

Original Article

Evaluation of platelet-to-lymphocyte ratio, red cell distribution width and neutrophil-to-lymphocyte ratio as potential biomarkers in the early detection of gastric cancer

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Abstract: Gastric cancer is the third highest malignity for cancer-related mortality worldwide. Reduction of morbidity and mortality requires early recognition and management of gastric cancer. In recent years, biomarkers reflecting the systemic inflammatory state have been used for both diagnostic and prognostic testing. Our objective was to determine whether global inflammatory markers such as platelet-to-lymphocyte ratio (PLR), red cell distribution width (RDW), and neutrophil-to-lymphocyte ratio (NLR) have clinical utility in the early diagnosis of gastric cancer. We included 53 individuals diagnosed as stomach cancer, and 53 healthy age- and sex-matched subjects. Pre-operative clinical and pathological data as well as information on hemoglobin levels, neutrophil, lymphocyte and platelet counts were derived from the medical records of patients. A receiver-operating characteristic (ROC) curve was calculated to identify potential criteria for using these biomarkers in the diagnosis of gastric cancer. In patients with gastric cancer, PLR, RDW, and NLR were significantly elevated when compared to healthy control subjects ($P < 0.001$). The optimal diagnostic cut-off was 2.17 in the ROC curve analysis [area under the curve (AUC): 0.750, sensitivity: 73%, specificity: 61%] for NLR, 128 (AUC: 0.747, sensitivity: 72%, specificity: 64%) for PLR, and 14 (AUC: 0.768, sensitivity: 70%, specificity: 74%) for RDW. The present study suggests that NLR, PLR and RDW, which are easily obtained from a routine complete blood count may be useful as potential, biomarkers for determination of early diagnosis and prognosis of gastric cancer

Keywords: Gastric cancer, inflammation, neutrophil, lymphocyte, red cell distribution width

Introduction

Gastric cancer is among the top five most common forms of cancer and cancer-related mortality worldwide. Gastric cancer is largely asymptomatic and is often diagnosed late, resulting in a 5-year survival rate of 20-30% [1]. Early detection and treatment is essential in the successful treatment of gastric cancer [2]. Gastric cancer screening programs have successfully reduced the burden of disease in countries like Japan [3]. Commonly used screening methods for early detection of gastric cancer include serum pepsinogen and gastrin levels, *Helicobacter pylori* serology, radiographic tests and endoscopy [4]. However,

these methods are not commonly available and involve significant discomfort and cost.

Inflammation is an important component of carcinogenesis. Inflammatory cells are involved in formation and progression of cancer [5]. Platelet-to-lymphocyte ratio (PLR), red blood cell distribution width (RDW) and neutrophil-to-lymphocyte ratio (NLR) are useful diagnostic and prognostic factors that reflect the systemic inflammatory state in many different types of cancer [6]. A routine complete blood count provides the number of neutrophils, lymphocytes, platelets, and RDW. The NLR and PLR are calculated dividing the neutrophil and platelet counts by the lymphocyte count, respectively.

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Table 1. Clinical and pathological characteristics of patients with gastric cancer vs. control group

| Variables | Mide CA patients (N = 53) | Control group (N = 53) | P-value |
|--------------------------------------------|------------------------------|---------------------------|---------|
| Age (mean ± SD) years | 65.5 ± 11.6 | 65.9 ± 10.5 | 0.885 |
| Sex (male/female) | 42/11 | 41/12 | 0.814 |
| Tumor location [n (%)] | | | |
| Cardia | 12 (22.6) | | |
| Corpus | 19 (35.8) | | |
| Antrum | 22 (41.6) | | |
| TNM staging [n (%)] | | | |
| I | 2 (3.8) | | |
| II | 6 (11.3) | | |
| III | 23 (43.4) | | |
| IV | 22 (41.5) | | |
| Anemia [n (%)] | | | |
| Yes | 29 (54.7) | | |
| No | 24 (45.3) | | |
| Hb (mean ± SD) (g/dL) | 12.2 ± 2.5 | 14.6 ± 1.1 | < 0.001 |
| Platelets (mean ± SD) (10 ⁹ /L) | 306.2 ± 103.5 | 232 ± 47.5 | < 0.001 |
| NLR (mean ± SD) | 3.6 ± 2.1 | 2.1 ± 0.7 | < 0.001 |
| PLR (mean ± SD) | 188.1 ± 92.6 | 120.4 ± 35.4 | < 0.001 |
| RDW (mean ± SD) (%) | 16.2 ± 4.2 | 13.6 ± 0.6 | < 0.001 |

TNM: tumor-nodes-metastases; Hb: hemoglobin; NLR: neutrophil/lymphocyte ratio; PLR: platelet/lymphocyte ratio; RDW: red cell distribution width.

The aim of the present study was to evaluate values in commonly available complete blood count data, the NLR, PLR and RDW, as potential biological markers for gastric cancer screening.

Methods

Study selection

We conducted a retrospective review of all patients diagnosed with gastric cancer at the Sivas Numune Hospital between 1/2010 and 1/2015. The Ethics Committee of Cumhuriyet University Faculty of Medicine reviewed and approved the study design. The retrospective data analysis includes the demographic, clinical, pathological, and laboratory records of patients undergoing endoscopy and subsequent gastric surgery. Patients with concomitant infection, hematological disease, renal disease, coronary artery and cerebrovascular disease and other types of cancers were excluded. The Tumor location and stage were determined according to the tumor-nodes-metastases (TNM) classification. We included

53 gastric cancer patients and 53 age- and sex-matched healthy subjects in the study. Data including preoperative hemoglobin (Hb) levels, neutrophil, lymphocyte and platelet counts and RDW were collected and analyzed. NLR and PLR were computed as the ratio of neutrophils or platelets, respectively, to the total number of lymphocytes per unit volume. Anemia was defined as Hb < 13.5 g/dL in male patients, and < 12 g/dL in female patients. The complete blood count was performed using a Beckman Coulter LH 780 hematology analyzer (Beckman Coulter Biotechnology, Pasadena, California, USA) with ethylenediamine tetraacetic acid blood samples. The analysis of samples was performed 1 hour after the venous access.

Statistical analysis

SPSS (Statistical Package for the Social Sciences version 22.0, Chicago, Illinois, USA) software was used for all statistical analyses. While continuous variables were expressed as mean ± SD, categorical variables were expressed as number and percentage (%). Independent sample t test was used for comparing the groups which were normally distributed (Kolmogorov-Smirnov). Categorical variables were compared by using Chi-square test. Cut-off values for NLR, PLR and RDW for the diagnosis of gastric cancer were computed using receiver-operating characteristic (ROC) analysis. A P-value of less than 0.05 was established as the threshold of statistical significance.

Results

The retrospective dataset included 53 individuals with gastric cancer and a control group of 53 healthy research subjects. The patients with gastric cancer had a mean age of 65.50 ± 11.62 years (18-86 years). Of these patients, 11 (20.8%) were female, 42 (79.2%) were male. **Table 1** includes the clinical and pathological

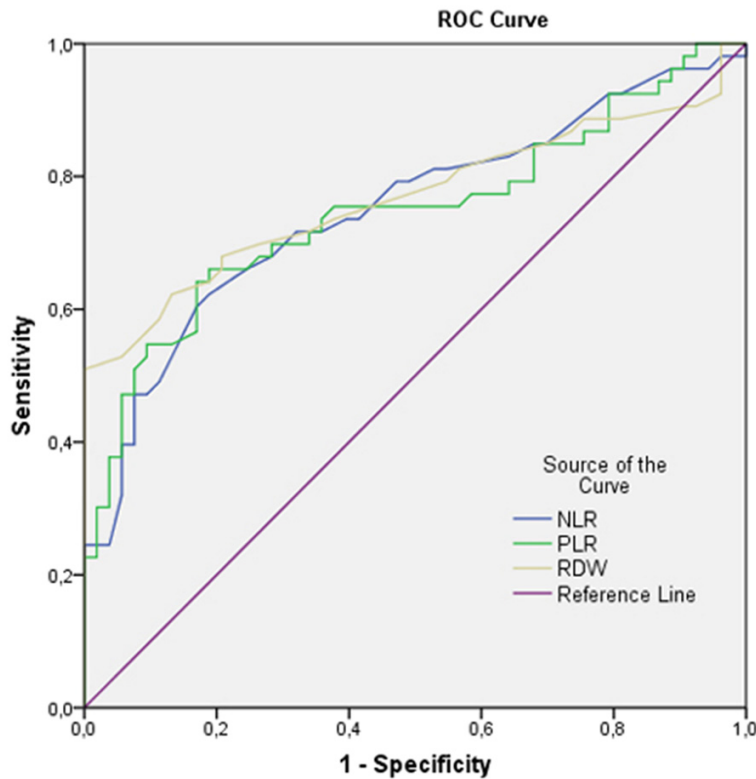


Figure 1. ROC curves for NLR, PLR and RDW in patients with gastric cancer vs. control group. NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; RDW, red cell distribution width; ROC, receiver-operating characteristic.

characteristics of both the patients and control subjects. The study groups did not differ significantly in age ($P = 0.885$) or gender distribution ($P = 0.814$). In the patients with gastric cancer, tumor location was recorded as cardia in 12, corpus in 19, and antrum in 22 patients. Among these patients, 29 (54.7%) were anemic, and 24 (45.3%) were non-anemic. Anemia was significantly more common among the gastric cancer patients relative to the control group ($P < 0.001$). NLR, PLR and RDW were significantly elevated among cancer patients relative to healthy subjects (3.6 vs. 2.1, $P < 0.001$; 188.1 vs. 120.4, $P < 0.001$; 16.2 vs. 13.6, $P < 0.001$, respectively; **Table 1**). Based on the ROC analysis, the cutoff value was 2.17 [area under the curve (AUC): 0.750, sensitivity: 73%, specificity: 61%] for NLR; 128 (AUC: 0.747, sensitivity: 72%, specificity: 64%) for PLR; and 14 (AUC: 0.768, sensitivity: 70%, specificity: 74%; **Figure 1**) for RDW. In a subgroup analysis, NLR, PLR and RDW values were significantly elevated among non-anemic cancer patients relative to the healthy control group (3.43 vs. 2.14, $P < 0.001$;

177.9 vs. 120.4, $P < 0.001$; 14.2 vs. 13.6, $P < 0.001$, respectively; **Table 2**).

Discussion

Our data demonstrates that NLR, PLR and RDW measured during the preoperative period are significantly elevated in patients with gastric cancer relative to healthy control subjects. Additionally, a subgroup analysis showed that NLR, PLR and RDW values are significantly elevated among non-anemic cancer patients relative to the healthy control group. This result suggests that these widely available biomarkers obtained through the complete blood count can be used for early detection and screening of patients with gastric cancer.

Despite declining incidence in recent years, gastric cancer remains one of the most common forms of cancer. The prevalence of gastric cancer differs according to geographic region. Gastric cancer incidence is high in East Asia, South America and Eastern Europe and lower in the United States and Western Europe [7]. Gastric cancer represents 7% of newly diagnosed cancers and 9% of cancer-related deaths worldwide. Late detection of gastric cancer results in high mortality and the death of approximately 700,000 people every year [8]. However, early detection of resectable gastric cancers can improve prognosis for many patients. Although fewer than 30% of gastric cancer patients survive more than 5 years after diagnosis in many areas, screening programs in East Asia have resulted in 5-year survival rates as high as 70% despite high prevalence of the disease [9, 10]. Therefore, early detection and treatment of gastric cancer is essential.

Screening efforts can reduce morbidity and mortality due to gastric cancer even in areas where prevalence is high. A number of diagnostic and screening tests have been developed for gastric cancer including radiographic tests,

Table 2. NLR, PLR and RDW values of non-anemic patients with gastric cancer vs. control group

| Variables | Mide CA (nonanemic) | Control group | P-value |
|--------------------------------------------|---------------------|---------------|---------|
| Platelets (mean ± SD) (10 ⁹ /l) | 264.6 ± 54.1 | 232.5 ± 47.9 | < 0.001 |
| NLR (mean ± SD) | 3.43 ± 2.24 | 2.14 ± 0.77 | < 0.001 |
| PLR (mean ± SD) | 177.9 ± 105.1 | 120.4 ± 35.4 | < 0.001 |
| RDW (mean ± SD) (%) | 14.22 ± 1.23 | 13.62 ± 0.67 | < 0.001 |

NLR: neutrophil/lymphocyte ratio; PLR: platelet/lymphocyte ratio; RDW: red cell distribution width.

endoscopy, Helicobacter pylori serology, and serum Pepsinogen I, II and gastrin levels [10]. A Japanese study showed a 40-60% decrease in gastric cancer mortality after the application of photofluorography screening. However, this method is associated with high inter observer variability. Endoscopy substantially reduces the rate of mortality and is highly preferred. Therefore, endoscopic screening is recommended in regions with a high rate of gastric cancer [10, 11]. However, these methods are not commonly available and are associated with significant cost, radiation exposure, and discomfort. Helicobacter pylori serology, screening of serum Pepsinogen I, Pepsinogen II and gastrin have not been adequately evaluated [12, 13].

Inflammatory cells contribute to cell proliferation, angiogenesis and metastasis of cancerous cells. Generation of reactive nitrogen and oxygen species, cytokines, chemokines, and growth factors associated with inflammation disrupts cellular hemostasis, contributing to the genomic instability and cancer formation. Chemokines and cytokines secreted under inflammatory conditions act as chemotactic signals for circulating leukocytes. Extravasation and proliferation of lymphocytes, neutrophils and macrophages associated with increased cytokines, cytotoxic mediators, proteases, tumor necrosis factor alpha (TNF-α), interleukins and soluble mediators leads to progression of the disease [4, 5]. Furthermore, cancer-activated platelets contribute to the tumorigenesis and angiogenesis and may decrease treatment response. Circulating platelets may become activated at sites of tumorigenesis following secretion of platelet derived growth factors (PDGFs), vascular endothelial growth factor (VEGF), transforming growth factor beta (TGFβ), and fibroblast growth factor (FGF), and [14]. While lymphocytes inhibit formation and proliferation of tumor cells, while neutrophils

enhance formation of tumor cells and promote angiogenesis and disease progression. As the inflammatory response in parallel with the tumor size; neutrophil count increases while there is decrease in lymphocyte count. In cancer patients PLR is increased along with platelet

counts, while lymphocyte count is decrease [15, 16]. RDW is one of the complete blood count parameters measuring variation in red blood cell size. RDW may also reflect increased expression of cytokines such as interleukin and TNF-α. RDW is elevated in cardiovascular disease, neurovascular complications and inflammatory conditions including sepsis, exhibiting a close relationship with mortality. Studies have shown that RDW is elevated in several forms of cancer including cancers of the colon, pancreas and breast. RDW has also been identified as a potential prognostic factor [17, 18].

Recently, markers of systemic inflammatory state have become important prognostic indicators for cancer patients. Systemic inflammatory markers such as NLR, PLR, RDW and albumin derived from the complete blood count are used to determine prognosis in some types of cancer [19, 20]. No previous study has demonstrated that NLR, PLR and RDW are potential markers for early detection of gastric cancer in preoperative patients. The relationship between NLR, PLR, and RDW and disease prognosis has been examined previously. High NLR and PLR is considered as a poor prognostic factor and is associated with low 5-year survival rates in gastric cancer patients [20, 21]. NLR and PLR can also be used to determine prognosis in advanced disease [22]. Kilincalp *et al.* demonstrated that NLR and PLR are biomarkers of gastric cancer disease both in screening and during postoperative follow-up of patients with colorectal cancer [23]. Elevated RDW is associated with poor survival [24, 25]. A study by Ay *et al.* reported high levels of RDW in patients with colon cancer, and concluded that RDW could be used as a biomarker for screening [26].

The present study represents the first in the literature to demonstrate that NLR, PLR and RDW are potential gastric cancer biomarkers. NLR,

PLR and RDW are markedly elevated in individuals with gastric tumors relative to control subjects regardless of the anemia absence. This study may be partly limited by its small number of patients and, retrospective design. Future studies with larger number of patients should be planned.

In summary, NLR, PLR and RDW data derived from inexpensive, rapid and commonly available peripheral blood counts represent additional clinical indicators for early diagnosis and screening of gastric cancer in populations where disease prevalence is high. Further multi-centered and comprehensive studies are required.

Disclosure of conflict of interest

None.

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