ORIGINAL ARTICLE

Predictive Value of Neutrophil-to-Lymphocyte Ratio for Differentiating Organic Dyspepsia from Functional Dyspepsia

H Köseoğlu[1], SO Sarı[1], M Akar[2], T Solakoğlu[3], ÖT Yurekli[1], AD Bolat[1], NŞ Büyükaşık[1], O Ersoy[4]

ABSTRACT

Objective: *Dyspepsia, one of the most commonly seen symptoms, can be due to organic dyspepsia (OD) or functional dyspepsia (FD). The aim of this study is to evaluate neutrophil-to-lymphocyte ratio (NLR) for the predictability of OD due to peptic ulcer disease (PUD) and gastric cancer (GC).*

Methods: *We investigated retrospectively the patients with dyspepsia who underwent endoscopy. The study included 119 patients with OD (41 patients with biopsy-proven GC and 78 patients with PUD) and 100 patients with FD diagnosed.*

Results: *The NLR among the patients with GC and PUD was significantly higher than FD subject (*$p < 0.001$ *each). The NLR in patients with GC was also significantly higher than that in patients with PUD (*$p < 0.005$*). When OD was compared with FD, NLR and white blood cell were statistically significantly higher (*$p < 0.001$ *and* $p < 0.05$ *respectively). The best predictive cut-off value of NLR was 1.72 with a specificity of 63% and a sensitivity of 66% for OD, on receiver-operating characteristic curve analysis.*

Conclusion: *Neutrophil-to-lymphocyte ratio was higher in patients with OD compared with those with FD, and even higher in patients with GC. Our findings suggest that NLR should be calculated in patients with dyspepsia and patients with high levels of NLR should undergo endoscopy.*

Keywords: Functional dyspepsia, gastric cancer, neutrophil-to-lymphocyte ratio, organic dyspepsia, peptic ulcer disease.

INTRODUCTION

The symptoms postprandial fullness, early satiety and epigastric pain are described as dyspepsia by the Rome III Committee (1). Dyspepsia is a common problem affecting about one out of four people in the Western world (2–4). It can be classified into two groups: organic dyspepsia (OD), when the laboratory investigations identify an underlying organic disease that is likely to be the reason of the symptoms; functional dyspepsia (FD), when no evidence of structural disease (including upper endoscopy) is detected that is likely to explain the dyspepsia symptoms (1, 5). Gastro-oesophageal reflux, medications, peptic ulcer disease (PUD) and malignancy are commonly seen causes leading to OD (6). Peptic ulcer disease is a common reason for OD, but the prevalence of PUD in patients with dyspepsia is only 5% to 15% (5–8). Gastric cancer (GC) and oesophageal cancer are uncommon reasons for dyspepsia. Gastric cancer and oesophageal cancer were detected in 2% of patients who underwent gastroscopy for dyspeptic symptoms in a large multicentre database (9).

Upper endoscopy can demonstrate structural diseases for dyspepsia, but because of the large number of patients with dyspepsia, it is not practical to perform upper

From: [1]Department of Gastroenterology, Ankara Ataturk Education and Research Hospital, Ankara, Turkey, [2]Department of Gastroenterology, Faculty of Medicine, Erciyes University, Ankara, Turkey, [3]Department of Gastroenterology, Corlu State Hospital, Ankara, Turkey and [4]Department of Gastroenterology, Faculty of Medicine, Yildirim Beyazit University, Ankara, Turkey.

Correspondence: H Köseoğlu, Department of Gastroenterology, Faculty of Medicine, Yildirim Beyazit University, Atatürk Eğitim ve Araştırma Hastanesi Lodumlu mevki Bilkent/Ankara, Turkey.
Email: huseyinko@yahoo.com

 DOI: 10.7727/wimj.2015.394

endoscopy in all dyspeptic patients (10). Patients with older age and alarm symptoms are advised to undergo initial endoscopy (6, 10). The probability of malignancy is low in young patients without alarm symptoms (11), but many patients with early stage esophagogastric cancer do not have alarm symptoms (12). The commonly accepted alarm symptoms are anemia, mass, dysphagia, weight loss and vomiting. Neutrophil-to-lymphocyte ratio (NLR) is an inexpensive and simple indicator of systemic inflammatory burden that correlates with activity and prognosis in distinct inflammatory and malignant diseases (13–22). The aim of this study is to evaluate the usefulness of NLR before endoscopy, to differentiate FD from OD due to PUD and GC.

SUBJECTS AND METHODS

We investigated retrospectively the patients with dyspepsia who underwent endoscopy at the department of Gastroenterology between February 2011 and May 2013. The study included 119 patients with OD (41 patients with biopsy-proven GC and 78 patients with PUD) and 100 patients with functional FD diagnosed.

The patients' demographic features, endoscopic and laboratory findings were investigated. The endoscopic and laboratory data were obtained from the recorded computerized database. All patients underwent endoscopy using Olympus video-endoscopes (GIF type-160 and 180). In case of any suspected malignancy and gastric ulcer, multiple biopsy specimens were taken from the lesion. If duodenal ulcer was detected, biopsy specimens were taken from the stomach to identify *Helicobacter pylori* infection.

Total white blood cell (WBC), neutrophil and lymphocyte counts, haemoglobin (Hb) and platelet (PLT) levels were determined on samples obtained from peripheral blood in the first medical examination. Neutrophil-to lymphocyte ratio was calculated by dividing the plasma absolute neutrophil count to the plasma absolute lymphocyte count in peripheral blood. The total cell count was measured by Sysmex XE-2100, and blood samples were measured with potassium-ethylendiaminetetraacetic acid.

The local Medical Ethics Committee approved the study design and methods. According to Rome III criteria, FD was determined as no organic abnormality by upper endoscopy, with dyspepsia symptoms for at least 3 months (1). All patients presented with dyspepsia symptoms like upper abdomen pain or discomfort, postprandial fullness, early satiation and abdominal bloating for at least 3 months. Patients with complicated PUD (bleeding or obstruction due to PUD), haematological diseases, heart failure, chronic infection, rheumatic diseases, hepatic disorders, renal disease, other known cancers, leucocytosis, leukopenia, and severe anaemia (Hb <10 g/dL) and patients who were taking steroids were excluded from the study. Patients older than 80 years and younger than 20 years were also excluded.

All statistical analyses were performed with the SPSS 20.0 software (IBM Corp., Armonk, NY, USA). The Kolmogorov–Smirnov test was used to determine whether the distributions of continuous variables were normal or not. Independent samples *t*-test and one-way analysis of variances were used to determine the differences of laboratory variables and NLR between groups.. Pearson correlation analysis was used to identify the correlation between parameters. Receiver-operating characteristic (ROC) curve analysis was performed to identify optimal cut-off value of the NLR for prediction of OD. p values of less than 0.05 were considered as significant.

RESULTS

The sociodemographic features and laboratory values are summarized in the Table. No statistically significant difference among the groups was detected with respect to gender and age. The NLR among the patients with GC and PUD was significantly higher than FD subjects ($p < 0.001$ each). The NLR in patients with GC was also significantly higher than that in patients with PUD ($p < 0.005$). The mean WBC count was not significantly different between PUD, GC and FD. Mean Hb and PLT levels were not statistically different between PUD and FD groups, but compared to FD and PUD significantly low Hb ($p < 0.001$) was detected in patients with GC. When OD was compared with FD, the Hb and PLT counts were not statistically significantly different; NLR and WBC were statistically significantly higher ($p < 0.001$ and $p < 0.05$, respectively) among patients with OD.

A total of 10 patients in the PUD group had duodenal and gastric ulcer, 28 patients had duodenal ulcer and 40 patients had gastric ulcer. No significant differences were found in WBC, NLR, Hb and PLT levels between gastric ulcer and duodenal ulcer. Among the patients with PUD, 58 patients had *H. pylori* and 20 patients had no *H. pylori* on biopsy specimens. The mean NLR for *H. pylori* and non-*H. pylori* PUD was 1.98 and 2.05, respectively, with no statistically significant difference.

Among GC group, 19 patients had metastatic disease and 23 patients had no metastasis on the time of diagnosis. The mean NLR was 2.39 and 3.29 in patients

Table: Sociodemographic features and laboratory values of the groups

	FD patients	PUD patients	GC patients	OD patients (PUD+GC)	*p* value (OD *vs* FD)
Gender (male/female)	45/55	39/39	27/14	66/53	0.08
Age, mean (years)	52.0	51.8	56.4	53.4	0.441
Haemoglobin (g/dL)	13.96	13.94	12.75	13.53	0.075
WBC ($\times 10^9$/l)	7.12	7.52	7.65	7.57	0.041
NLR	1.67	1.99	2.83	2.28	< 0.001
PLT ($\times 10^9$/l)	269.8	275.1	302.0	284.4	0.181

$p < 0.05$ is significant.
WBC = white blood cell count; NLR = neutrophil/lymphocyte ratio; PLT = platelet count; FD = functional dyspepsia; PUD = peptic ulcer disease; GC = gastric cancer; OD = organic dyspepsia.

without metastasis and with metastasis, respectively ($p = 0.014$). The levels of Hb, WBC and PLT were not statistically different with regard to presence of metastasis. Correlation analysis was performed, and there was no significant correlation between age and Hb, WBC, NLR and PLT levels. A statistically significant positive correlation between WBC and NLR, and a negative correlation between PLT and Hb were found. The best predictive cut-off value of NLR for detecting OD was 1.72 with a specificity of 63% and sensitivity of 66% on ROC curve analysis (area under the curve [AUC] = 0.71, 95% CI: 0.64, 0.77). The cut-off value of NLR for differentiating GC from PUD was 2.10 (sensitivity = 73%, specificity = 68%, AUC = 0.74; 95% CI: 0.65, 0.83).

DISCUSSION

In this study, we evaluated NLR as a marker to differentiate OD from FD. A higher NLR was detected in patients with GC and PUD compared to those with FD and a higher NLR was detected in patients with GC compared with those with PUD. No difference in NLR was found between gastric and duodenal ulcers, and *H. pylori* induced gastric ulcer and non-*H. pylori* gastric ulcer. These findings indicate that high NLR before endoscopy can estimate the probability of OD in patients with dyspepsia.

Neutrophil-to-lymphocyte ratio is an inexpensive and simple indicator of systemic inflammatory burden that correlates with activity and prognosis in distinct diseases. It has been investigated in inflammatory diseases, such as acute pancreatitis, ulcerative colitis and non-alcoholic fatty liver disease (13–15). It has also been investigated for various cancers, and data show that NLR is a prognostic factor in gastrointestinal system cancers, such as oesophageal cancer, GC, hepatocelluler carcinoma, colorectal cancer, pancreatic cancer, and gastrointestinal stromal tumour (16–22). Gastric cancer is the fourth most common cancer and the second most common cancer-related deaths (23). Studies have shown a link between GC and chronic inflammation (24, 25), and the high NLR values observed in patients with GC in our study support the presence of gastric inflammation. Some studies have revealed that NLR can be used as a prognostic factor for GC (22, 26–30). Normalization of high NLR by neoadjuvant chemotherapy in stages III and IV (30) or by the first cycle of chemotherapy in advanced GC (29) indicates a good chemotherapy response and prognosis. Although high NLR values show poor prognosis, there is no data comparing NLR in patients with GC with FD. Our findings demonstrate that NLR can predict GC detection in patients with dyspepsia, and could be an easily available and promising biomarker for the diagnosis of GC in patients with dyspepsia.

Polyporphonuclear neutrophil activity is an indicator of acute inflammation, and neutrophil activity is probably linked to tissue damage (31). The intensity of intraepithelial neutrophils in the stomach is correlated with the density of *H. pylori* infection and with the mucosal damage (31, 32). In our study, the high NLR detected in the OD group may reflect gastric inflammation and the neutrophil existence in the gastric mucosa. Recently, Jafarzadeh *et al* reported that NLR was significantly higher in *H. pylori* infected patients with peptic ulcer (33). Compared with the control group, NLR was also higher in asymptomatic subjects with *H. pylori* infections (33). Another study demonstrated that *H. pylori* eradication decreases blood neutrophil and monocyte counts, whereas it has no effect on eosinophil and lymphocyte counts (34). In our study, no difference was found between *H. pylori* and non-*H. pylori* PUD, and due to this finding we suggest that PUD causes an increase in NLR, instead of *H. pylori*. However, the low number of non-*H. pylori* PUD in our study weakens this suggestion.

Although many patients with early stage esophagogastric cancer do not have alarm symptoms (12), patients with older age and alarm symptoms are advised to undergo initial endoscopy (6). Our study demonstrates

that high levels of NLR may predict OD due to PUD or GC. The cut-off values of NLR for various diseases are not well defined, but in our study the best predictive cut-off value of NLR was 1.72. To our knowledge, this is the first study to describe the use of NLR in patients with dyspepsia, and we found that NLR may be a predictor of OD. In the light of these data, we can speculate that endoscopy should be performed in dyspeptic patients with high NLR levels, and NLR should be used like an 'alarm symptom'. However, we need further studies to determine a set point for NLR to use this recommendation.

CONCLUSION

Neutrophil-to-lymphocyte ratio is higher in patients with OD compared with those with FD, and even higher in patients with GC. Our findings suggest that NLR should be calculated in patients with dyspepsia and patients with high levels of NLR should undergo endoscopy. However, prospective studies with larger number of patients are needed to support this recommendation.

REFERENCES

1. Tack J, Talley NJ, Camilleri M, Holtmann G, Hu P, Malagelada JR et al. Functional gastroduodenal disorders. Gastroenterology 2006; **130:** 1466–79.
2. Mahadeva S, Goh KL. Epidemiology of functional dyspepsia: a global perspective. World J Gastroenterol 2006; **7:** 2661–6.
3. Drossman DA, Li Z, Andruzzi E, Temple RD, Talley NJ, Thompson WG et al. U.S. householder survey of functional gastrointestinal disorders. Prevalence, sociodemography, and health impact. Dig Dis Sci 1993; **38:** 1569–80.
4. Jones RH, Lydeard SE, Hobbs FD, Kenkre JE, Williams EI, Jones SJ et al. Dyspepsia in England and Scotland. Gut 1990; **31:** 401–5.
5. Oustamanolakis P, Tack J. Dyspepsia: organic versus functional. J Clin Gastroenterol 2012; **46:** 175–90.
6. Talley NJ, Vakil NB, Moayyedi P. American Gastroenterological Association technical review on the evaluation of dyspepsia. Gastroenterology 2005; **129:** 1756–80.
7. Wai CT, Yeoh KG, Ho KY, Kang JY, Lim SG. Diagnostic yield of upper endoscopy in Asian patients presenting with dyspepsia. Gastrointest Endosc 2002; **56:** 548–51.
8. Vakil N, Moayyedi P, Fennerty MB, Talley NJ. Limited value of alarm features in the diagnosis of upper gastrointestinal malignancy: systemic review and meta-analysis. Gastroenterology 2006; **131:** 390–401.
9. Wallace MB, Durkalski VL, Vaughan J, Palesch YY, Libby ED, Jowell PS et al. Age and alarm symptoms do not predict endoscopic findings among patients with dyspepsia: a multicentre database study. Gut 2001; **49:** 29–34.
10. Ikenberry SO, Harrison ME, Lichtenstein D, Dominitz JA, Anderson MA, Jagannath SB et al. The role of endoscopy in dyspepsia. Gastrointest Endosc 2007; **66:** 1071–5.
11. Williams B, Luckas M, Ellingham JHM, Dain A, Wicks AC. Do young patients with dyspepsia need investigation? Lancet 1988; **2:** 1349–51.
12. Bowrey DJ, Griffin SM, Wayman J, Karat D, Hayes N, Raimes SA. Use of alarm symptoms to select dyspeptics for endoscopy causes patients with curable esophagogastric cancer to be overlooked. Surg Endosc 2006; **20:** 1725–8.
13. Azab B, Jaglall N, Atallah JP, Lamet A, Raja-Surya V, Farah B et al. Neutrophil-lymphocyte ratio as a predictor of adverse outcomes of acute pancreatitis. Pancreatology 2011; **11:** 445–52.
14. Alkhouri N, Morris-Stiff G, Campbell C, Lopez R, Tamimi TA, Yerian L et al. Neutrophil to lymphocyte ratio: a new marker for predicting steatohepatitis and fibrosis in patients with nonalcoholic fatty liver disease. Liver Int 2012; **32:** 297–302.
15. Torun S, Tunc BD, Suvak B, Yildiz H, Tas A, Sayilir A et al. Assessment of neutrophil-lymphocyte ratio in ulcerative colitis: a promising marker in predicting disease severity. Clin Res Hepatol Gastroenterol 2012; **36:** 491–7.
16. Perez DR, Baser RE, Cavnar MJ, Balachandran VP, Antonescu CR, Tap WD et al. Blood neutrophil-to-lymphocyte ratio is prognostic in gastrointestinal stromal tumor. Ann Surg Oncol 2013; **20:** 593–9.
17. Stotz M, Gerger A, Eisner F, Szkandera J, Loibner H, Ress AL et al. Increased neutrophil-lymphocyte ratio is a poor prognostic factor in patients with primary operable and inoperable pancreatic cancer. Br J Cancer 2013; **109:** 416–21.
18. Xiao WK, Chen D, Li SQ, Fu SJ, Peng BG, Liang LJ. Prognostic significance of neutrophil-lymphocyte ratio in hepatocellular carcinoma: a meta-analysis. BMC Cancer 2014; **14:** 117.
19. Chua W, Charles KA, Baracos VE, Clarke SJ. Neutrophil/lymphocyte ratio predicts chemotherapy outcomes in patients with advanced colorectal cancer. Br J Cancer 2011; **104:** 1288–95.
20. He W, Yin C, Guo G, Jiang C, Wang F, Qiu H et al. Initial neutrophil lymphocyte ratio is superior to platelet lymphocyte ratio as an adverse prognostic and predictive factor in metastatic colorectal cancer. Med Oncol 2013; **30:** 439.
21. Sharaiha RZ, Halazun KJ, Mirza F, Port JL, Lee PC, Neugut AI et al. Elevated preoperative neutrophil: lymphocyte ratio as a predictor of postoperative disease recurrence in esophageal cancer. Ann Surg Oncol 2011; **18:** 3362–9.
22. Shimada H, Takiguchi N, Kainuma O, Soda H, Ikeda A, Cho A et al. High preoperative neutrophil–lymphocyte ratio predicts poor survival in patients with gastric cancer. Gastric Cancer 2010; **13:** 170–6.
23. Brenner H, Rothenbacher D, Arndt V. Epidemiology of stomach cancer. Methods Mol Biol 2009; **472:** 467–77.
24. Ilhan N, Ilhan Y, Akbulut H, Kucuksu M. C-reactive protein, procalcitonin, interleukin-6, vascular endothelial growth factor and oxidative metabolites in diagnosis of infection and staging in patients with gastric cancer. World J Gastroenterol 2004; **10:** 1115–20.
25. Hussain SP, Harris CC. Inflammation and cancer: An ancient link with novel potentials. Int J Cancer 2007; **121:** 2373–80.
26. Xu AM, Huang L, Zhu L, Wei ZJ. Significance of peripheral neutrophil-lymphocyte ratio among gastric cancer patients and construction of a treatment-predictive model: a study based on 1131 cases. Am J Cancer Res 2014; **4:** 189–95.
27. Aizawa M, Gotohda N, Takahashi S, Konishi M, Kinoshita T. Predictive value of baseline neutrophil/lymphocyte ratio for T4 disease in wall-penetrating gastric cancer. World J Surg 2011; **35:** 2717–22.
28. Aliustaoglu M, Bilici A, Ustaalioglu B, Konya V, Gucun M, Seker M et al. The effect of peripheral blood values on prognosis of patients with locally advanced gastric cancer before treatment. Med Oncol 2010; **27:** 1060–5.
29. Lee S, Oh SY, Kim SH, Lee JH, Kim MC, Kim KH et al. Prognostic significance of neutrophil lymphocyte ratio and platelet lymphocyte ratio in advanced gastric cancer patients treated with FOLFOX chemotherapy. BMC Cancer 2013; **13:** 350.
30. Jin H, Zhang G, Liu X, Liu X, Chen C, Yu H et al. Blood neutrophil-lymphocyte ratio predicts survival for stages III-IV gastric cancer treated with neoadjuvant chemotherapy. World J Surg Oncol 2013; **11:** 112.
31. Dixon MF, Genta RM, Yardley JH, Correa P. Classification and grading of gastritis. The updated Sydney System. International Workshop on the Histopathology of Gastritis, Houston 1994. Am J Surg Pathol 1996; **20:** 1161–81.
32. Fiocca R, Villani L, Luinetti O, Gianatti A, Perego M, Alvisi C et al. Helicobacter colonization and histopathological profile of chronic gastritis in patients with or without dyspepsia, mucosal erosion and peptic

ulcer: a morphological approach to the study of ulcerogenesis in man. Virchows Arch A Pathol Anat Histopathol 1992; **420:** 489–98.
33. Jafarzadeh A, Akbarpoor V, Nabizadeh M, Nemati M, Rezayati MT. Total leukocyte counts and neutrophil-lymphocyte count ratios among *Helicobacter pylori*-infected patients with peptic ulcers: independent of bacterial CAG—a status. Southeast Asian J Trop Med Public Health 2013; **44:** 82–8.
34. Kondo Y, Joh T, Sasaki M, Oshima T, Itoh K, Tanida S et al. *Helicobacter pylori* eradication decreases blood neutrophil and monocyte counts. Aliment Pharmacol Ther 2004; **20(Suppl 1):** 74–9.