

Neutrophil-Lymphocyte Ratio Could Be a Marker for Erectile Dysfunction

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Purpose: The literature reveals lots of information about the relationship between inflammatory markers and many diseases. In this study, we aimed to determine the relationship between erectile dysfunction and the neutrophil-lymphocyte ratio (NLR), which is a simple and nonspecific inflammatory marker.

Materials and Methods: Ninety patients with erectile dysfunction (ED) and ninety-four healthy subjects were included in this study from our internal medicine and urology clinics. As diagnosis criteria, we used the first 5 questions of International Index for Erectile Function. The duration of erectile dysfunction was asked and recorded. Height, weight and waist circumference of patients were measured. We performed total blood count, sedimentation, C-reactive protein, and blood chemistry.

Results: There were statistically significant differences between the control [1,038 (0,507-1,92)] and ED [59,5 (52,0-68,0)] groups in terms of NLR ($P < .001$). According to the multivariate logistic regression analysis, Duration of ED (Cut off: 7,5 month) predicted ED with 78,8% sensitivity and 63,1% specificity (AUC: $< .001$, 95% CI 1,030 (1,010-1,050), $P = .003$). Moreover, NLR (Cut off: 1,574) predicted ED with 81,8% sensitivity and 67,0% specificity (AUC: $< 0,001$, 95% CI 1,994 (1,139-3,490), $P = .016$) according to the multivariate logistic regression analysis.

Conclusion: It was found that the neutrophil-lymphocyte ratio was higher in patient group than the control group. Also, the neutrophil-lymphocyte ratio (NLR) predicted ED and it might be helpful in diagnosing erectile dysfunction.

Keywords: erectile dysfunction; neutrophil-lymphocyte ratio; inflammation; diabetes mellitus; coronary artery disease

INTRODUCTION

Erectile dysfunction (ED) is described as the inability to obtain or sustain an erection sufficiently in order to enable convincing sexual intercourse.⁽¹⁾

Erectile dysfunction develops from inadequate penile tissue response to a sexual indication. The reaction can be interrupted at several points. For instance, impairing of vascular smooth muscle cells (obesity, age) and endothelial cells (diabetes, smoking), and compression of the vascular lumen (hypertension, CAD) have all led to congestion of the corpus cavernosum.⁽²⁾ Furthermore, denervation from spinal trauma or prostatic surgery and psychological issues should be considered in discussions with patients.

Erectile dysfunction (ED) is estimated to affect about 75% of men over the age of 75 and 20% of men over the age of 20.⁽³⁾ In age-adjusted models, erectile dysfunction has been indicated to be related with: high cholesterol, diabetes, cardiovascular disease history, hypertension, hormone problems, alcohol consumption, stress, anxiety, smoking, BMI greater than 30 kg/m² and less than 25 kg/m².⁽⁴⁾

Although guidelines such as the International Index of Erectile Function (IIEF-5) have been developed to assess erectile dysfunction, it is most often diagnosed on the basis of the clinical notion, while validated evaluation procedures are reserved for clinical trials.⁽⁵⁾

The association among many diseases, inflammatory markers and also their roles in the disease etiopathogenesis are important. The literature reveals that emergence and severity of ED are related with markers and mediators of inflammation and endothelial dysfunction.⁽⁶⁾ Routinely available markers and mediators (interleukin (IL)-1^α, TNF-^α, IL-6, CRP, IL-10,) and endothelial/prothrombotic factors of the systemic inflammatory response is the neutrophil-lymphocyte ratio (NLR), a ratio of the neutrophil to lymphocyte count, and it has been reported to have prognostic value in a variety of diseases.⁽⁷⁻¹¹⁾

This study was aimed to identify the relationship between ED and the NLR, which is a simple and nonspecific inflammatory marker.

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Table 1. Comparison of the demographic characteristics and biochemical parameters in groups.

Variables	Control (n=94) Mean±SEM or Median (min-max)	ED (n=90)	p value
Age (year)	59.5 (52.0 - 68.0)	61.0 (53.0 - 66.25)	0.690
Smoking (%)	15.1	20	0.413
CHF (%)	2.7	1.1	0.449
COPD (%)	4.1	1.1	0.224
CAD (%)	5.5	16.7*	0.05(OR:2.457%95CI:0.951-6.348)
HT (%)	29.7	42.2	0.195
DM (%)	14.9	28.9	0.05 (OR:1.980 %95 CI:0.979-.008)
Goiter (%)	1.9	1.4	0.852
Size (m)	1.70 ± 0.060	1.70 ± 0.058	0.907
Weight (kg)	81.04 ± 15.094	83.86 ± 12.055	0.183
BMI (kg/m ²)	27.048 (25.102 - 30.44)	28.871 (26.72 - 30.85)	0.053
Waist circumference	101 (95 - 108)	102 (94 - 108)	0.903
Hemoglobin (g/dl)	14.43 ± 1.196	14.57 ± 1.41	0.375
Lymphocytes	2.28 (1.64-3.03)	1.86 (1.0 - 2.39)	0.194
RDW	14.30 ± 1.132	14.0 ± 1.31	0.111
Neutrophil	2.67 (1-3.94)	4.49 (3.62-5.35)***	< 0.001
NLR	1.038 (0.507 - 1.92)	2.38 (1.67 - 3.90)***	< 0.001
ESR	12.50 (9.0-19.5)	11 (4.75 - 17.25)	0.251
CRP (mg/l)	0.681 (0.14-0.59)	0.42 (0.12 - 1.0)	0.626
BUN (mg/dl)	15.0 (13.0 - 17.0)	15.8 (13.0 - 18.6)	0.099
Creatine (mg/dl)	0.90 (0.82-0.95)	0.92 (0.80 - 1.06)	0.229
Cholesterol (mg/dl)	205.75 ± 35.22	196.902 ± 48.75	0.321
Triglyceride (mg/dl)	159 (88 - 211)	143 (92 - 213)	0.686
LDL-C (mg/dl)	132.10 (104.90 - 153.20)	128 (110.0 -156.0)	0.949
HDL-C (mg/dl)	42.0 (38.0-51.25)	42.0 (35.0 - 48.0)	0.222

Abbreviations: ED: Erectile dysfunction, COPD: Chronic obstructive pulmonary disease, CAD: Coronary artery disease, HT: Hypertension, DM: Diabetes mellitus, CHF: chronic heart failure, BMI: Body mass index, RDW: Red Cell Distribution Width, NLR: neutrophil-lymphocyte ratio, ESR: Sedimentation, CRP: C-reactive protein, BUN: Blood Urea Nitrogen, LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol. *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$

MATERIAL AND METHODS

Ethics standards

This planned research complies with the Helsinki Declaration rules including ethical guidelines and patient's rights were confirmed by the Ordu University, Ethics Committee (Date: May 2014, Number: 2014/05).

Patient selection

Patients evaluated in urology and internal medicine out-patient clinics of Ordu University between September 2016 and July 2017 were enrolled in this study. 90 patients with erectile dysfunction and 94 healthy subjects were included in this study.

Inclusion and exclusion criteria

As diagnosis criteria, we used the first 5 questions of International Index for ED. The exclusion criteria used for both ED and Control group. The exclusion criteria were as follows: current treatment (Cialis, Levitra, Staxyn, Stendra, Viagra etc.) for ED, aged older than 70 years and younger than 40 years, psychiatric disease, being of an endocrine disturbance (except for type 2 DM), diabetic complications (neuropathy, ketoacidosis) concomitant malignancies, background of prior penile, pelvic surgery-trauma, neurological disease, penile bending disease and chronic diseases (hepatic, renal).

Measurements

Comprehensive anamnesis and a thorough medical examination were applied to all participants. Drug usage and prior operation history were asked, and cigarette habits (at least 10 years) were also noted. Body mass index (BMI), waist circumference, weight, and height were measured for each individual. Total blood count, sedimentation, C-reactive protein, BUN (Blood Urea Nitrogen), creatine, cholesterol, LDL-C (Low-density

lipoprotein cholesterol) and HDL-C (High-density lipoprotein cholesterol) measurements of the patients were recorded. The NLR was computed as the total neutrophil count separated by the total lymphocyte count.

Statistical analysis

SPSS 25.0 statistics package software was used for statistical analysis. The normality of the distribution of variables was analyzed by the Kolmogorov-Smirnov normality test. For normally distributed data, comparisons between the two groups were made using a t-test. Comparisons between the two groups were made using a Mann-Whitney U test for not normally distributed data. All values were reported as mean ± SEM or Median (min-max). Statistical significance was considered as $P < 0.05$. The categorical data analysis was realized using the Fisher's Exact, Pearson chi-square test and Fisher-Freeman-Halton test. Variables having unadjusted p-value lower than 0.10 in univariate analysis were considered as possible risk markers for ED and included in the multivariate model. Multivariate logistic regression analysis with backward elimination was applied to define independent predictors of ED. A stepwise linear regression model was established with variables related to the dependent variables.

RESULTS

The comparisons of the demographic characteristics and biochemical parameters in groups are shown in Table 1. The mean age of the patients with ED was 61.0 (53.0-66.25) and the mean age of control group was 59.5 (52.0-68.0) ($P = .69$). The ratio of smokers was 20% in patient group and 15.2% in control group ($P = .41$). There weren't statistical differences between the groups in terms of BMI and weight. The NLR was 2.38 (1.67-3.90) in patient group and 1.038 (0.507-1.92) in

Table 2. Univariate and multivariate logistic regression analysis for the independent predictors of ED.

Variables	Univariate <i>p</i> value	Multivariate OR and 95% CI	Multivariate <i>p</i> value
Neutrophil	< 0.001	1.541 (0.987 - 2.406)	0.057
NLR	< 0.001	1.994 (1.139 - 3.490)	0.016
DM	0.05	2.528 (0.814 - 7.852)	0.109
CAD	0.05	0.058	0.096

Abbreviations: CI: Confidence interval, OR: Odds ratio, NLR: neutrophil-lymphocyte ratio, DM: Diabetes mellitus, CAD: Coronary artery disease

control group ($P < .001$) (**Figure 1**). NLR over 1.574 (cut-off value) is predictive for ED with 81.8% sensitivity and 67.0% specificity (AUC: $< .001$, 95% CI: 1.994 (1.139-3.490), $P = .016$) according to the multivariate logistic regression analysis (**Figure 2**). In univariate analysis, increased neutrophil and the NLR values and the presence of DM and CAD were seen to be related with increased ED possibility. However, The BMI was not related with increased ED possibility. Consequently, multivariate logistic regression analysis pointed that the NLR could be an independent predictor of ED (**Table 2**).

DISCUSSION

ED is a well-known disease with increasing frequency that affects both the individual and his/her partner. In a recent study, Aytac et al. predicted that there were over 152 million men who experienced ED in the world in 1995, and the projections for 2025 show a prevalence of around 322 million patients with ED, an increase of nearly 170 million.⁽¹²⁾ Therefore, the reliable and fast diagnosis and treatment of ED is important. In general population ED prevalence ranges between 18 and 51%.⁽¹³⁾ ED incidence raises with age; its frequency between men aged 60-69 is 20 - 40%, whereas along the eighth and ninth decades this ratio raises up to 50–100%.⁽¹⁴⁾ Several ratios declared by multiple researches are possibly owing to variations in the research methodology and the age distribution and socio-economic status of the research groups. ED decreases the general health and life quality of both the patient and partner. It is a multifactorial disease with hormonal, psychogenic, iatrogenic and anatomical

factors supporting to its pathophysiology.⁽¹⁵⁾ The most important reason of ED among aged men is organic disease owing to atherosclerosis mediated vascular disturbance.⁽¹⁶⁾ In our study, we investigated psychogenic ED, which is the principle reason of ED in men aged 40–70, and we accepted other reasons of ED (e.g., hormonal disturbance, psychogenic disorders, history of pelvic surgery or previous trauma and neurological disease). The relation between DM and ED was reported by Corona et al.⁽¹⁷⁾ In our study, there are significant differences between the control groups and ED in terms of diabetes. Furthermore, in univariate regression analysis DM was showed to be related with increased possibility of ED. Besides that aging, cardiovascular risks (diabetes, hypertension, dyslipidemia, obesity and smoking status) are given to be firmly associated with the ED pathophysiology.⁽¹⁸⁾ Thus, it is reputed that ED is an early trail of a systemic disorder that could arise in CVD. Exposed to atherogenic risk factors lead to endothelial injury and finally result in atherosclerosis. Atherosclerosis affects all vascular beds at a comparable rate, however the time of symptom initiation diverge relying on the affected artery diameter.⁽¹⁹⁾ In our study, there are significant differences between the control and ED groups in terms of coronary artery disease (CAD). Furthermore, in univariate regression analysis, CAD was found to be associated with increased probability of ED. Endothelial injury plays a considerable role in the ED and coronary artery diseases pathogenesis.⁽²⁰⁻²²⁾ Sub-clinical inflammation with low-degree may affect endothelial function and result in prothrombotic cases. Some researches have represented that the onset and ED severity are weakly related with increased levels of

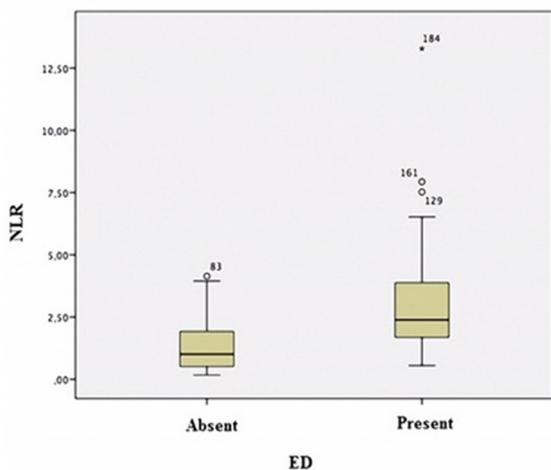


Figure 1. Comparison of NLR in patient group and in control group.

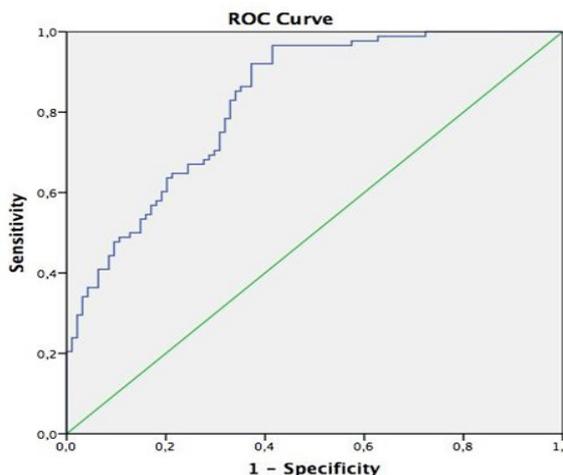


Figure 2. NLR over 1.574 (cut-off value) is predictive for ED with %81.8 sensitivity and %67.0 specificity.

inflammatory markers.^(21,23-25) Researches have reported that ED patients showed increased formation of inflammatory mediators (interleukin (IL)-1 β , TNF- α , IL-6, CRP, IL-10), markers, and endothelial/prothrombotic factors. As reported in these research, ED is related with many inflammatory mediators and markers.^(21,23,25) Based on these knowledge, we aimed to investigate the relation of ED with the NLR, which is the marker of inflammation and has been extensively studied in several recent studies.⁽²⁶⁻²⁸⁾ There are numerous research that studied the NLR in CAD progression. The NLR is related with prognosis in cardiac failure and CAD.⁽²⁹⁾ Demirkol et al. sighted significantly increased levels of the NLR among patients with cardiac syndrome X and CAD. Also, they showed a correlation between the NLR and the carotid intima thickness.⁽³⁰⁾ Kalay et al. reported that NLR was significantly elevated in the patients with atherosclerosis and showed that NLR is a biomarker for atherosclerosis development.⁽³¹⁾ Sambel et al. showed that the neutrophil-to-lymphocyte ratios are associated with a ED diagnosis, and they could assist as applied parameters that will not expense additional charge.⁽³²⁾ Ventimiglia et al. and Seftel made two separate studies showed that increased NLR (greater than 3) the risk of having severe ED, enhancing the already existing evidence linking systemic inflammation to ED.^(33,34) Some studies have linked ED with enhanced inflammatory state in men with obesity or metabolic syndrome.^(35,36) Although, Eaton et al did not find any association between the level of inflammatory activation and ED.⁽³⁷⁾ In our study, it was found that the NLR, which is the marker of the systemic inflammatory response, was higher in patient group than control group. Also, NLR over 1.574 (cut-off value) is predictive for ED and could be helpful in diagnosing ED. According to our findings, neutrophil, NLR, DM and CAD were found to be related to increased possibility of ED.

CONCLUSIONS

This study showed that NLR value could be a potential parameter for diagnosing ED. In addition, increased neutrophil, and the presence of DM and CAD should be considered in diagnosis of ED.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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