent laboratory investigations (complete blood count (CBC), cardiac markers (troponin-I). Every patient underwent GRACE risk score calculation.
Results: NLR was significantly lower in low GRACE group than Intermediate and high GRACE group (P value <0.001) and in intermediate than high GRACE group (P Value=0.002). There was a positive correlation between NLR and GRACE score (r= 0.521, P value < 0.001). NLR can significantly predict high and intermediate grace score (P <0.001 and AUC = 0.755) at cut-off >5.9 with 66.15% sensitivity, 81.82% specificity, 81.1% PPV and 67.2% NPV. NLR can significantly predict high grace score (P<0.001 and AUC =0.801) at cut-off >8.2 with 74.07% sensitivity, 79.57% specificity, 51.3% PPV and 91.4% NPV.
Conclusion: NLR has a positive correlation with the GRACE Score in ACS cases and modest prediction to high GRACE score.
Keywords: Global Registry of Acute Coronary Events Score, Neutrophil Lymphocyte Ratio, Acute Coronary Syndrome.

Introduction

Acute coronary syndrome (ACS) is the most frequent admission diagnosis to a coronary care unit (CCU), including those with ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), and unstable angina (UA). As more advanced and effective therapeutic alternatives become available, it is crucial to target the appropriate therapy to the appropriate patient. Therefore, an effective risk prediction tool is required to optimize therapy [1].
Atherosclerosis is a key mechanism underlying myocardial infarction (MI), through inflammation, initiation, progression and plaque de-stabilization [2, 3].
White blood cell (WBC) and its subtype are one of the inflammatory indicators in cardiovascular disease that have been extensively researched. In cases with MI, relative lymphopenia and neutrophilia were potential predictors of recurrence and mortality [4].
The Global Registry of Acute Coronary Events (GRACE) risk score is a validated scoring system used for risk stratification and predicting hospital mortality in ACS cases. [5].

The neutrophils to lymphocytes (NLR) ratio is a combination of two independent indicators that may easily predict the inflammatory state in MI cases, in addition to morbidity and mortality. Conservative approaches for cases with low risk GRACE score (<140) and an invasive approaches for cases with high-risk GRACE scores (>140) are recommended by the American College of Cardiology Foundation / American Heart Association guidelines [4, 6].

This research aimed to study NLR and its relationship to GRACE Score in ACS cases.

Patients and Methods:

This cross-sectional study was performed on 120 cases, aged ≥ 18 years, both sexes, with ACS either STEMI, NSTEMI or UA, clinically confirmed by ischemic symptoms along with changes in the electrocardiography (ECG) consistent with ischemia, and diagnosed based on the last ESC guidelines for diagnosing and managing ACS [7], admitted in CCU in in Menoufia University Hospital and Shebin Elkom Teaching Hospital after ethical committee approval and taking written consent from all participants.

Exclusion criteria were hematological disorders (hematological malignancies and all types of anemia), clinically active infection, malignancy, severe liver disease, steroid therapy, chronic or active autoimmune disease, chemotherapy, and blood transfusion.

Cases were further subdivided into three groups: STEMI group (n=40), NSTEMI group (n=40), UA group (n=40).

All cases underwent history taking and demographic data collection (Age, sex, risk factors including DM, HTN, smoking and dyslipidemia, family history, medical history, and patient presentation on admission (arrested or not), general examination (neck veins, blood pressure, pulse, lower limb edema), local examination (heart auscultation for detecting additional sounds and murmurs, auscultation of chest to detect fine basal crepitations), laboratory examination (complete blood count (CBC), kidney function tests (creatinine (Cr) and serum urea), cardiac markers), and 12-lead ECG to detect ischemic changes as ST/T changes and arrhythmias.

Cases with STEMI were diagnosed if new left bundle branch block was found on the index, or new or presumed new ST-segment elevation ≥ 1 mm was found in any ECG location, or qualifying ECG with one positive biomarker for myocardial necrosis at least (i.e., creatine kinase (CK) and/or troponin and/or CK-MB above the upper normal/reference limit based on every hospital's laboratory) was reported.

Cases with NSTEMI were diagnosed with one positive cardiac biomarker of necrosis at least with no new ST-segment elevation visualized by ECG. UA is defined any of the following clinical presentations, with or without ECG evidence of ischemia and with normal troponin: crescendo angina: angina that increases in frequency, intensity, or duration often requiring a more frequent use of nitroglycerin, new onset (< 2 months) severe angina occurring during normal activities performed at a normal pace, rest angina, and post-myocardial infarction: angina occurring within 2 weeks after a myocardial infarction [7].

Blood sample collection and CBC parameter assessment:

Blood samples were taken either from vein or artery of the arm as 3 ml blood on EDTA tube sample. The CBC was performed by loading the sample in automated hematology analyzer, that counts cells and collects information based on their shape and size, the sample was forced in a small tube while the automated cell counter counted the number of cells that go through the tube using electrical impedance or optical sensors. The WBCs count, lymphocytes and neutrophils, were documented; then, neutrophil to lymphocyte ratio (NLR) was determined as neutrophil count/lymphocyte count.

Global registry of acute coronary events (GRACE):

The GRACE risk score was calculated upon arrival at hospital for every case using a total 8 clinical parameters: age; systolic blood pressure (SBP); heart rate (HR); serum Cr; Killip classification; ST-segment deviation on ECG; cardiac arrest; and elevated myocardial enzymes **[8]**.

Killip classification used to quantifies heart failure (HF) severity in ACS and predicts 30-day mortality. It consists of four classes: **Class I:** No HF findings, **Class II:** Evidence of mild to moderate HF (e.g, lung rales < one-halfway up the posterior lung fields, S3 gallop, or jugular venous distension), **Class III:** Overt pulmonary edema, and **Class IV:** cardiac shock. **Table 1**.

GRACE score has three risk categories as in **Table 2**.

Table 1: GRACE score [8]

Age	Points	HR	Points	SBP	Points	Cr	Points	Killip class	Points
<39	0	<70	0	<80	40	0.0–0.39	1	I	0
40–49	18	70–89	5	80–99	37	0.4–0.79	4	II	15
50–59	36	90–109	10	100–119	30	0.8–1.19	7	III	29
60–69	55	110–149	17	120–139	23	1.2–159	10	IV	44
70–79	73	150–199	26	140–159	17	1.6–1.99	13	**Cardiac arrest**	30
80–89	91	≥200	34	160–199	7	2.0–3.99	21	**Elevated cardiac markers**	13
>90	100	–	–	≥200	0	≥4	28	**ST-segment deviation**	17

Table 2: GRACE score and the subsequent mortality rates [9]

Risk Categorization	GRACE Score	Mortality
Low risk	<108	<1% (in hospital)
	<88	<3% (6 months after discharge)
Intermediate risk	109-140	1-3% (in hospital)
	89-118	3-8% (6 months after discharge)
High risk	>140	>3% (in hospital)
	>118	>8% (6 months after discharge)

Statistical analysis

SPSS v27 was utilized for conducting the statistical analysis (IBM©, Chicago, IL, USA). The normality of data distribution was calculated by Shapiro-Wilk test and histograms. Categorical variables were presented as frequency and percentage (%) and were analyzed using the Chi-square test. Numeric parametric variables were presented as mean and standard deviation (SD) and were analyzed using ANOVA (F) test to compare between the studied groups then the difference between the each group test via post hoc (Tukey) analysis. Pearson correlation assessed association between NLR and GRACE. Univariate regression using risk factor and NLR was used to study relationship between risk factor, NLR and GRACE score, then the same parameters included in multivariate analysis for assessing their relationship to GRACE score. ROC was generated to evaluate the accuracy of NLR for predicting GRACE score. A two tailed P value < 0.05 was deemed statistically significant.

Results:

Our Cohort was homogenous in demographic parameters except in family history of CAD. SBP was significantly lower in STEMI group than (NSTEMI group and UA group) (P value<0.001) and NSTEMI group than UA group (P value <0.001). Killip class at admission was significantly different among the three groups. Peak troponin level was higher in STEMI group and NSTEMI group than UA group (P value <0.001 and 0.023 respectively) and insignificantly different between STEMI group and NSTEMI group. ST segment deviation was higher in STEMI group than NSTEMI group and UA group (P value =0.004 and<0.001 respectively) and in NSTEMI group than UA group (P value <0.001). GRACE score was low GRACE score in 13 (32.5%) patients, Intermediate GRACE score in 13 (32.5%) patients and high GRACE

score in 14 (35%) patients in STEMI group. GRACE score was low GRACE score in 13 (32.5%) patients, Intermediate GRACE score in 17 (42.5%) patients and high GRACE score in 10 (25%) patients in NSTEMI group. GRACE score was low GRACE score in 29 (72.5%) patients, Intermediate GRACE score in 8 (20%) patients and high GRACE score in 3 (7.5%) patients in UA group. GRACE Score was significantly higher in STEMI group and NSTEMI group than UA group (P value<0.001) and insignificantly different between STEMI group and NSTEMI group. LVEF at admission and ECG changes at admission were insignificantly different among the three groups. **Table 3**

Table 3: Demographic data and GRACE risk score parameters of the studied groups (n = 120)

			STEMI group (n=40)	NSTEMI group (n=40)	UA group (n=40)	P value	Post Hoc
Demographics	**Age (years)**		51.7 ± 12.94	54.8 ± 8.31	57.3 ± 10.97	0.072	
	Sex	**Male**	35 (87.5%)	30 (75%)	26 (65%)	0.062	
	BMI (kg/m^2)		28.9 ± 5.29	28.4 ± 5.7	30.9 ± 8.14	0.191	
	Comorbidities	**Hypertension**	11 (27.5%)	11 (27.5%)	16 (40%)	0.382	
		DM	11 (27.5%)	8 (20%)	11 (27.5%)	0.670	
		Hyperlipidemia	4 (10%)	3 (7.5%)	2 (5%)	0.697	
		Family history of CAD	34 (85%)	26 (65%)	19 (47.5%)	0.002*	P1=0.07 P2=0.009* P3=0.176
		Smoking	25 (62.5%)	25 (62.5%)	19 (47.5%)	0.293	
GRACE risk score parameters	**Age (years)**		51.7 ± 12.94	54.8 ± 8.31	57.3 ± 10.97	0.072	
	Creatinine (mg/dL)		0.9 ± 0.38	1.1 ± 0.57	1.2 ± 0.44	0.122	
	SBP (mmHg)		110.9 ± 27.42	116.2 ± 31.59	127.8 ± 33.95	**0.049***	**P1< 0.001* P2<0.001* P3<0.001***
	Killip class at admission	**I**	6 (15%)	4 (10%)	7 (17.5%)	**0.018***	
		II	13 (32.5%)	6 (15%)	2 (5%)		
		III	4 (10%)	8 (20%)	1 (2.5%)		
		IV	3 (7.5%)	5 (12.5%)	1 (2.5%)		
	Cardiac arrest at admission		2 (5%)	1 (2.5%)	2 (5%)	0.812	
	HR on admission (beats/min)		102.8 ± 22.79	101.9 ± 29.54	90 ± 30.61	0.075	
	Peak troponin level (ng/mL)		0.7 ± 0.22	2.2 ± 5.88	0 ± 0.01	0.017*	P1= 0.108 P2 < 0.001* P3= 0.023*
	ST segment deviation		40 (100%)	29 (72.5%)	10 (25%)	<0.001*	P1=0.004* P2< 0.001* P3< 0.001*
GRACE Score			118.3 ± 36.89	119.8 ± 24.65	92.9 ± 32.72	<0.001*	P1=0.977 P2<0.001* P3<0.001*
LVEF at admission (%)			45.4 ± 7.73	45.8 ± 8.78	43 ± 15.18	0.495	
ECG changes at admission	**Normal sinus rhythm**		36 (90%)	38 (95%)	33 (82.5%)	0.194	

Data are presented as mean ± SD or frequency (%). *Significant as P value≤0.05, BMI: Body mass index, DM: Diabetes mellitus, CAD: Coronary artery disease, SBP: systolic blood pressure, HR: heart rate, GRACE score: global registry of acute coronary events, LVEF: Left ventricular ejection fraction, ECG: electrocardiogram, P1: P value between STEMI group and NSTEMI group, P2: P value between STEMI group and UA group, P3: P value between NSTEMI group and UA group.

WBCs, neutrophil count, lymphocyte count were insignificantly different among the three groups. Haemoglobin and red blood cells were significantly higher in STEMI group and NSTEMI group than UA group (P value<0.05) and insignificantly different between STEMI group and UA group. Neutrophil to lymphocyte ratio was significantly higher in STEMI group than NSTEMI group and UA group (P value =0.04 and <0.001 respectively) and significantly higher in NSTEMI group than UA group (P value=0.019). **Table 4**

Table 4: CBC parameters of the studied groups

	STEMI group (n=40)	NSTEMI group (n=40)	UA group (n=40)	P value	Post Hoc
Hemoglobin (g/dL)	15 ± 1.24	14.4 ± 1.45	13.2 ± 1.39	0.001*	P1=0.171 P2<0.001* P3<0.001*
WBCs ($x10^3/mm^3$)	15.2 ± 3.54	13.6 ± 4.49	14.4 ± 6.03	0.300	
Neutrophil count ($x10^3/mm^3$)	11.2 ± 4.04	11.5 ± 4.68	10.4 ± 5.26	0.584	
Lymphocyte count ($x10^3/mm^3$)	2.2 ± 0.9	2.5 ± 0.99	2.5 ± 1.16	0.367	
Neutrophil to lymphocyte ratio	5.5 ± 1.67	4.8 ± 1.09	4.1 ± 0.61	0.001*	P1=0.040* P2<0.001* P3=0.019*

*Significant p value as< 0.05, Data presented as Mean ± SD, P1: P value between STEMI group and NSTEMI group, P2: P value between STEMI group and UA group. P3: P value between NSTEMI group and UA group

Neutrophil count and lymphocyte count were insignificantly different among the three groups. NLR was significantly lower in low GRACE group than Intermediate and high GRACE group (P value <0.001) and in intermediate than high GRACE group (P Value=0.002). Table 5

Table 5: Comparison between N, L, and NLR regarding to GRACE score categories

	Low GRACE group (n=55)	Intermediate GRACE group (n=38)	High GRACE group (n=27)	P value	Post Hoc
Neutrophil count ($x10^3/mm^3$)	10.9 ± 4.94	10.9 ± 4.64	11.4 ± 4.29	0.829	
Lymphocyte count ($x10^3/mm^3$)	2.4 ± 1.11	2.3 ± 1	2.4 ± 0.89	0.838	
NLR	5.2 ± 1.95	6.8 ± 2.66	8.9 ± 2.43	<0.001*	P1<0.001* P2<0.001* P3=0.002*

*Significant P value as≤0.05, GRACE score: Global registry of acute coronary events, NLR: neutrophil to lymphocyte ratio

There was a positive correlation between GRACE group and NLR in low GRACE group, intermediate GRACE group and high GRACE group (r=0.277, 0.368 and 0.440 respectively). Table 6

Table 6: Correlation between neutrophil to lymphocyte ratio (NLR) and GRACE score (low, intermediate and high) of the studied groups

	Low GRACE group	Intermediate GRACE group	High GRACE group
GRACE score	80.3 ± 19.38	122 ± 9.22	154.8 ± 14.34
NLR	5.2 ± 1.95	6.8 ± 2.66	8.9 ± 2.43
r value	0.277	0.368	0.440
P value	0.008*	0.023*	0.022*

GRACE score: Global registry of acute coronary events, r: Pearson coefficient.

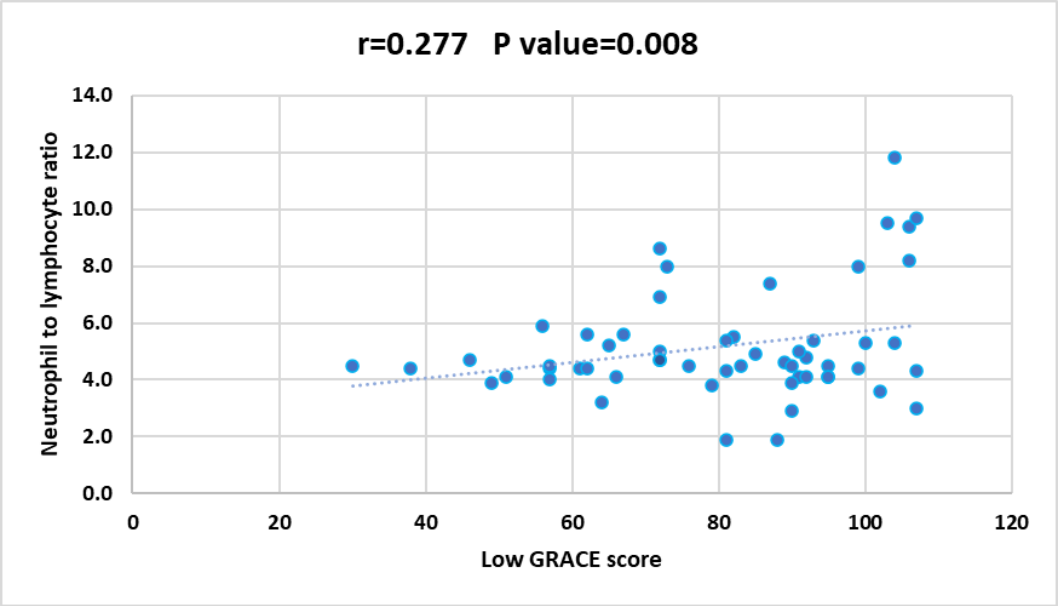


Figure 2: Correlation between neutrophil to lymphocyte ratio and low GRACE score

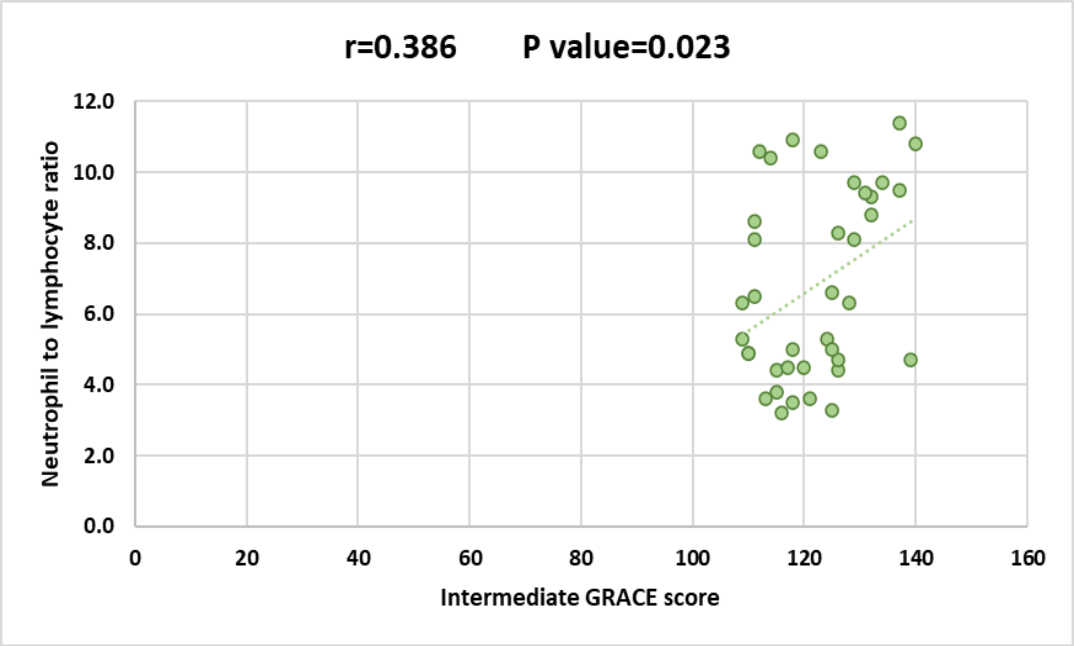


Figure 3: Correlation between neutrophil to lymphocyte ratio and intermediate GRACE score

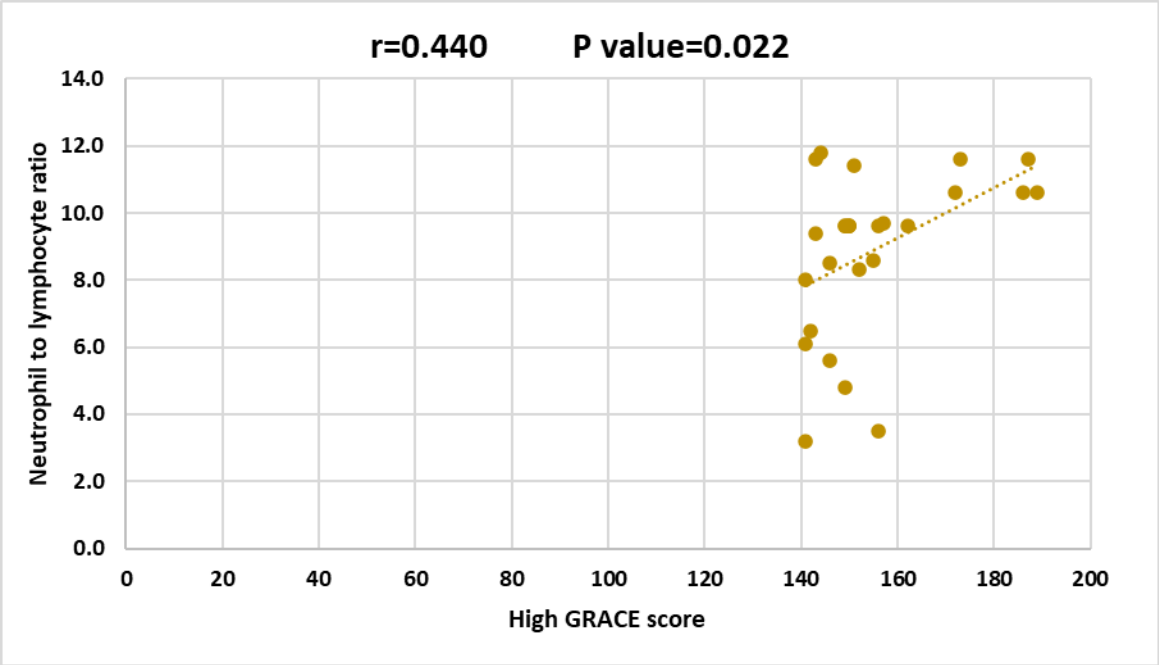


Figure 4: Correlation between neutrophil to lymphocyte ratio and high GRACE score

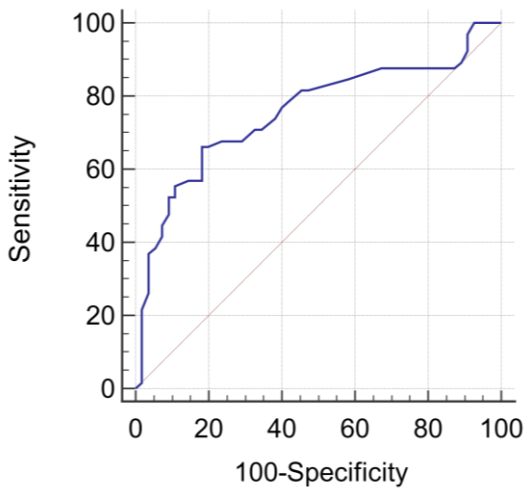
In univariate regression, hypertension, DM, hyperlipidemia, family history of CAD, smoking, neutrophil to lymphocyte ratio were independent predictors of GRACE score (P value <0.001). In Multivariate regression, DM and neutrophil to lymphocyte ratio were independent predictors of GRACE score (P value =0.038 and <0.001 respectively) while hypertension, hyperlipidemia, family history of CAD and smoking were not.

Table 7: Univariate and multivariate regression of comorbidities, smoking, neutrophil to lymphocyte ratio versus GRACE score (Low, Intermediate and high GRACE score)

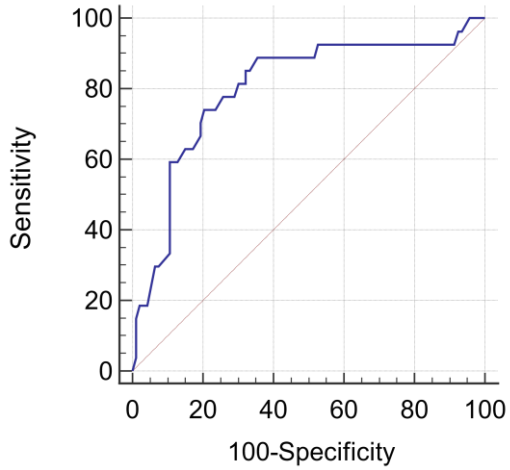
	Univariate			Multivariate		
	Odds ratio	**95% CI**	**P**	**Odds ratio**	**95% CI**	**P**
Hypertension	1.017	0.19- 5.21	<0.001*	3.386	0.90 - 12.64	0.069
DM	3.272	0.90- 11.78	<0.001*	4.552	1.08 - 19.07	0.038*
Hyperlipidaemia	1.017	0.19 - 5.21	<0.001	0.497	0.19 - 11.80	0.701
Family history of CAD	2.112	0.77-5.73	<0.001*	0.645	0.18 - 2.26	0.494
Smoking	1.340	0.55 -3.23	<0.001*	0.817	0.27 - 2.41	0.715
Neutrophil to lymphocyte ratio	0.635	0.52 -0.77	<0.001*	0.639	0.51 - 0.78	<0.001 *

CI: Confidence interval, DM: Diabetes mellitus, CAD: Coronary artery disease

Neutrophil to lymphocyte ratio could predict high and intermediate grace score (AUC = 0.755, P <0.001) at cut-off >5.9 with 66.15% sensitivity, 81.82% specificity, 81.1% PPV and 67.2% NPV. Neutrophil to lymphocyte ratio could predict high grace score (AUC =0.801, P<0.001) at cut-off >8.2 with 74.07% sensitivity, 79.57% specificity, 51.3% PPV and 91.4% NPV.



(A) AUC = 0.755



(B) AUC =0.801

Figure 2: ROC curve of Neutrophil to lymphocyte ratio (NLR) in prediction of (A) high and intermediate grace score, and (B) high grace score.

Discussion:

In our present study, neutrophil to lymphocyte ratio (NLR) as a marker for inflammation were investigated for prediction of GRACE risk score in cases presented with ACS.

The white blood cell (WBC) count is considered an independent predictor of inflammation and long-term cardiovascular mortality in ACS [15]. The incidence of coronary artery disease (CAD) is higher in individuals with higher total WBC counts (hazard ratio: 1.04; 95% CI: 1.02-1.07; p=0.001) [15]. Neutrophils have also been shown to be essential for the development of atherogenesis [16]. Low lymphocyte counts can potentially signal the possibility of impaired hemodynamics and aerobic ability [17]. Therefore, the neutrophil to lymphocyte ratio (NLR) as a biomarker can be used to predict the risk of future cardiovascular events which is the ratio of the absolute number of neutrophils to the number of lymphocytes. [8].

The current European Acute Coronary Syndrome guidelines propose using the GRACE risk score to be applied on admission and at discharge in routine clinical practice since it has a high diagnostic performance for worse outcomes in ACS [20].

Our study reported that NLR is positively correlated with GRACE score in ACS diagnosed cases, and it has modest prediction ability to high GRACE score at cut-off >8.2 with 74.07% sensitivity, 79.57% specificity, 51.3% PPV and 91.4% NPV. In addition to NLR was significantly higher in STEMI group than NSTEMI group and UA group (P value =0.04 and <0.001 respectively) and significantly higher in NSTEMI group than UA group (P value=0.019). The same for GRACE risk score categories in which the higher the NLR, the higher the GRACE score is.

In line with our finding, Siregar et al. [27] conducted a cross-sectional retrospective study to determine the association and cut-off value NLR with risk stratification GRACE score. There was significant difference between NLR values with GRACE risk score (p<0.001). NLR values were significantly higher in high risk and intermediate-risk compared low risk stratification (7.9 ± 2.7 vs 3.6 ± 1.7; p=0.001) (5.2 ± 2.3 vs 3.6 ± 1.7; p=0.018). In Siregar et al study, the Spearman correlation test was conducted to find the correlation between NLR and GRACE score. The result shows that there is significant correlation between NLR values and GRACE scores (r=0.570; p<0.001).

Like our results, Karim et al. [19] reported that the GRACE risk score was significantly higher in the group with high NLR value compared to those with moderate and low NLR value respectively 155 (132.2- 178), 134 (115-156), 125 (107.5-144.25), p<0.001).

Moreover, Zhou et al. (2016) [15] conducted a similar study to evaluate the relationship between GRACE risk score and NLR. In this prospective, observational, and single-center study, NLRs (neutrophil count/lymphocyte count) were calculated from the complete blood count of patients with ACS, whereas GRACE risk scores were calculated from patients clinical parameters obtained on arrival at our hospital. NLR was positively correlated with the GRACE risk score (r=0.66, p<0.001), and both the GRACE risk score (HR: 1.01; 95% CI: 1.01–1.02; p<0.001) and NLR (HR: 1.09; 95% CI: 1.06–1.14; p<0.001) independently predicted cardiovascular events.

Regarding GRACE risk score parameters, our study reported that Killip class at admission was significantly higher in STEMI group and NSTEMI group than UA group (P value<0.001 and 0.012 respectively) and insignificantly different between STEMI group and NSTEMI group. GRACE Score was significantly higher in STEMI group and NSTEMI group than UA group (P value<0.001) and insignificantly different between STEMI group and NSTEMI group. Similar to our findings, Karim et al. [19] reported that the GRACE score had higher correlation with STEMI and NSTEMI patients compared to UA patients.

Limitations: It was a single-center study, and the sample size was relatively small.

Conclusions:

In ACS situations, NLR shows a positive association with the GRACE score and a modest prediction to a high GRACE score.

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Conflict of Interest: Nil

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