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Neutrophil to lymphocyte ratio is increased in chronic helicobacter pylori infection and returns to normal after successful eradication

Kronik helicobacter pilori enfeksiyonunda nötrofil lenfosit oranı artmıştır ve başarılı eradikasyon sonrası normale döner

Mehmet Asil, Ramazan Dertli

Necmettin Erbakan University, Meram faculty of Medicine, Department of Gastroenterology, Konya, Turkey

Abstract

Aim: Neutrophil to lymphocyte ratio (NLR) is a useful, low cost marker and it was studied in several diseases. This study was conducted to investigate NLR in chronic Helicobacter pylori infection.

Materials and Methods: Clinic and laboratory data of 286 patients with chronic Helicobacter pylori infection and 130 Helicobacter pylori negative controls were analyzed retrospectively.

Results: Mean neutrophil to lymphocyte ratio was higher in Helicobacter pylori (+) group than Helicobacter pylori (-) controls (1.98±0.76 vs. 1.64±0.44, p<0.001 respectively) Mean white blood cell and neutrophil counts were also significantly higher in Helicobacter pylori (+) group than Helicobacter pylori (-) controls (7.28±1.55/µL vs. 6.90±1.38 /µL, p=0.011 and 4.27±1.17 /µL vs. 3.82±1.04 /µL, p<0.001 respectively). Lymphocyte count, Hb, Hct, RDW, Plt, MPV, PDW were similar in both groups. 253 patients (88.5%) were given Helicobacter pylori eradication regimen. Post-treatment data were available in 76 (26.6%) patients. Helicobacter pylori, eradication treatment was successful in 45 (59.2%) patients (Group 1) and unsuccessful in 31 (40.8%) patients (Group 2). In group 1, mean pretreatment and post-treatment NLR were 1.99±0.75 and 1.70±0.60 respectively and difference was statistically significant (p=0,004). In group 2 mean pretreatment and post-treatment NLR were 1.93±0.59 and 1.76±0.56 respectively but the difference was not statistically significant (p=0.11).

Conclusion: NLR is increased in chronic H.pylori infection and returns to normal after successful H.pylori eradication treatment.

Keywords: Neutrophil To Lymphocyte Ratio; Helicobacter Pylori, disease eradication.

Öz

Amaç: Nötrofil lenfosit oranı birçok hastalıkla ilişkisi gösterilmiş ucuz bir belirteçtir. Biz de bu çalışmada kronik Helicobacter pylori enfeksiyonu olan hastalarda nötrofil lenfosit oranını araştırmayı planladık.

Gereç ve Yöntem: Kronik Helicobacter pylori enfeksiyonu olan 286 hasta ve 130 Helicobacter pilori (-) kontrol grubuna ait klinik ve laboratuar verileri retrospektif olarak analiz edildi.

Bulgular: Ortalama nötrofil lenfosit oranı Helicobacter pylori (+) grupta 1,98±0,76 ve Helicobacter pylori (-) grupta 1,64±0,44 olup aradaki fark istatistiksel olarak anlamlıydı (p<0,001). Ortalama lökosit ve nötrofil sayıları, Helicobacter pylori (+) grupta sırasıyla 7,28±1,55/µL ve 4,27±1,17 /µL ve Helicobacter pylori (-) grupta sırasıyla 6,90±1,38 /µL ve 3,82±1,04 /µL olarak saptanmış olup her iki grup arasındaki fark gerek ortalama lökosit sayısı açısından (p=0,011) gerek se ortalama nötrofil sayısı açısından (p<0,001) anlamlı bulundu. Her iki grup arasında ortalama lenfosit sayısı, hemoglobin, hematokrit, RDW, trombosit sayısı, MPV, PDW açısından fark yoktu. 253 hastaya Helicobacter pylori eradikasyon tedavisi verilmişti. 76 hastada tedavi sonrası hematolojik veriler mevcuttu. Bu hastaların 45'inde (%59,2) eradikasyon tedavisinin başarılı olduğu (grup 1), 31 hastada (%40,8) ise eradikasyonun başarısız olduğu görüldü. Grup 1 için tedavi öncesi ve sonrası ortalama nötrofil lenfosit oranlarının 1,99±0,75 ve 1.70±0.60 olduğu ve aradaki farkın istatistiksel olarak anlamlı olduğu (p=0,004), grup 2 için ise tedavi öncesi ve sonrası ortalama nötrofil lenfosit oranlarının 1,93±0,59 ve 1.76±0.56 olduğu ve aradaki farkın istatistiksel olarak anlamlı olmadığı görüldü.

Sonuç: Kronik Helicobacter pylori enfeksiyonunda nötrofil lenfosit oranı artmıştır. Başarılı eradikasyon tedavisi sonrası artmış nötrofil lenfosit oranı normale döner.

Anahtar Kelimeler: Nötrofil Lenfosit Oranı; Helicobacter Pylori; Hastalık Eradikasyonu.

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Correspondence/İletişim
Mehmet Asil
Necmettin Erbakan University, Meram faculty of Medicine, Department of Gastroenterology, Konya, Turkey
E-mail: drmehmetasil@yahoo.com.tr

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INTRODUCTION

Helicobacter pylori (H. pylori) infection is the most common infection worldwide. Approximately 50% of the world population (over 3 billion) is estimated to be infected with H. pylori (1). The prevalence of H. pylori is different among various regions in the world and it is more prevalent in developing countries. Humans are the only reservoirs for H. pylori and transmission is believed to occur via oral-fecal route. Chronic gastritis, gastric ulcer, duodenal ulcer, gastric mucosa-associated lymphoid tissue (MALT) and gastric adenocarcinoma are H. pylori associated gastrointestinal diseases. H. pylori was also found to be related to several other extra-gastrointestinal diseases (2). Given its worldwide prevalence H. pylori is accused as the leading cause of gastric cancer and recently research has been focused on H. pylori eradication as a strategy to prevent gastric cancer.

Although H. pylori itself is a non-invasive microorganism, it triggers host immune response through various mechanisms causing gastric inflammation. The inflammatory changes in chronic H. pylori gastritis are peculiar and neutrophils are shown to take important roles (3). Neutrophil to lymphocyte ratio (NLR) is a novel marker studied extensively in several gastrointestinal diseases, autoimmune and inflammatory diseases and different cancers including gastric cancer (4-8). But there are only a few studies in the literature questioning the relation between chronic H. pylori infection and NLR. Moreover, to our knowledge there is no study in the literature searching for the effect of H. pylori eradication treatment on NLR. Thus this study was conducted to investigate the association of NLR as well as other hematologic parameters with H. pylori infection and also to evaluate the effect of H. pylori eradication on these parameters.

MATERIALS and METHODS

This study was conducted in a retrospective manner. Study group consisted of 286 H. pylori positive (H. pylori (+)) patients and 130 H. pylori negative (H. pylori (-)) controls who applied to the Gastroenterology Clinic of Necmettin Erbakan University Faculty of Medicine with dyspeptic complaints between January 2015 and January 2016. H. pylori (+) group consisted of patients with a positive stool antigen test or H. pylori presence confirmed with histological examination of gastric biopsies obtained in upper gastrointestinal endoscopy. H. pylori (-) group on the other hand consisted of patients with a negative stool antigen test. Data were collected from the medical and laboratory records of the patients using the hospital management and achieving software. Absolute neutrophil and lymphocyte counts and other hematologic parameters were recorded from the complete blood count reports from automated counters on the same day with stool antigen test or upper gastrointestinal endoscopy. Neutrophil to lymphocyte ratio was calculated as absolute neutrophil count/absolute lymphocyte count.

H. pylori (+) group were also evaluated in terms of H. pylori eradication. For those patients to whom eradication treatment is prescribed, post-treatment NLR was calculated when data were available. Successful eradication was described as a negative stool antigen test at least 6 weeks after the completion of the treatment regimen and eradication failure was described as the positivity of the stool antigen test at least 6 weeks after the completion of the treatment regimen. Hematologic parameters including absolute neutrophil and lymphocyte counts were again recorded from the hospital archives from the same date with stool antigen tests in patients with available data. Patients with a known history of malignancies, hematologic diseases, autoimmune or inflammatory diseases and acute infection were excluded from the study.

The study protocol was approved by the Ethical Committee of Necmettin Erbakan University Faculty of Medicine and written informed consent were taken from all participants. Statistical analyses were done using computer software "IBM Statistical Package for Social Sciences V.18.0" for Windows. Continuous variables are expressed as mean±standard deviation. Independent Samples t Test was used to compare means between groups and Paired Samples t Test was used to compare dependent variables. Statistical significance was defined as $p<0.05$.

RESULTS

There were 286 patients in H. pylori (+) group. 118 (41.3%) of the patients were male and 168 (58.7%) of them were female. The mean age of the H. pylori (+) group was 45.24±14.54 years. On the other hand H. pylori (-) control group consisted of 57 (43.8%) males and 73 (56.2%) females, a total of 130 subjects with a mean age of 47.21±15.70 years. Two groups were found to be similar in terms of demographical characteristics.

Mean NLR was higher in H. pylori (+) group than H. pylori (-) controls and the difference between the groups was statistically significant (1.98±0.76 vs. 1.64±0.44, $p<0.001$). Mean white blood cell count was also found to be significantly higher in H. pylori (+) group than H. pylori (-) controls (7.28±1.55/μL vs. 6.90±1.38 /μL, p=0,011). Focusing on the absolute neutrophil and lymphocyte counts, statistical analyzes revealed that mean neutrophil count was significantly higher in H. pylori (+) group than H. pylori (-) controls (4.27±1.17 /μL vs. 3.82±1.04 /μL, p<0,001). Mean absolute lymphocyte count on the other hand was 2.29±0.60 /μL in H. pylori (+) group and 2.39±0.58 /μL in H. pylori (-) control group respectively and the difference between the groups was not statistically significant (p=0.09).

Other tested hematologic parameters such as serum hemoglobin concentration (Hb), hematocrit (Hct), red cell distribution width (RDW), platelet count (Plt), mean platelet volume (MPV) and platelet distribution width (PDW) were found to be similar in both H. pylori (+) group and H. pylori (-) controls except mean corpuscular volume (MCV). MCV was significantly lower in H. pylori (+) group than H. pylori (-) group (82.59±6.90 fL vs. 84.90±4.20 fL, $p<0.001$). Demographical characteristics and hematological parameters of both groups are summarized in table 1.

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Table 1. Demographical characteristics and hematologic parameters in helicobacter pylori (+) and helicobacter (-) groups

	Helicobacter pylori	N	Mean	p
Age (years)	NEGATİVE	130	47.21±15.70	
	POSİTİVE	286	45.24±14.54	>0,05
NLR	NEGATİVE	130	1.64±0.44	
	POSİTİVE	286	1.98±0.76	**<0,001**
WBC (1/µL)	NEGATİVE	130	6.90±1.38	
	POSİTİVE	286	7.28±1.55	**=0.011**
Neutrophil count (1/µL)	NEGATİVE	130	3.82±1.04	
	POSİTİVE	286	4.27±1.17	**<0,001**
Lyphocyte count (1/µL)	NEGATİVE	130	2.39±0.58	
	POSİTİVE	286	2.28±0.59	>0,05
Hemoglobin (g/dL)	NEGATİVE	130	14.26±1.49	
	POSİTİVE	286	14.04±1.82	>0,05
Hematocrit	NEGATİVE	130	42.31±3.96	
	POSİTİVE	286	42.17±16.57	>0,05
MCV (fL)	NEGATİVE	130	84.90±4.20	
	POSİTİVE	286	82.59±6.90	>0,05
RDW	NEGATİVE	130	13.32±1.15	
	POSİTİVE	286	13.48±1.67	>0,05
PLT (1/µL)	NEGATİVE	130	268.83±64.65	
	POSİTİVE	286	272.26±71.74	>0,05
MPV (fL)	NEGATİVE	130	10.31±1.04	
	POSİTİVE	286	10.52±4.94	>0,05
PDW	NEGATİVE	130	13.29±2.60	
	POSİTİVE	285	12.86±2.44	>0,05

NLR: neutrophil to lymphocyte ratio, WBC: white blood cell count, MCV: mean corpuscular volume, RDW:red cell distribution width, PLT: platelet count, MPV: mean platelet volume, PDW: platelet distribution width

Upper gastrointestinal endoscopy with gastric biopsy were available in 78 patients. Statistical analyses didn't show any relation between biopsy findings (degree of inflammation, helicobacter pylori density, presence or absence of atrophy, presence or absence of intestinal metaplasia) and any of the tested parameters (NLR, Hb, Hct, RDW, MCV, WBC, Plt, MPV, PDW). But although statistically insignificant NLR seemed to be higher in patients with moderate and severe inflammation in gastric biopsy specimens; In 26 patients (%33.3) with mild inflammation in gastric biopsy mean NLR was 1.89±1.12. On the other hand in 40 patients (%51.2) with moderate inflammation, mean NLR was 2.03±0.72 and in 12 patients (15.4%) with severe inflammation mean NLR was 2.06±0.81 (p>0.05).

Of the 286 patients in the H. pylori (+) group 253 patients (88.5%) were given H. pylori eradication regimen. Post-treatment data required for statistical analyses were available in 76 (26.6%) patients. In 45 (59.2%) of the 76 patients (Group 1) H. pylori, eradication was successful, confirmed with a negative stool antigen test at least 6 weeks after the completion of the treatment. On the other hand, in 31 (40.8%) patients (Group 2), post treatment stool antigen tests were still positive indicating eradication failure. Mean pretreatment NLR were similar in both groups. On the other hand mean pretreatment NLR in both group 1 and group 2 were significantly higher than H. pylori (-) controls (1.99±0.75 in group 1, 1.93±0.59 in group 2 and 1.64±0.44 for H. pylori (-) controls, p=0.002).

In group 1, mean pretreatment NLR, WBC and neutrophil counts were 1.99±0.75, 7.26±6.94 /µL and 4.26±3.84 respectively. Mean post-treatment values for NLR, WBC and neutrophil counts were 1.70±0.60, 6.94±1.55 /µL and 3.84±1.16 /µL in group 1 patients and the differences between pretreatment and post-treatment values for all three parameters were found to be statistically significant (p values for NLR, WBC and neutrophil counts were 0,004, 0.049 and 0.003 respectively).

In group 2, mean pretreatment NLR, WBC and neutrophil counts were 1.93±0.59, 7.51±1.74 /µL and 4.34±1.11 respectively. On the other hand mean post-treatment NLR, WBC and neutrophil counts were found to be 1.76±0.56, 7.44±1.82 /µL and 4.14±1.27 /µL. Although post-treatment values were again lower than pretreatment values the differences were not statistically significant (p values for NLR, WBC and neutrophil counts were 0.11, 0.079 and 0.36 respectively).

Pre and post-treatment data regarding all tested hematological parameters are summarized in table 2 and pretreatment and post-treatment NLR in group 1, group 2 and H. pylori (-) controls are summarized in figure 1.

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Table 2. Pretreatment and post-treatment values of tested hematological parameters in group 1 and group 2

	Group 1			Group 2		
	Pretreatment	Posttreatment	p	Pretreatment	Posttreatment	p
NLR	1.99±0.75	1.70±0.60	**0.004**	1.93±0.59	1.76±0.56	0.11
WBC (1/μL)	7.26±6.94	6.94±1.55	**0.049**	7.51±1.74	7.44±1.82	0.079
Neutrophil count (1/μL)	4.26±3.84	3.84±1.16	**0.003**	4.34±1.11	4.14±1.27	0.36
Lyphocyte count (1/μL)	2.29±0.60	2.36±0.57	0.28	2.39±0.74	2.46±0.60	0.48
Hemoglobin (g/dL)	13.89±1.63	14.07±1.46	0.19	13.53±1.76	13.98±1.71	0.06
Hematocrit	47.40±3.90	41.50±3.59	0.34	40.16±4.33	41.40±4.54	0.07
MCV (fL)	83.14±5.80	82.99±4.61	0.69	79.47±3.95	81.93±3.55	0.29
RDW	13.46±1.73	13.66±1.42	0.06	13.83±1.44	13.65±1.16	0.34
PLT (10^3/μL)	280.47±70.0	267.68±70.10	0.17	278.48±57.41	265.68±58.10	0.54
MPV (fL)	12.01±1.25	11.46±0.87	0.40	10.40±0.96	10.54±1.06	0.62
PDW	13.11±2.41	13.08±2.29	0.88	12.84±2.28	13.03±2.57	0.45

NLR: neutrophil to lymphocyte ratio, WBC: white blood cell count, MCV: mean corpuscular volume, RDW:red cell distribution width, PLT: platelet count, MPV: mean platelet volume, PDW: platelet distribution width

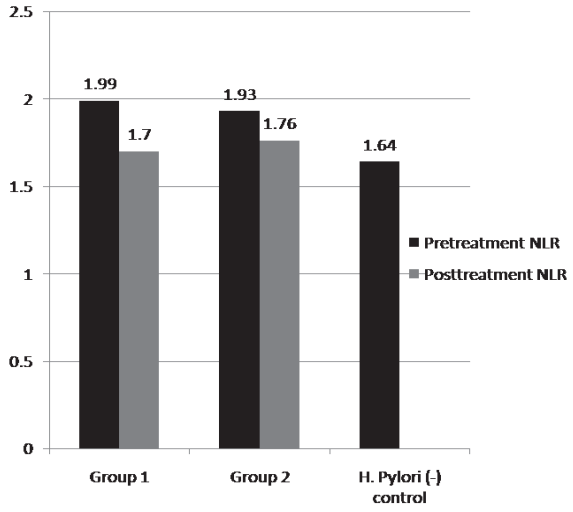

Figure1. Pretreatment and post-treatment neutrophil lymphocyte ratios in patients with successful (group 1) and unsuccessful (group 2) Helicobacter pylori eradication.

DISCUSSION

H. pylori associated gastritis describes the inflammation of the gastric mucosa associated with H. pylori infection and it was first described by Marshall and Warren approximately 30 years ago (9). Neutrophils constitute major component of WBC. Blood neutrophil count increases in numerous infectious and inflammatory diseases. There are studies in the literature describing increased WBC and absolute neutrophil count in H. pylori infected patients (10,11). Neutrophils as well as lymphocytes, eosinophils, macrophages, plasma cells and mast cells participate in the pathogenesis of chronic H. pylori gastritis but neutrophils are of particular importance. Neutrophilic foveolitis is characteristic of H. pylori gastritis. There are two forms of neutrophilic foveolitis; surface neutrophilic foveolitis and neutrophilic proliferative zone foveolitis. Surface neutrophilic foveolitis is associated with gastric erosions and ulcers. On the other hand neutrophilic proliferative zone foveolitis where neutrophils cause inflammation in the pit proliferative zone is almost specific to H. Pylori infection and it is believed to have strong pathobiological implications. Intense inflammation in this area triggers destruction of the pits and epithelial proliferation. Inflammatory mediators secreted from neutrophils and other inflammatory cells may also facilitate random genomic alteration in proliferating epithelial cells starting the cascade from chronic gastritis to gastric cancer (12, 13).

The results of this study are consistent with the literature in that NLR is increased in H. pylori (+) patients. Although mean WBC count in H. pylori (+) patients was found to be within normal limits, it was still significantly higher than H. pylori (-) controls. Since H. pylori causes chronic inflammation in gastric mucosa it is possible that this continuous inflammation also has systemic effects causing a low level of leukocytosis. Several studies demonstrated an increase in the levels of several inflammatory mediators and cytokines in serum and gastric biopsy specimens of H. pylori (+) patients supporting the presence of this continuous low level inflammation (14, 15). This low level of inflammation and resultant cytokine abnormalities may also explain the association of H. pylori with various extra-gastrointestinal diseases such as cardiovascular diseases, stroke and diabetes mellitus (16-18). This study also showed that increased NLR in H. pylori (+) patients decreases after successful H. pylori eradication. This is again consistent with the findings in the literature. Kondo et al. reported there is a sustained decrease in blood neutrophil count after successful H. pylori eradication (19).

It is also noteworthy to mention that mean, although statistically insignificant, NLR decreased to some extend in patients with eradication failure. This decrease was again in parallel to decrease in WBC and neutrophil counts. This decrease may implicate transient suppression of H. pylori and associated gastric inflammation due to eradication treatment in these patients. But since eradication had failed the difference probability didn't reach statistical significance. It can be postulated that these parameters may return to pretreatment levels after some time.

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Although there were no difference between mean hemoglobin concentration and hematocrit values between H. pylori (+) patients and H. pylori (-) controls, MCV was significantly lower in H. pylori (+) group. This may reflect a subclinical iron deficiency in these patients. Chronic H. pylori infection is well known to be associated with iron deficiency. Possible mechanisms of iron deficiency in these patients are impaired gastric acid secretion, occult blood loss from from erosions or ulcers and increased hepcidin levels (20,21).

CONCLUSION

In conclusion NLR is increased in H. pylori (+) patients. Although still within normal limits, total WBC and absolute neutrophil counts are also significantly higher in H. pylori (+) patients which explains the increased NLR. Although the exact clinic implications of increased NLR, WBC and neutrophil counts are not known, it may imply a low level of inflammatory state ongoing in H. pylori (+) patients and all seem to normalize after successful H. pylori eradication treatment.

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