Predictive Value of Neutrophil/lymphocyte Ratio for Differentiating Organic Dyspepsia from Functional Dyspepsia

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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 organic dyspepsia due to peptic ulcer disease (PUD) and gastric cancer (GC).

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

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

Conclusion: NLR was detected higher in OD patients compared 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: Gastric cancer, functional dyspepsia, organic dyspepsia, neutrophil/lymphocyte ratio, peptic ulcer disease

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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 1 out of 4 people in the western world (2-4). It can be classified into 2 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). Gastroesophageal reflux, medications, PUD and malignancy are commonly seen causes leading to OD (6). PUD is a common reason for OD, but the prevalence of PUD in patients with dyspepsia is only 5% to 15% (5-8). GC and esophageal cancer are uncommon reasons for dyspepsia. GC and esophageal cancer was detected in 2% of patients who underwent gastroscopy for dyspeptic symptoms in a multicenter large database (9).

Upper endoscopy can demonstrate structural diseases for dyspepsia, but because the large numbers of patients with dyspepsia, it is not practical to perform upper 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 don't have alarm symptoms (12). Neutrophil/lymphocyte ratio (NLR) is an inexpensive and simple indicator of systemic inflammatory burden, and correlates with activity and prognosis in distinct inflammatory and malign 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.

METHODS

We investigated retrospectively the dyspepsia patients 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 respectively. The endoscopic and laboratory data was 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 *H, Pylori* infection.

Total white blood cell (WBC), neutrophil and lymphocyte counts, Hemoglobine (Hb) and platelet (PLT) levels were determined on samples obtained from peripheral blood in the first medical examination. NLR was calculated by dividing the serum absolute neutrophil count to the serum 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, abdominal bloating for at least 3 months. Patients with complicated PUD (bleeding or obstruction due to PUD), hematological diseases, heart failure, chronic infection, rheumatic diseases, hepatic disorders, renal disease, other known cancers, leucocytosis, leucopenia and severe anemia (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. Kolmogorov–Smirnov test was used to determine whether the distributions were significantly different. Independent Samples T-Test and One way ANOVA were used to determine the differences in variables. Pearson correlation analyze 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 table. No statistically significant difference among the groups was detected regarding gender and age. The NLR among the GC and PUD patients were significantly higher than FD subject (p<0.001 each). The NLR in GC patients was also significantly higher than PUD patients (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 GC patients. When OD was compared with FD, the Hb and PLT counts were not statistically significantly different; NLR and WBC was statistically significantly higher (p<0.001 and p<0.05 respectively) among OD patients.

Table: Sociodemographic features and laboratory values of the groups

	FD patients	PUD patients	GC patients	OD patients (PUD+GC)	*P* (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
Hemoglobin (g/dl)	13.96	13.94	12.75	13.53	0.075
WBC (x10^9/l)	7.12	7.52	7.65	7.57	*0.041*
NLR	1.67	1.99	2.83	2.28	*<0.001*
PLT (x10^9/l)	269.8	275.1	302.0	284.4	0.181

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

Ten 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. Mean NLR for H Pylori and non-H pylori PUD were 1.98 and 2.05 respectively, with no statistically significant difference.

Among GC group 19 patients had metastatic disease and 23 had no metastasis on the time of diagnosis. The mean NLR was 2.39 and 3.29 in patients without metastasis and with

metastasis, respectively (p: 0.014). Hb, WBC and PLT levels were not statistically different with regard to presence of metastasis. Correlation analyze 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 was found. The best predictive cut-off value of NLR for detecting OD was 1.72 with a specifity of 63% and sensitivity of 66% on ROC curve analysis [(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 FD and a higher NLR was detected in patients with GC compared with PUD. No difference in NLR was found between gastric and duodenal ulcer, and H pylori induced gastric ulcer and non-H pylori gastric ulcer. These finding indicate that high NLR before endoscopy can estimate the probability of organic dyspepsia in patients with dyspepsia.

NLR is an inexpensive and simple indicator of systemic inflammatory burden, and correlates with activity and prognosis in distinct diseases. It has been investigated in inflammatory diseases, such as acute pancreatitis, ulcerative colitis and nonalcoholic 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 esophageal cancer, gastric cancer, hepatocelluler carcinoma, colorectal cancer, pancreatic cancer and gastrointestinal stromal tumor (16-22). GC is the fourth most common cancer and the second most common cancer-related deaths (23). Studies have shown a link between gastric cancer

and chronic inflammation (24,25), and the high NLR values observed in GC patients in our study supports the presence of gastric inflammation. Some studies have revealed that NLR can be used as a prognostic factor for gastric cancer (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 shows 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 complaining 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 existency in the gastric mucosa. Recently Jafarzadeh et al investigated NLR for H pylori infected patients with peptic ulcer and found that NLR was significantly higher in patients with helicobacter 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 count (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. But the low number of non-H pylori PUD in our study weakens this suggestion.

Because the large numbers of patients with dyspepsia it is not practical to perform upper endoscopy in all dyspeptic patients. Although many patients with early stage esophagogastric cancer don't 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'. But we need further studies to determine a set point for NLR to use this recommendation.

CONCLUSION

NLR is higher in OD patients compared 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.

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