Original Article

Role of Neutrophil to Lymphocyte and Platelet to Lymphocyte Ratios in Early Detection of Gastric Cancer in Patients with Uncomplicated dyspepsia

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ABSTRACT

Background:
Dyspepsia is a common presentation in both benign and serious conditions, such as gastric cancer. Early recognition and management of gastric cancer in patients with dyspepsia play a crucial role in improving survival rates. This study aimed to assess the paraclinical utility of the neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) as potential screening biomarkers for the early diagnosis of gastric cancer in patients with uncomplicated dyspepsia.

Material and Methods:
The case-control study included 64 patients diagnosed with gastric cancer who initially presented with dyspepsia and 102 patients with dyspepsia who were not diagnosed with gastric cancer as controls. All participants were selected based on the absence of alarming symptoms and signs, except for dyspepsia. Retrospective analysis of selected blood parameters was performed. A receiver-operating characteristic (ROC) curve analysis was performed to define the best cut-off value for NLR and PLR to identify gastric cancer.

Results:
The mean values of neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) levels showed a statistically significant difference between the two groups (respectively $P<0.003$, $P<0.001$). The cut-off value of NLR was 2.79 (area under the curve [AUC]:0.75, sensitivity: 70.3%, specificity: 67.6%) and 129.2 as the cut-off value of PLR (AUC: 0.77, sensitivity: 71%, specificity: 64.7%).

Conclusions:
The present study suggests that NLR and PLR may be useful as potential screening markers in patients with uncomplicated dyspepsia. Additionally, parameters, even without the presence of alarm signs and symptoms, might alert physicians and lead them to perform an upper gastrointestinal endoscopy.

Keywords: Uncomplicated dyspepsia, Gastric cancer, NLR, PLR

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INTRODUCTION

Gastric cancer is one of the most common neoplasms in the world and accounts for approximately 783,000 deaths each year, making it the third most deadly cancer among males worldwide (1). The incidence rate of gastric cancer varies significantly among different regions and cultures. The highest number of gastric cancer cases is reported in East-Central Asia and Latin America. Stomach cancer is more frequently diagnosed in developed nations compared with low- and middle-income countries (2).

Dyspepsia is a common symptom observed in both early and advanced gastric cancer; however, it is also associated with a variety of benign gastrointestinal (GI) diseases, such as gastritis (3). Dyspepsia refers to various groups of symptoms that are localized in the epigastric region. Typical dyspeptic symptoms include postprandial fullness, early satiation, epigastric pain, and epigastric burning. Additionally, other upper GI symptoms, such as nausea, belching, or abdominal bloating, can sometimes be the primary complaints (4). GI malignancy is present in up to 3% of patients with dyspepsia (5). Uncomplicated dyspepsia is defined as dyspepsia without alarm symptoms or signs, including dysphagia, vomiting, weight loss, early satiety, GI bleeding, and anemia (6). Early detection of gastric cancer is essential in patients with dyspepsia, as it is associated with a better response to treatment plans (3).

Upper GI endoscopy is the most accurate diagnostic test for dyspepsia, which may arise from either benign or malignant etiologies. Patients with dyspepsia who are older and/or exhibit alarm symptoms are advised to undergo an initial diagnostic endoscopy (7). However, a considerable proportion of younger patients with gastric cancer may present without alarm symptoms (8).

A cost-effective early screening test for patients with dyspepsia without alarm signs, potentially using routine blood tests such as the complete blood count (CBC), can be vital due to the significantly improved response to early treatment (9).

Inflammation is believed to play a critical role in the formation and progression of gastric cancer (10). Neutrophils are representative components of the innate immune system, while lymphocytes are indicative of the adaptive immune system. The neutrophil-lymphocyte ratio (NLR) and the platelet-lymphocyte ratio (PLR) have been proposed as indicators of systemic inflammation. In previous studies, certain blood parameters, including platelet count (PC), NLR, and PLR, have been associated with the progression and diagnosis of gastric cancer (11-14).

Our study aimed to evaluate various hematological parameters, specifically the NLR and the PLR, before endoscopy to differentiate gastric cancer from benign conditions in patients with dyspepsia without alarm symptoms or signs.

MATERIALS AND METHODS

We conducted a case-control retrospective study involving data from 572 patients with gastric cancer who underwent upper GI endoscopy at the endoscopy center of Imam Khomeini Hospital in Ardabil, Iran, between May 2012 and June 2019. Among these patients, we identified 64 individuals whose initial presentation was dyspepsia; all of these patients were without alarm symptoms or signs, including dysphagia, vomiting, weight loss, early satiety, GI bleeding, or anemia. A total of 102 patients with dyspepsia who did not have stomach cancer, according to histopathology, served as a control group and were randomly selected from patients of the same department between Dec 2021 and June 2024, again without the presence of alarm signs and symptoms mentioned above.

The Medical Ethics Committee of Ardabil University of Medical Sciences approved the study.

Demographic, clinical, pathological, and laboratory data of patients with gastric cancer were extracted from the hospital's medical database. Patients with dyspepsia presenting without alarm signs and symptoms who were scheduled for endoscopy were selected as controls. Following confirmation that these patients had non-gastric cancer conditions, complete blood counts (CBC) were subsequently ordered on the day of the endoscopic visit to evaluate their hematological parameters

The data collected included age, sex, white blood cell count (WBC), pre-endoscopic hemoglobin (Hb) levels, as well as neutrophil, lymphocyte, monocyte, and platelet counts for both groups. The absolute neutrophil and lymphocyte values were used to calculate the NLR values. The total number of platelets and absolute values of lymphocytes were used to calculate the PLR values.

Patients with a history of anemia, hypertension, diabetes mellitus, anticoagulant use, hyperlipidemia, thyroid disorders, autoimmune diseases, rheumatological conditions, heart failure, chronic liver disease, chronic renal disease, systemic metabolic disease, and signs of viral infection and those with a previous diagnosis of cancer, were excluded from the study. In the end, 166 patients were included in the study.

In this laboratory investigation, anemia was defined according to established criteria: Hb levels <13 g/dL in males and <12 g/dL in females. CBC analyses were performed using a Sysmex XT-1800i Hematology Analyzer, utilizing blood samples treated with ethylenediaminetetraacetic acid (EDTA).

Statistical analysis

Statistical analysis was performed using SPSS software (SPSS 26, Chicago, IL). Continuous variables were expressed as mean±standard deviation (SD). An independent sample t test was used for group comparisons. A P value of less than 0.05 was considered statistically significant. Before regression analysis, the Pearson correlation test was performed. The optimal cut-off values for the NLR and PLR were estimated using the receiver operating characteristic (ROC) curve. The area under the curve (AUC), sensitivity, and specificity were calculated.

RESULTS

The case-control study included 166 patients with uncomplicated dyspepsia, comprising 64 patients with gastric cancer and 102 patients without gastric cancer. The demographic data and blood parameters of the patients are presented in Table 1. The age and sex distributions did not differ significantly between the groups.

There was no statistically significant difference in hemoglobin (Hb) levels between the two groups (P<0.115). However, the mean NLR, PLR, and platelet count levels differed significantly between gastric cancer and non-gastric cancer patients (respectively P<0.003, P<0.001, and P<0.004). According to the correlation test, only NLR (r=0.443, P< 0.001), PLR (r=0.441, P<0.001), and platelet count (r=0.349, P<0.01) were significantly correlated with outcome (Table 2).

ROC analysis (Figure 1) showed that the ideal cut-off value for NLR was 2.79 (AUC: 0.75, sensitivity: 70.3%, specificity: 67.6%), and 129.2 was the cut-off value for PLR (AUC: 0.77, sensitivity: 71%, specificity: 64.7%).

Table 1. Demographic and laboratory values for blood parameters of the study groups

	Patients with gastric cancer (n=64)	Control group (n=102)	P value
Age [years]	60.63±9.5	56.91±9.39	0.115
Sex [male: female]	38:26	60:42	0.44
WBC [× 103 /µ]	6.939±1.7	6.571±1.3	0.335
Hb [g/dL]	13.53±0.72	13.94±0.91	0.115
NLR	3.159±0.58	2.68±0.38	0.003
PLR	168.20±71.59	120.58±23.59	0.001
Pc [× 103 /µL]	288.93±50.74	255.20±41.02	0.004

Age and laboratory values of blood parameters are expressed as mean ± SD, PC: platelet count, WBC: white blood cell, NLR: neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio.

Table 2. Correlation of independent variables with outcome

Variables	Pearson Correlation	P value
Age [years]	0.196	0.115
Sex [male: female]	0.097	0.440
WBC [× 103 /µ]	0.122	0.331
Hb [g/dL]	-0.193	0.120
NLR	0.443	
	< 0.001	
PLR	0.441	< 0.001
Pc [× 103 /µL]	0.349	0.004

PC: platelet count, WBC: white blood cell, NLR: neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio

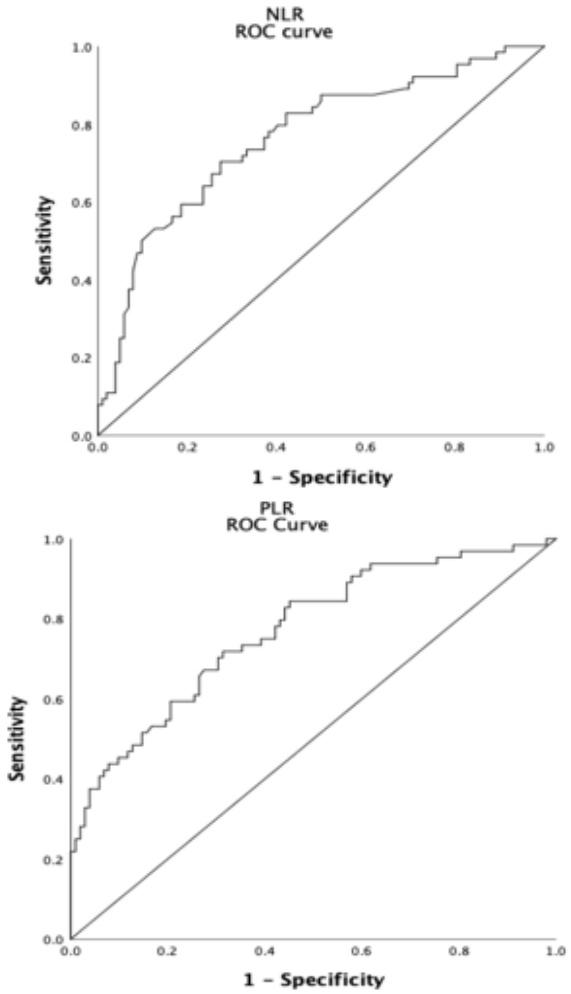

Figure 1. ROC curve analysis to determine the cut-off value of neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios

DISCUSSION

Dyspepsia is a widespread disorder affecting approximately 21% of the population worldwide; however, prevalence rates vary among countries depending on the criteria used for its definition. It is more common in smokers, non-steroidal anti-inflammatory drug (NSAID) users, and individuals positive for helicobacter pylori (H. pylori). Patients with dyspepsia present with various clinical manifestations and diverse underlying etiologies, including peptic ulcer disease, erosive esophagitis, and gastroesophageal malignancy (15).

Many guidelines have suggested drafting treatment protocols for dyspepsia, but the appropriate initial management strategy remains controversial. Most guidelines recommend that prompt endoscopy be reserved for high-risk patients exhibiting alarm features such as dysphagia, weight loss, GI bleeding, and recurrent vomiting, as well as for patients older than 50 to 55 years. Adhering to these guidelines may result in missed diagnoses of gastric cancer in a considerable number of patients with dyspepsia who do not present alarm symptoms, particularly in regions with a high prevalence of gastric cancer, such as Asia (16).

A significant challenge in gastroenterology practice that needs to be addressed is whether a patient presenting with uncomplicated dyspepsia has gastric cancer. The necessity of conducting an upper GI endoscopy to definitively diagnose gastric cancer often encounters reluctance from patients. This apprehension may stem from concerns regarding procedural discomfort, the potential for complications, and the psychological impact associated with undergoing invasive diagnostic procedures.

In one study, approximately 8.6% of patients with gastric cancer and dyspepsia did not meet the criteria for endoscopy due to being under 55 years of age and the absence of alarm symptoms (e.g., weight loss, decreased appetite, anemia, epigastric pain, nausea, and vomiting). Furthermore, 41.4% of patients with dyspeptic gastric cancer were diagnosed at a potentially curable stage (defined as T1–3 Nx M0), with 30.2% of these patients lacking alarm features (17). Although endoscopy remains the most effective method recommended by guidelines, its widespread use for early gastric cancer detection is limited by discomfort and high economic considerations (18).

Several inflammation-related mechanisms have been identified in the carcinogenic pathway, including genomic instability, promoting proliferation and survival, immunomodulation of the tumor microenvironment, and facilitating metastatic spread. Systemic inflammation plays a crucial role in the development of both early and advanced stages of gastric cancer (10).The epithelium of the GI tract is continuously exposed to the extraluminal environment and is thus susceptible to inflammatory changes induced by various pathogens, which may cause cellular damage (19). H. pylori-induced gastric carcinoma serves as a classic example of inflammation-associated malignancy. Infection with H. pylori leads to chronic inflammation, significantly increasing the risk of gastric cancer (20).Understanding the role of inflammation in gastric cancer development and their coexistence provides valuable insights for discovering new strategies for early disease identification (21).

Neutrophils, lymphocytes, and platelets serve as mediators of the tumor-induced systemic inflammatory response (22). Elevated neutrophil counts, induced by this systemic inflammatory response, are believed to contribute to cell proliferation, vascularization, and metastasis by producing pro-angiogenic chemokines and vascular endothelial growth factor (VEGF) (23). Lymphocytes in peripheral blood are thought to exert synergistic cytotoxicity and possess tumor suppressor properties (24). A reduction in lymphocyte levels has been directly linked to the occurrence of gastric cancer (25). Additionally, platelet levels are typically elevated in patients with cancer, indicating their involvement in tumor development (26, 27). Tumor cells can promote platelet production and activation by secreting active substances, such as interleukin-6 (IL-6), while activated platelets release VEGF, platelet-derived growth factor (PDGF), and transforming growth factor-β (TGF-β), all of which promote cancer angiogenesis (28, 29). Previous studies have demonstrated that patients with gastric cancer exhibit significantly increased neutrophil and platelet counts, along with markedly reduced lymphocyte counts, compared with healthy individuals (11).

Earlier studies have examined the significance of CBC parameters, such as the NLR and PLR in the screening of gastric cancer among healthy populations (12, 13, 30). Furthermore, some studies have highlighted the effectiveness of PLR and NLR in predicting the prognosis and survival of patients with gastric cancer. Notably, the NLR can also serve as a non-invasive indicator of the presence of duodenal ulcers related to H. pylori in patients with dyspepsia (31). Moreover, NLR values measured in patients presenting with dyspeptic complaints were significantly higher in patients with peptic ulcers than in patients with non-ulcer dyspepsia (32).

Our findings demonstrate that NLR and PLR, measured in patients with dyspepsia prior to endoscopy, are significantly elevated in those diagnosed with gastric cancer compared with non-gastric cancer patients. These results suggest that high NLR and PLR are easily and widely available biomarkers obtained through routine complete blood counts, which can estimate the probability of gastric cancer in patients with dyspepsia without alarm signs and

symptoms.

To the best of our knowledge, this is the first study to evaluate the association of NLR and PLR in patients with dyspepsia without alarm symptoms to distinguish between gastric cancer and non-gastric cancer.

However, our study has certain limitations, including its retrospective design, small sample size, reliance on patients' self-reported prior symptoms, and being single-centered.

CONCLUSIONS

We propose that the NLR and PLR ratios derived from CBC parameters have diagnostic value in distinguishing between patients with gastric cancer and those without gastric cancer among dyspeptic individuals without alarm symptoms. Given that peripheral blood sampling is a routine procedure, easily accessible, and cost-effective, the comparison of these blood parameters with clinical symptoms may prompt physicians to refer patients for upper GI endoscopy. This approach could significantly enhance the probability of early detection of gastric cancer, particularly in patients with dyspepsia lacking distinct indications for endoscopy.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare related to this work.

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ETHICAL CONSIDERATIONS

Approval for the study was obtained from the Medical Ethics Committee of Ardabil University of Medical Sciences.

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