Relationship between Neutrophil-to-lymphocyte Ratio and the Severity of Coronary Artery Disease in Patients Undergoing Cardiac Catheterization

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ARTICLE INFO	ABSTRACT
	Introduction: Neutrophil-to-lymphocyte ratio (NLR) is considered as an independent predictor of long-term prognosis in the individual patients with coronary artery disease (CAD). This study sought to assess the relationship between NLR and CAD severity in Iranian patients undergoing cardiac catheterization. **Material and Methods:** This prospective study was conducted on 500 patients with acute coronary syndrome (ACS) presented to Shahid Beheshti Hospital, Qom, Iran, for admission and underwent cardiac catheterization between March 2015 and May 2017. The patients were assigned into three groups of high NLR (more than 3), intermediate NLR (between 2 and 3), and low NLR (less than 2). Then the CAD severity and its relationship with NLR were assessed. **Results:** According to the results, there was a significant difference between the groups in terms of CAD severity (P<0.001), and high NLR was independently associated with more severe CAD. **Conclusion:** Given the results of this study, high NLR was associated with CAD severity.

Introduction

Globally, coronary artery disease (CAD) is the leading cause of morbidity and mortality (1). Various risk factors affect the pathogenesis of atherosclerosis, such as dyslipidemia, diabetes mellitus (DM), smoking, genetic susceptibility, and endothelial cell injuries; however, there might be several other risk factors (2). According to the literature, inflammatory cell count, which includes monocytes, lymphocytes, eosinophils, and neutrophils, are associated with CAD pathogenesis (3).

The adhesion of neutrophils and monocytes to endothelial cells is the initial phase of acute inflammation, which plays a crucial role in all stages of CAD (4, 5). Atherogenic lipoproteins such as low-density lipoprotein (LDL) have several pro-inflammatory properties, while high-density lipoprotein exerts anti-atherogenic and anti-inflammatory functions. Oxidized-LDL may stimulate monocyte-derived macrophage generation, and the entry of monocytes and lymphocytes into forming atherosclerotic plaque results in aggravated

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inflammatory response.

Macrophage and monocytes produce a variety of inflammatory cytokines and intensify the inflammatory process leading to cardiovascular (CV) events (6, 7). In addition, several clinical trials used C-reactive protein (CRP), as an inflammatory biomarker, in CAD patients for cardiac risk stratification and in high-risk patients for long-term prediction. According to evidence, patients with low risk of CAD were characterized by normal levels of CRP, which increases during CV events.

Nevertheless, the absence of the risk factors such as high CRP level does not guarantee that no CV event will occur; accordingly, another marker for the prediction of CV events should be considered (1, 8, 9). Regarding the literature, leukocytosis is associated with increased CAD morbidity and mortality in different population; additionally, it is an independent risk factor for atherosclerosis.

Consequently, leukocyte count is considered as a readily available and less expensive test in comparison to the other indicators (3). Recently, a relationship between NLR and long-term mortality of CAD was found in patients undergoing cardiac catheterization, percutaneous coronary intervention, coronary artery bypass graft, or patients with stable or unstable angina (10).

Although the relationship between NLR and CV mortality was confirmed, to the best of our knowledge, there was no evidence regarding the association between NLR and the severity of CAD in Iran. Therefore, this study aimed to investigate the relationship between NLR and CAD severity in Iranian patients undergoing cardiac catheterization.

Materials and Methods

Study Population and Protocol.

This prospective study was conducted on 500 patients older than 18 years old with ACS referred to Shahid Beheshti Hospital, Qom, Iran, who underwent cardiac catheterization between March 2015 and May 2017. The patients who underwent cardiac catheterization after at least two weeks of ACS were included in this study. The exclusion criteria entailed active infection, end stage liver or renal disease, history of surgery in the last three years, heart failure, malignancy, history of autoimmune disease, and use of corticosteroid therapy.

Demographic data, CV risk factors, and comorbidities including aging-associated diseases, hypertension (HTN), hyperlipidemia (HLP), and DM were assessed by comprehensive medical records retrieval. In

the hospital, venous blood samples were taken from each patient prior to any medical intervention, and NLR was calculated. Thereafter, the patients were divided into three groups of high NLR (more than 3), intermediate NLR (between 2 and 3), and low NLR (less than 2).

Epicardial coronary stenosis of more than 50% was considered as CAD, and its severity was categorized into three classes according to the number of involved vessels (from one to three). Severe left main coronary artery stenosis was considered equivalent to three-vessel CAD.

Statistical Analysis

In this study, the sample size was computed as 500 subjects according to the study conducted by Uysal et al. (11). The demographic data of the patients were presented as mean and standard deviation for normally distributed continuous variables median and quartile for non-normally continuous variables, and as percentages for categorical variables. The distributions of data were assessed using one-sample Kolmogorov-Smirnov test.

Moreover, one-way analysis of variance was applied to compare the means between the groups. Crosstabs statistics and the measures of association were computed for the tables with two rows and two columns using the Chi-squared test. All the tests were applied with the help of SPSS software, version 20. In all the measurements, P-value less than 0.05 was considered statistically significant.

Ethical Consideration

The institutional ethics committee approved the proposed protocol of this study, and a written informed consent was obtained from all the enrollees.

Results

As mentioned above, this study was conducted on 500 subjects in three groups. The demographic data and baseline characteristics of the patients are presented in Table 1. There were significant differences between the study groups considering age, gender, and the prevalence of HTN, DM and HLP. A significant difference was observed between the NLR and mean age, for instance, older people were in the high NLR (P<0.001; figures 1). Furthermore, male patients had significant higher NLR and more severe CAD (P<0.001; figures 2).

The comparison of the mean absolute neutrophil and lymphocyte counts between the groups revealed significant differences.

Table 1. Baseline clinical characteristics of the patients grouped by NLR

Variables	Low NLR (<2)	Intermediate NLR (2-3)	High NLR (>3)	P-value*
Age (year) [mean ± SD]	56 ± 10	60 ± 11	61 ± 10	<0.001
Male [n (%)]	143 (28)	79 (15)	35 (7)	0.006
HTN [n (%)]	171 (55)	85 (62)	28 (52)	<0.001
Diabetes [n (%)]	91 (29)	45 (32)	19 (35)	<0.001
HLP [n (%)]	157 (50)	83 (60)	22 (41)	<0.001

*Data are presented as mean or number (%); One-way analysis of variance was applied to compare the means between the groups. NLR, Neutrophil-to-lymphocyte ratio; HTN, hypertension; HLP, hyperlipidemia
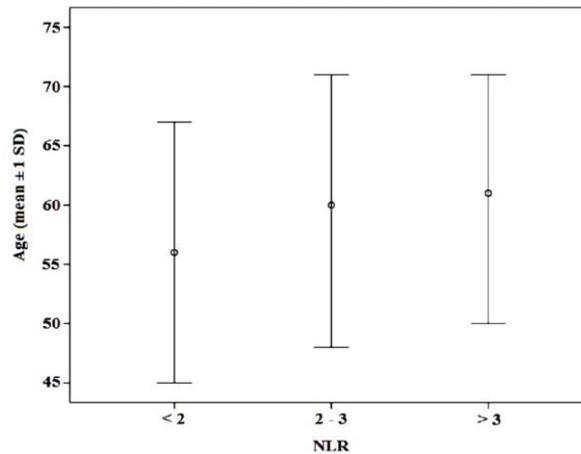
Figure 1. Association between the NLR and mean age; older people were in the high NLR
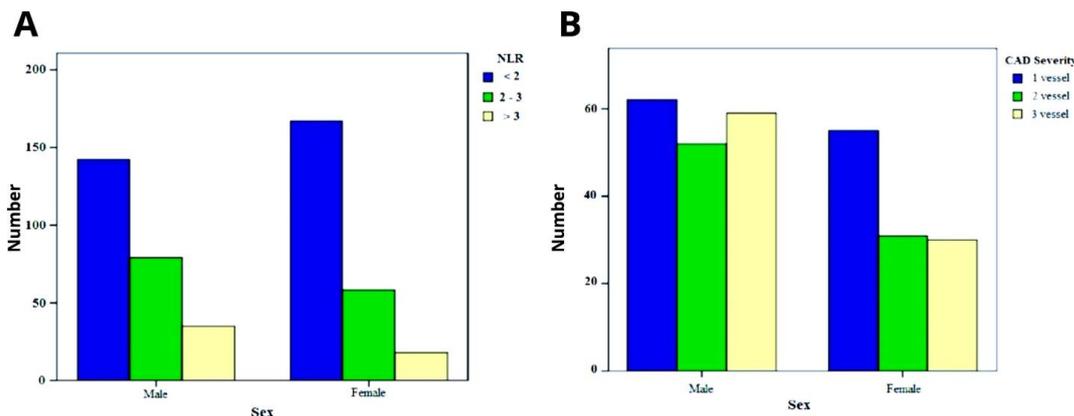
Figure 2. Association between gender and NLR and CAD severity; A. Male patients had significant higher NLR. B. Male patients had significant more severe CAD

The patients with one-vessel CAD had the least neutrophil and highest lymphocyte counts, and those with three-vessel CAD had the highest neutrophil and least lymphocyte counts (P<0.001; Table 2).

Further, there was a significant difference between different groups of NLR considering CAD severity (P<0.001; Table 3; Figure 3). Regarding the results of the current study, high NLR is independently

**Table 2.** Association of neutrophil and lymphocyte counts between CAD groups

Parameter	1-vessel CAD	2-vessel CAD	3-vessel CAD	P-value*
Neutrophils [mean ± SD]	57.1 ± 9.2	58.1 ± 9.5	58.1 ± 10.1	0.007
Lymphocytes [mean ± SD]	32.9 ± 9.1	32.6 ± 8.8	31.1 ± 9.7	<0.001

*Data are presented as mean ± SD; Between-group comparisons were assessed using the Kruskal-Wallis for non-normally distributed values. CAD, coronary artery disease.

Table 3. Procedural characteristics of the patients grouped by NLR

CAD severity	Low NLR (<2)	Intermediate NLR (2-3)	High NLR (>3)	P-value
1-vessel [n (%)]	64 (54.7)	41 (35)	12 (10.3)	
2-vessel [n (%)]	46 (55.4)	29 (34.9)	8 (9.6)	<0.001
3-vessel [n (%)]	48 (53)	26 (29.2)	15 (16.9)	

*Data are presented as number (%); The categorical variables were compared through using chi-square test. CAD, coronary artery disease; NLR, Neutrophil-to-lymphocyte ratio
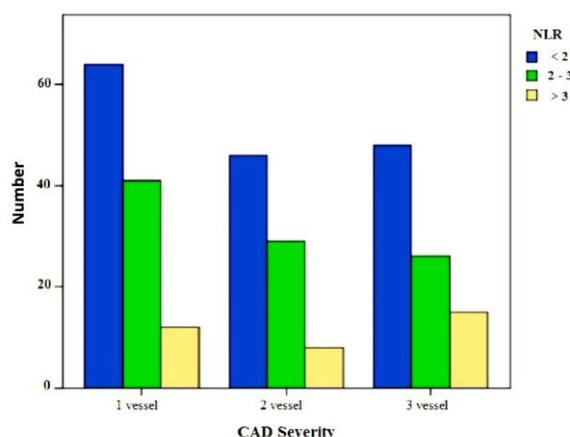
Figure 3. Number of patients in different NLR groups according to severity of coronary disease

associated with more severe CAD.

Discussion

Several studies suggest that NLR can be used as an inflammatory biomarker and can be considered as an independent prognostic marker. The NLR is a readily available biomarker, which is obtained from a universally convenient low-cost test (differential leukocyte count). This test that is routinely performed on admission develops relevant classification to predict mortality.

As the results of this study indicated, high NLR was associated with CAD severity; therefore, it affects the outcome of CV events. In addition, a significant relationship was observed between high NLR and age, gender, DM, HTN and HLP. Our findings were in agreement with the results of previous studies, which reported that high NLR was independently associated with increased severity of CAD (11, 12, 13, 14).

In the study carried out by Arbel et al., 3005 patients undergoing cardiac catheterrization were divided into three NLR groups including more than 3 (high), between 2 and 3 (intermediate), and less than 2 (low). High NLR was independently associated with more CAD severity and higher rate of major CV events during up to three years of follow-up. The mentioned study was the first one demonstrating the relationship between NLR and CAD severity (12).

Zhang et al. conducted a study on 219 patients, who were assigned into two groups according to their NLR value. The results of the mentioned study demonstrated a strong correlation between age, gender, CAD severity, and NLR value (13). In the present study, the patients with one-vessel CAD had the least neutrophil and the highest lymphocyte counts, and the patients with

three-vessel CAD had the highest neutrophil and the least lymphocyte counts.

Moreover, Uysal et al. and Trakarnwijitr et al. revealed that more severe CAD was related to elevated neutrophil and decreased lymphocyte counts (11, 15). All of these studies confirmed that NLR has the potential of being a highly useful predictor of outcomes in patients with CVD. However, our results were inconsistent with the results of several studies (10, 11). The results of a study performed by Kaya et al. on 172 patients demonstrated no significant relationship between age, gender, HTN, DM, and CAD severity (10).

Furthermore, in various studies, different values of NLR were considered as normal or acceptable. Consistent with our study, in Arbel'study, NLR>3 was considered as abnormal high value; other trials mentioned that NLR<2.2 and <5 were normal (12, 16). Nevertheless, this inconsistency might be due to the different states of inflammation in the studies.

Conclusion

According to the results, high NLR could be considered as an independent predictor of CAD severity. Globally, differential leukocyte count is a cost-effective and available test for providing additional information regarding CVD prognosis. Nevertheless, further wide scale epidemiological studies are recommended to establish a normal value.

Acknowledgments

Conflict of Interest

The authors declare no conflict of interest.

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