

RELATIONSHIP BETWEEN NEUTROPHIL-TO-LYMPHOCYTE RATIO AND NUMBER OF DISEASED CORONARY ARTERIES IN PATIENTS UNDERWENT CORONARY ANGIOGRAPHY IN IMAM ALI HOSPITAL, KERMANSHAH, IRAN, 2012-14

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ABSTRACT

Neutrophil-to-lymphocyte ratio (NLR) has been noted recently as a prognostic factor in patients with cardiovascular diseases. The present study was done to find any relationship between NLR and number of diseased coronary arteries in patients underwent coronary angiography in Imam Ali University Hospital of Kermanshah, Iran between 2012 and 2014. In this retrospective study, medical records of 1,498 patients who underwent coronary angiography were reviewed. The data extracted were entered into a checklist. NLR was calculated using complete blood count (CBC) reports and the number of diseased coronary arteries was determined using coronary angiography reports. The data were analyzed using SPSS software (ver. 20.0) by analysis of variance (ANOVA), t test, Kruskal-Wallis, and Pearson correlation tests. There were significant ($P < 0.05$) relationships between NLR, history of cardiovascular diseases, diabetes mellitus, hypertension, left ventricular ejection fraction (LVEF), fasting blood sugar, serum creatinine and urea, white blood cell (WBC) count, hemoglobin, platelet count, MCV (mean corpuscular volume), and with the number of diseased coronary arteries detected on coronary angiography. However, there was no significant relationship ($P > 0.05$) between history of hyperlipidemia, cigarette smoking, alcohol drinking, type of cardiac chest pain (acute or chronic), serum total cholesterol, HDL (high-density lipoprotein), LDL (low-density lipoprotein), and triglyceride with the number of diseased coronary arteries. NLR was effective on the number of diseased coronary arteries (i.e., the severity of disease). Application of this laboratory factor can be helpful in patients with ischemic heart disease.

Key words: Neutrophil-to-lymphocyte ratio (NLR); coronary artery disease; angiography.

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Introduction

Coronary artery disease (CAD) is the leading cause of death nowadays. This condition causes significant morbidity, disability and patient's productivity loss and is considered as the first cause of healthcare costs. Clinical spectrum of CAD varies and includes silent ischemia (asymptomatic) to chronic stable angina, unstable angina, acute myocardial infarction (MI), sudden cardiac arrest, arrhythmias, and cardiogenic shock. Currently, 900,000 patients suffer acute MI in the US and 225,000 patients die. The major causes of death include arrhythmias or heart failure⁽¹⁾.

There are several risk factors for CAD including hypertension, hyperlipidemia, family history of CAD, cigarette smoking, etc. Most of these risk factors are effective in mortality and morbidity after MI. Therefore, recognition of these risk factors in any stage, whether the patient has not yet developed CAD or when the patient is at post-MI stage with a high mortality risk is important. One of these CAD risk factors which its role has been established is inflammatory factors⁽²⁾. Inflammation plays a crucial role in initiation and progression of CAD^(1, 2). White blood cells and their components, as inflammatory biomarkers, can be assayed in CAD patients with or without coronary artery involvement and be

used in determining the prognosis of these patients⁽³⁻⁸⁾. Various inflammatory markers such as C-reactive protein (CRP), interleukin-6 (IL-6), myeloperoxidase, and erythrocyte sedimentation rate (ESR) are among predictive factors for CAD⁽⁹⁾. The relationship between increased number of WBCs and CAD has been investigated in several studies. However, the question that does a subset of these cells has relationship with CAD or not has not been responded. Several studies have noted the relationship between CAD and neutrophils and eosinophils⁽⁷⁾ as well as monocytes⁽⁸⁾. Also, it has been demonstrated that with increasing the number of risk factors, mean number of WBCs rises significantly⁽⁹⁾.

Other studies have also shown that eosinophils and other WBCs have relationship with increased morbidity and mortality in CAD patients^(10, 11). However, limited studies have investigated the association between number of WBCs and severity of CAD. There have been reports indicating significant relationship between band neutrophils⁽¹²⁾ and total number of peripheral blood WBCs⁽¹³⁾ with severity of coronary arteries involvement. Neutrophil-to-lymphocyte ratio (NLR) has been advocated recently as a prognostic factor even in non-cardiac diseases⁽⁹⁾. This ratio can be accessed easily and widely and is inexpensive. There is strong evidence that NLR is associated with clinical outcomes, especially in patients undergoing percutaneous coronary intervention (PCI) and coronary angiography^(4, 5). Anx study (2012) showed that high NLR is an independent risk factor for cardiovascular diseases mortality in patients under peritoneal dialysis⁽¹⁴⁾. Also, Arbel et al. (2012) in a study with three-year follow-up of patients with cardiovascular diseases reported that NLR is associated with more severe CAD⁽¹⁵⁾.

Regarding the importance of NLR and lack of similar studies in Kermanshah Province, Iran, the current study was done in order to investigate the relationship between NLR and the number of diseased coronary arteries in patients who underwent coronary angiography in Imam Ali University Hospital, Kermanshah, Iran from 2012 to 2014.

Materials and methods

In this retrospective descriptive-analytical study, the study population consisted of patients who required coronary angiography and presented to Imam Ali University Hospital, Kermanshah, Iran

from 2012 to 2014. The sample size was 1500 subjects which collected via simple random sampling method. Inclusion criteria were having typical chest pain, or positive exercise stress test, or previous history of hospitalization because of ischemic heart disease (IHD). Exclusion criteria were having history of inflammatory conditions such as collagen-vascular disorders, acute or chronic infectious diseases, auto-immune diseases, neoplastic diseases, chronic hepatic diseases, renal failure, thyroid disorders, or a history of cardiac valvular disease. Patients with one or more of these diseases were excluded from the study.

Firstly, the medical records of the patients were reviewed and demographic data (age and gender), cardiovascular diseases risk factors (history of diabetes mellitus, hypertension, hyperlipidemia, cigarette smoking, and alcohol drinking), laboratory data (serum total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride, fasting blood sugar (FBS), urea, creatinine, WBC count, platelet count, MCV (mean corpuscular volume), and NLR) were extracted and entered into a checklist. In addition the type of chest pain (acute or chronic) and left ventricular ejection fraction (LVEF) were documented in the checklist. Those who were active smoker at the time of coronary angiography or had quit smoking in less than one month preceding the procedure were considered as smokers.

Hyperlipidemia was defined as serum total cholesterol level of more than 200 mg/dL, LDL cholesterol level of more than 130 mg/dL, HDL cholesterol of less than 40 mg/dL, or triglyceride of higher than 250 mg/dL. History of hypertension was defined as blood pressure of more than 140/90 mmHg or taking anti-hypertensive agents. Diabetes mellitus was defined as taking insulin or hypoglycemic agents. Coronary angiography reports were reviewed as well. The results of angiography, which was done by Seldingers method and the records were reviewed by a cardiologist was categorized by Gensini score to determine the severity of coronary artery involvement. This scoring system was first introduced by Gensini in 1983.

In this system, after determining the percentage of stenosis of the coronary arteries (0, 25, 50, 75, 90, 99, and 100) their equivalent numbers are calculated as respectively 0, 1, 2, 4, 8, 16, and 32. Then considering the location of stenosis and involved vessel, a coefficient is determined. After multiplying the Gensini number and adding the numbers, the final

Gensini score is calculated. Finally the patients, based on Gensini score, are categorized into five groups as follows: without any obstruction (lack of coronary artery involvement), mono-vessel (involvement of single coronary artery), two-vessel (involvement of two coronary arteries), three-vessel (involvement of three coronary arteries), and ectasia (dilation of coronary artery). The data were analyzed by SPSS software (ver. 22.0). Descriptive indices were used for categorical data (frequency and percentage) and for continuous data (mean and standard deviation). Analysis of variance (ANOVA) and independent t test were used for parametric data. For non-parametric data the chi-squared test and Kruskal-Wallis tests were used.

In order to determine the relationship between NLR and the number of diseased coronary arteries, Pearson’s correlation test was used.

Results

In this study, 1,498 patients who required coronary angiography were included. There were 885 males (59.1%).

Mean age of the patients was 57.08 years. About 41.4% had hypertension, 18.9% had hyperlipidemia, 11.4% were smokers, 0.7% had history of alcohol drinking, 13.6% had history of cardiovascular diseases, and 20% had history of diabetes mellitus. Mean FBS was 122.38 mg/dL, serum total cholesterol was 175.12 mg/dL, hemoglobin was 13.19, platelet was 228,707.28, creatinine was 1.15, triglyceride was 154.85, urea was 36.2 mg/dL, HDL was 45.21 mg/dL, LDL was 100.17 mg/dL, WBC was 8,167.72, and MCV was 84.39 (Tables 1 and 2).

The analyses showed that significant relationship existed between age and gender with the number of diseased coronary arteries (P< 0.05). Also, ANOVA and Kruskal-Wallis tests results showed that significant relationship existed between FBS, WBC count, hemoglobin level, platelet count, and urea with severity of coronary artery involvement (P < 0.05). However, no significant relationship (P> 0.05) existed between serum total cholesterol level, HDL, LDL, triglyceride, MCV, and creatinine with severity of coronary artery involvement (Tables 1 and 2).

		Total	Severity of coronary artery involvement based on coronary angiography reports					P value
			Normal	Mild	One-vessel	Two-vessel	Three-vessel	
Age, year, mean (±SD)		57.08 (±10.84)	51.65 (10.91)	57.42 (9.33)	56.67 (10.18)	59.46 (10.15)	61.05 (10.19)	< 0.001
Gender	Male	885 (40.9%)	176 (46.2%)	114 (57.6%)	164 (60.3%)	181 (63.7%)	250 (68.9%)	< 0.001
	Female	613 (40.9%)	205 (53.8%)	84 (42.4%)	108 (39.7%)	103 (36.3%)	113 (31.1%)	
Hypertension	Yes	620 (41.4%)	142 (37.3%)	83 (41.9%)	106 (39%)	119 (41.9%)	170 (46.8%)	0.099
	No	878 (58.6%)	239 (62.7%)	115 (58.1%)	166 (61%)	165 (58.1%)	193 (53.2%)	
Hyperlipidemia	Yes	283 (18.9%)	65 (17.1%)	38 (19.2%)	60 (22.1%)	63 (22.2%)	57 (15.7%)	0.134
	No	1215 (81.1%)	316 (82.9%)	160 (80.8%)	212 (77.9%)	221 (77.8%)	306 (84.3%)	
Smoking	Yes	170 (11.4%)	36 (10.7%)	19 (11%)	28 (11.2%)	28 (10.8%)	43 (13.1%)	0.882
	No	1328 (88.6%)	300 (89.3%)	153 (89%)	222 (88.8%)	231 (89.2%)	286 (86.9%)	
Alcohol drinking	Yes	10 (0.7%)	3 (0.9%)	0	1 (0.4%)	1 (0.4%)	5 (1.5%)	0.295
	No	1488 (99.3%)	333 (99.1%)	172 (100%)	249 (99.6%)	258 (99.6%)	324 (98.5%)	
Cardiac disease	Yes	203 (13.6%)	37 (9.7%)	23 (11.6%)	38 (14%)	40 (14.1%)	65 (17.9%)	0.022
	No	1295 (86.4%)	344 (90.2%)	175 (88.4%)	234 (86%)	244 (85.9%)	298 (82.1%)	
DM	Yes	299 (20%)	49 (12.9%)	36 (18.2%)	56 (20.6%)	63 (22.2%)	95 (26.2%)	< 0.001
	No	1199 (80%)	332 (87.1%)	162 (81.8%)	216 (79.4%)	221 (77.8%)	268 (73.8%)	
Chest pain	ACS	822 (54.9%)	211 (55.4%)	101 (51%)	144 (52.9%)	156 (54.9%)	210 (57.9%)	0.012
	CSA	181 (12.1%)	58 (15.2%)	20 (10.1%)	45 (16.5%)	27 (9.5%)	31 (8.5%)	
	Unknown	495 (23%)	112 (29.4%)	77 (38.9%)	83 (30.5%)	101 (35.6%)	122 (33.6%)	

Table 1: Demographic data, coronary artery disease risk factors, and type of chest pain based on the number of diseases coronary arteries.

The results of Chi-squared test and Kruskal-Wallis test showed that significant relationship ($P < 0.05$) existed between history of cardiovascular disease, diabetes mellitus, type of chest pain, and LVEF with the number of diseased coronary arteries. Conversely, no significant relationship ($P > 0.05$) existed between history of hypertension, hyperlipidemia, smoking, and alcohol drinking with CAD severity (Tables 1 and 2).

ders (16-20). In a study on 300 patients with ACS (acute coronary syndrome), it was reported that high NLR was associated with 30% more risk of in-hospital mortality (21). Another study noted that application of NLR and hemoglobin level yields useful information in order to categorize primary risk in patients with ST-segment elevation MI (STEMI) (22). Patients with high NLR and anemia experienced higher rate of 6-month mortality compared to

	Total	Severity of coronary artery involvement based on coronary angiography reports					P value
		Normal	Mild	One-vessel	Two-vessel	Three-vessel	
LVEF	48.17 (9.95)	51.09 (9.01)	49.02 (9.54)	48.73 (9.72)	46.97 (9.63)	45.14 (10.56)	< 0.001
FBS	122.38 (50.49)	109.07 (38.48)	114.47 (38.31)	118.62 (46.03)	128.04 (55.4)	139.04 (60.59)	< 0.001
Serum total cholesterol	175.12 (37.65)	177.78 (35.6)	166.48 (28.84)	180.05 (38.71)	169.8 (36.58)	176.05 (41.52)	0.428
Hemoglobin	13.19 (1.71)	13.28 (1.63)	13.44 (1.58)	13.34 (1.75)	13.25 (1.69)	12.82 (1.81)	< 0.001
Platelet	228,707.28 (73,027.38)	232,188 (63,062)	222,971 (61,971)	240,200 (77,461)	230,620 (80,800)	218,073 (77,117)	0.002
Creatinine	1.15 (0.97)	1.57 (7.31)	1.19 (1.14)	1.08 (0.59)	1.16 (1)	1.24 (1.22)	0.177
Triglyceride	154.85 (81.52)	152.91 (75.48)	151.15 (75.62)	152.2 (89.27)	150.38 (85.3)	162.39 (81.38)	0.909
Urea	36.2 (13.63)	34.22 (12.91)	35.691 (9.82)	35.2 (9.66)	35.87 (12.98)	39.58 (17.97)	< 0.001
HDL	45.21 (10.87)	45.89 (7.82)	42.41 (8.58)	47.86 (15.64)	43.33 (8.32)	45.04 (10.96)	0.133
LDL	100.17 (29.06)	102.48 (27.27)	94.85 (24.79)	104.73 (32.12)	96.36 (26.53)	99.54 (31.11)	0.454
WBC	8167.72 (2995.16)	7522.8 (2381)	6896.9 (2125)	8394.8 (3080)	8166.7 (2718)	9368.3 (3605)	< 0.001
MCV	84.39 (6.23)	83.7 (6.44)	84.29 (6.68)	84.65 (6.26)	84.86 (6.2)	84.61 (5.68)	0.122

Table 2: Left ventricular ejection fraction (LVEF) and laboratory data based on the number of diseased coronary arteries.

LVEF= left ventricular ejection fraction; FBS= fasting blood sugar; HDL= high-density lipoprotein; LDL= low-density lipoprotein; WBC= white blood cell; MCV= mean corpuscular volume Mean neutrophil was 64.03 mg/dL. Mean lymphocyte was 33.62 mg/dL and NLR was 2.05. There was significant relationship between neutrophil, lymphocyte and increased NLR with the number of diseased coronary arteries. With higher neutrophil, lymphocyte, and NLR the number of diseased coronary arteries increased.

Discussion

In this study with objective of investigating the relationship between NLR and CAD severity, it was revealed that with increased number of neutrophils, the number of diseased coronary arteries increased as well. With higher lymphocytes, the number of diseased arteries decreased; so with higher NLR the number of diseased coronary arteries increased. Previous studies show that high NLR is associated with poor outcome in various cardiovascular disor-

those with lower NLR and without anemia⁽²³⁾. In recent publications, it has been noted that high NLR is associated with higher mortality and poor prognosis in ACS patients, especially those with STEMI^(17, 18, 20, 21). Studies have indicated that severity of CAD is associated with NLR. Kaya et al. (2014) reported that NLR is a predictor for severe atherosclerosis which can be helpful for risk determination in CAD patients. They showed that significant relationship exists between NLR and Gensini score⁽²⁴⁾.

In another study, Sonmez et al. (2013) showed that NLR is a significant clinical laboratory marker associated with presence and complexity of CAD. They noted that strong association exists between NLR and SYNTAX score⁽¹⁹⁾. Sari et al. (2015) noted that NLR is a simple method to predict CAD in angiography patients and can be part of cardiovascular state examination before angiography. They reported that not only a relationship exists between NLR and SYNTAX score, but a relationship also exists between NLR and Gensini score⁽²⁵⁾. It has been well demonstrated that inflammation plays a pivotal role in atherosclerosis⁽¹⁶⁾.

Inflammation not only causes cardiovascular diseases, but also is associated with several chronic conditions such as malignancy, diabetes mellitus, high blood pressure, connective tissue diseases, and chronic kidney disease⁽²⁶⁻²⁹⁾. In the beginning of atherosclerotic plaque formation, inflammatory factors are released from endothelial cells and cause vascular damage⁽¹⁶⁾. In addition to the initial stages of atherosclerosis, inflammatory markers have important role in thrombosis formation due to plaque separation in ACS^(17, 18).

Therefore, it is expected to see raised levels of inflammatory markers in cardiovascular diseases. Many inflammatory markers such as CRP, tumor necrosis factor (TNF), IL-1 and IL-6 are known as inflammation process indicators. Recent studies show that WBC count and differential cells are useful to predict inflammation in patients with cardiovascular diseases⁽³⁰⁾. NLR is calculated considering WBC count, which is a widely accessible laboratory test, and inexpensive assay. The current study has important clinical implications. NLR can be used as a promising marker in prediction of the number of diseased coronary arteries and severity of CAD in coronary angiography patients. NLR is simple, inexpensive, and widely accessible and can be used to identify patients at risk for advanced CAD who are candidate for aggressive treatments to control CAD risk factors. It should be noted that in review of previous literature about pathophysiology of CAD, no definite causal relationship has been indicated between NLR with severity of CAD. It seems that discovering this relationship by future physiology and pathology scholarly activities will be so useful. Meticulous laboratory tests and a relative large sample size are of strengths of this study. However, of limitations we faced are the nature of the study which was retrospective and short follow-up period to determine exact relationship between inflammatory markers and cardiovascular events. Therefore, designing prospective studies is inevitable. Although we studied effective factors, we did not assess predictive value of NLR and other inflammatory markers such as CRP, TNF, IL-1, and IL-6 were not assessed.

Conclusion

Based on the results, NLR is effective on the number of diseased coronary arteries in patients undergoing coronary angiography. As a result, sooner recognition and application of this factor can be

helpful in treatment of patients. It seems that NLR is a simple factor to evaluate the number of diseased coronary arteries in patients undergoing coronary angiography. The results of this study can be presented to cardiologists to be used for patients before proceeding to angiography.

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