JBUON 2015; 20(1): 78-83
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

High levels of platelet/lymphocyte ratio are associated with metastatic gastric cancer

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Summary

Purpose: *The predictive and prognostic value of cheap, easily accessible and commonly available complete blood count parameters has already been studied in a variety of cancers. In the present study, we aimed to investigate the association between pretreatment platelet/lymphocyte ratio (PLR) and metastatic gastric cancer.*

Methods: *The records of 228 patients dating from January 2010 to June 2014 were retrospectively evaluated. Patients who had undergone radical (N=157) or palliative gastrectomy (N=71) for metastatic gastric cancer were included and divided into two groups according to stage (early-advanced) and metastasis (absence-presence) status, and PLR values were compared.*

Results: *38 (16.6%) of 228 patients had early gastric cancer (non metastatic cases). PLR values of advanced gastric cancer (not including metastatic cases) were significantly higher compared to early gastric cancer (231.6±107.45 and 160.3±71.5, respectively; p<0.001). Seventy one (31.1%) of 228 patients had distant metastasis. PLR values of metastatic gastric cancer were significantly higher than in non-metastatic gastric cancer (251.0±94.8 and 192.7±88.8, respectively; p<0.001). Logistic regression analysis showed that PLR was an independent predictive factor for tumor burden in both stage and metastasis groups (p<0.001 and p=0.003, respectively). Also, in correlation analysis, PLR showed mild correlation with stage and metastasis groups (r=0.291 and r=0.299, respectively).*

Conclusions: *Pretreatment PLR values were correlated with tumor burden, and most higher values were detected in metastatic disease. Our findings may be useful, especially in the decision-making for laparoscopic staging in patients who have no radiological evidence of metastatic disease.*

Key words: *gastric cancer, metastasis, platelet to lymphocyte ratio, predictive value*

Introduction

Despite the declining incidence rates over the past 50 years, particularly in developed countries, gastric cancer is one of the most common causes of cancer deaths worldwide [1]. In contrast to Asian countries, in Western world most gastric cancer patients are diagnosed in advanced stages [2]. Among a variety of reported tumor characteristics and biomarkers, the search for a reliable biomarker for predicting the clinical behavior of this disease is still going on. Recently, the relation between inflammatory processess and subclinical coagulation disorders has become an interesting field of research. Although the underlying mechanisms remain largerly unclear, there is increasing evidence to believe that a connection exists between them. Briefly, cancer growth creates a number of inflammatory cytokines and growth factors, and causes the release of inhibitory immunologic mediators [3]. Some of these proinflammatory cytokines (IL/interleukin-1, IL-3, and IL-6) promote megakaryocytes' proliferation, resulting in thrombocytosis [4]. Also, cancer-related systemic

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Received: 09/09/2014; Accepted: 27/09/2014

inflammation is a major cause of lymphocytopenia due to inhibitory immunologic mediators, such as IL-10 and transforming growth factor-beta (TGF β). From this aspect, the predictive and prognostic value of cheap, easily accessible and commonly available complete blood count parameters in a variety of cancers has been investigated in a number of studies [5-7]. In this study, we aimed to investigate the association between pretreatment PLR and metastatic gastric cancer.

Methods

After the local ethics committee approval, three hospitals' databases were searched for patients who had undergone gastrectomy for gastric cancer. The records of 284 patients dating from January 2010 to June 2014 were retrospectively evaluated. Tumor localisation, histopathologic features, PLR in the last 24 hours before the operation, distant metastasis, TNM stage and patient demographic characteristics were recorded. Fifty six patients who had history of blood transfusion in the last 2 months, active bleeding or bleeding disorders, infection, anticoagulant treatment, additional malignancy, immunesuppressive treatment and hematological diseases were excluded. Patients who had undergone radical, total or distal gastrectomy with sufficient lymphadenectomy (at least 15 lymph nodes harvested) were included and staged according to AJCC-TNM staging system (N=157). Also, patients who had palliative gastrectomy for metastatic gastric cancer were included (N=71). Early gastric cancer was defined as cancer invading not deeper than the submucosa, irrespective of lymph node metastasis (T1, any N). The leukocyte and platelet count and lymphocyte percentage were measured by an automated hematology analyzer (Coulter® LH 780 Hematology Analyzer, Beckman Coulter Inc., Brea, CA, USA). A total of 228 patients were divided into two groups, according to stage (early-advanced) and metastasis (absence-presence) status, in stage and metastasis groups. The comparison of PLR was made separately in both groups and the association between stage and metastasis was analysed.

Statistics

Data analysis was performed using SPSS for Windows, version 22 (SPSS Inc., Chicago, IL, USA). The normality of the distributions of continuous variables was determined by the Shapiro-Wilk test. The data were reported as means ± standard deviation or medians and range where applicable. Differences between the groups were compared by Student's t-test or the Mann-Whitney U test where appropriate. The categorical data were analyzed using Pearson's chi-square or Fisher's exact test where appropriate. Degrees of association between continuous variables were evaluated by Pearson's correlation analysis. Cox multivariate regression analysis was used to assess the differences between groups in age, gender and PLR. The coefficient of regression and the 95% confidence interval for each independent variable were also calculated. The cut-off values of parameters for discrimination of the groups were determined using the receiver operating characteristic (ROC) analysis. At each value, the sensitivity and specificity for each outcome under study were plotted, thus generating an ROC curve. A p value less than 0.05 was considered statistically significant.

Results

The patient median age was 65 years (range 24-88). Of the 228 patients, 157 (68.9%) were males and 71 (31.1%) females. Demographic characteristics, tumor localisation, tumor histopathology, distant metastasis and TNM stages are displayed in Table 1.

In stage grouping, 38 (16.6%) of 228 patients were found with early gastric cancer. Sex was similar in both early and advanced gastric cancer patients (p=0.224). Advanced-stage patients were younger (p=0.024). Pretreatment PLR values of advanced gastric cancer patients were significantly higher than those of the patients with early

Table 1. Demographic and tumor related characteristics of 228 patients

Characteristics	*Patients N (%)*
Age (years), mean±SD	63.5±13.1
Sex (female/male)	71/157 (31.3/68.7)
Early/advanced cancer	38/190 (20/80.0)
Metastasis (M0/M1)	157/71 (68.9/31.1)
Tumor localisation	
Cardia	33/228 (14.5)
Corpus	78/228 (21.1)
Antrum	112/228 (49.1)
Remnant	5/228 (2.2)
Tumor histopathologic features	
Adenocarcinoma	182/228 (79.8)
Signet ring cell	30/228 (13.2)
Mucinous	6/228 (2.6)
Miscellaneous	10/228 (4.3)
TNM stage	
1A	19 (8.3)
1B	25 (11.0)
2	26 (11.4)
3A	37 (16.2)
3B	30 (13.2)
4	91 (39.9)

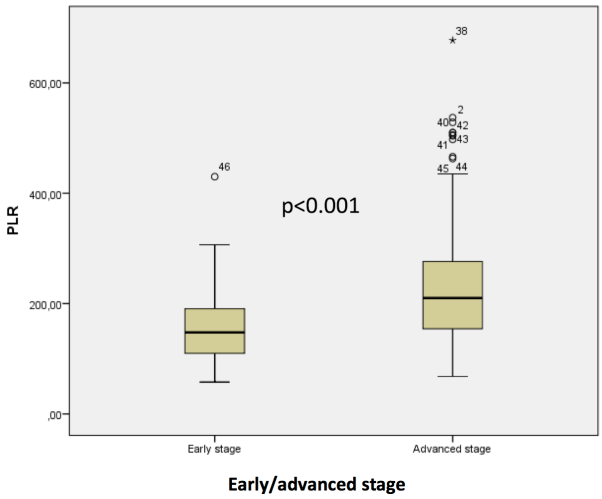

Figure 1. Distribution of PLR between early and advanced gastric cancer groups.

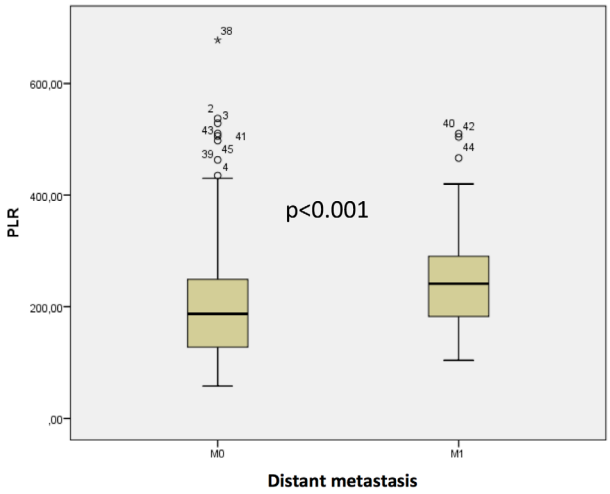

Figure 3. Distribution of PLR between metastatic and non metastatic gastric cancer groups.

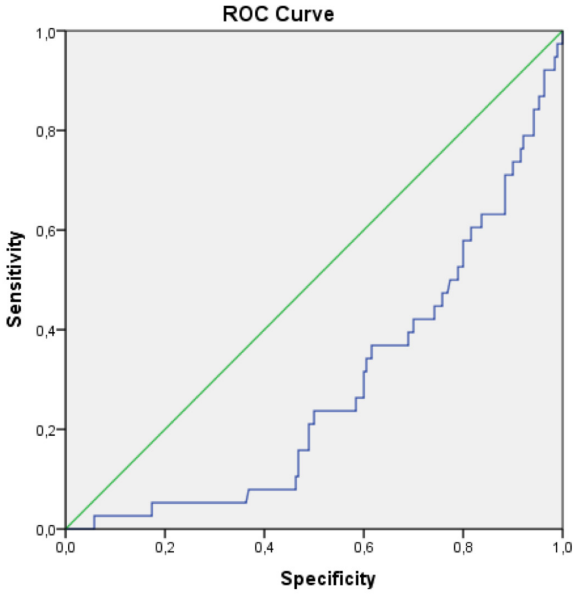

Figure 2. ROC curve for PLR in early/advanced gastric cancer. Area under the curve: 0.281 (p<0.001); 95% CI: 0.198 – 0.365; Sensitivity: 63.2%; Specificity: 63.2%; PPV: 89.6%; NPV: 25.5%.

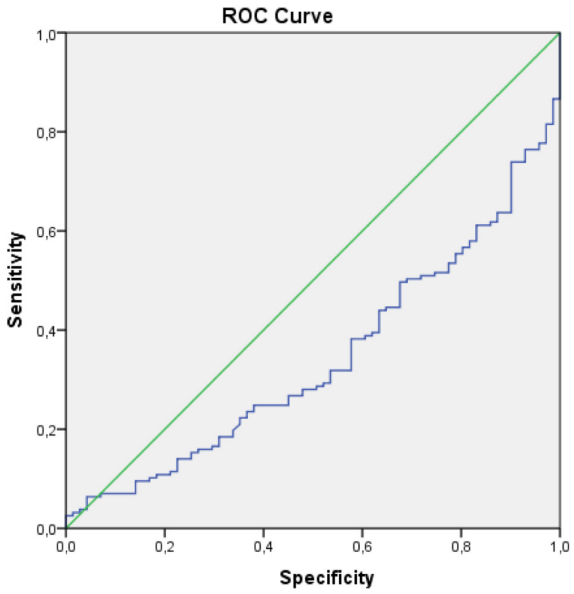

Figure 4. ROC curve for PLR in metastatic/non-metastatic gastric cancer. Area under the curve: 0.342 (p<0.001); 95% CI: 0.270 – 0.414; Sensitivity: 65.3%; Spesificity: 76.3%; PPV: 93.2%; NPV: 30.5%.

gastric cancer (231.6±107.45 and 160.3±71.5, respectively; p<0.001) (Figure 1). The recommended cutoff value of the PLR was based on the most prominent point on the ROC curve for sensitivity (63.2%) and specificity (63.2%). Because these two parameters indicated a cutoff value of 181.9, the recommended PLR cutoff value was defined as 181.9 (Figure 2). The area under the ROC curve was 0.281 (95% CI 0.198-0.365; p<0.001).

Seventy one (31.1%) of 228 patients had distant metastasis. Age and sex were similar between metastatic and non-metastatic gastric cancer patients (p>0.05). Pretreatment PLR values of metastatic gastric cancer patients were significantly higher compared to non-metastatic patients (251.0±94.8 and 192.7±88.8, respectively; p<0.001) (Figure 3). The recommended cutoff value of the PLR was based on the most prominent point on the ROC curve for sensitivity (65.3%) and specificity (76.3%). Because these two parameters indicated a cutoff value of 208.5 the recommended PLR cutoff value was defined as 208.5 (Figure 4). The area under the ROC curve was 0.342 (95% CI 0.270-0.414; p<0.001). Age, sex and PLR values of the groups are presented in Table 2.

In logistic regression analysis, PLR was

Table 2. Age, sex and PLR values of the groups

	Early cancer	*Advanced cancer*	*p value*	*M0*	*M1*	*p value*
Age, years mean±SD	67.0±14.2	62.8±12.8	0.024	63.6±13.5	63.3±12.4	0.662
Sex (F/M)	15/23	56/134	0.224	50/107	21/50	0.732
PLR Mean±SD (Min-Max-Med)	160.3±71.5 (57.6-430.0-147.7)	231.6±107.4 (67.9-677.5-210.0)	<0.001	205.6±107.4 (57.6-677.5-187.3)	251.0±94.8 (104.1-510.0-241.3)	<0.001

PLR: platelet/lymphocyte ratio, F: female, M: male, SD: standard deviation

found to be an independent predictive factor for tumor burden in both stage and metastasis groups (p<0.001 and p=0.003, respectively). Age was found to be an independent predictive factor for tumor burden in stage group (p=0.024; Table 3). Also, in correlation analysis, PLR has shown mild correlation with stage and metastasis groups (r=0.291 and r=0.299, respectively; Table 4).

Table 3. The effect of age, sex and PLR values on early/advanced and metastatic/non-metastatic cancer (Cox multivariate logistic regression analysis)

	Early/advanced cancer p value	*M0/M1 p value*
Age	0.023	0.665
Sex	0.364	0.909
PLR	<0.001	0.003

PLR: platelet/lymphocyte ratio

Table 4. Correlation between PLR and early/advanced and metastatic/non-metastatic cancer (Spearman's correlation test)

	Early/advanced cancer p value	*M0/M1 p value*
PLR	<0.001 +0.291 (Corr.)	<0.001 +0.299 (Corr.)

PLR: platelet/lymphocyte ratio

Discussion

Worldwide, gastric cancer is diagnosed at advanged stages or with metastases. Despite the advances in surgical and oncological treatment modalities, gastric cancer still remains the second most common cause of all cancer deaths, accounting for approximately 12% [1,9]. With the use of screening endoscopy, approximately 60% of all gastric cancers are diagnosed at an early stage in Japan [10]. Five-year survival of early gastric cancer can reach 90% if treated appropriately [11]. Higher survival rates of early gastric cancer patients have led physicians to search for reliable predictive biomarkers for this disease. Recently, a number of studies have investigated the predictive and prognostic value of the most commonly available hematological parameters in many malignant solid tumors [7,10-14]. The rationale of cheap, non-invasive and easily available biomarker search has drawn physicians' attention to complete blood count (CBC) parameters. Recent studies have shown an association between inflammation and cancer development, and the diagnostic and prognostic role of neutrophil-lymphocyte ratio and platelet-lymphocyte ratio has been studied [5-7,15-17]. Thrombocytosis was reported as a component of inflammatory response and a common hematological finding in cancer patients [18,19]. Thrombocytosis and lymphopenia were suggested as predictors of poor prognosis in gastric cancer patients [12,20,21]. Platelets and tumor cell association was originated from the platelet-releasing mediators, which are effective in angiogenesis and tumor development [22]. Also, it was shown that platelets can hinder the lysis of tumor cells by natural killer cells in mice [23]. Through the mechanism of decreased T4 helper lymphocytes and increased T8 suppressor lymphocytes, the immunological response to tumor cells induces lymphopenia and depresses innate cellular immunity [24]. The prognostic value of lymphopenia in a variety of cancer types has been investigated in previous studies [14,21,25,26]. Up to date, the association between high pretreatment PLR values and poor prognosis and survival of gastric cancer patients has been reported in a variety of studies, but, to the best of our knowledge, the association between pretreatment PLR levels and metastatic gastric cancer was not reported in English literature [5,12,27-29]. In this study we aimed to uncover the association of pretreatment PLR levels in metastatic gastric cancer patients who underwent palliative resection and compare it with early and advanced gastric cancer patients who underwent radical gastrectomy.

Aliustaoglu et al. divided calculated PLR val-

ues into two groups [12]. They defined 160 as a cutoff value for PLR, and found significantly higher median overall survival (OS) in locally advanced gastric cancer patients whose PLR value was ≤ 160. They also reported no association between PLR and tumor grade. In another study a similar cutoff value was used to uncover the prognostic significance of PLR in advanced gastric cancer patients who were treated with FOLFOX combination chemotherapy [5]. However, Lee et al. did not notice statistically significant OS advantage in patients who had lower PLR values [5]. Also, Wang et al. failed to show significant survival advantage in the lower PLR group in stage III gastric cancer patients [28]. As we did not analyse the survival of our patients because of the design of the study, we could not comment on survival data. In this study, we found statistically significant association between high pretreatment PLR levels and tumor stage, like Lee et al. [5]. Despite the calculated higher cutoff value of our study (181.9 for early/advanced cancer comparison and 208.5 for metastatic/non-metastatic cancer comparison), we found significant association between high PLR and advanced and metastatic gastric cancer. These findings could be interpreted as continuing linear increase in PLR value with disease progression to end-stage or the tumor burden in patients who were diagnosed with gastric cancer. From this aspect, the detected higher pretreatment PLR values in patients who were candidates for adjuvant chemotherapy in the study of Lee et al., could be explained as more advanced tumor stage and higher PLR association [5]. A recent meta-analysis reached a similar conclusion on PLR and tumor stage. There, the authors stated that "PLR can be a predictor of the stage of some tumors" [29]. In logistic regression analysis, PLR was found to be an independent predictive factor for tumor burden in both stage and metastasis groups. Also, PLR showed mild correlation with advanged stage and presence of metastasis. Despite the reported association between high PLR values and poor prognosis in gastric cancer patients, our results indicated continuing increase in PLR with increased tumor burden, such as metastatic disease. From this aspect, pretreatment PLR values could help the desicion on laparoscopic staging of gastric cancer patients, who will undergone curative-intent surgery with no radiological clues of metastatic disease.

In conclusion, we found that pretreatment PLR values were correlated with the tumor burden of gastric cancer patients, and most higher values were detected in metastatic disease. Our findings may be useful in the decision-making for laparoscopic staging in patients who have no radiological evidence of metastatic disease. However, our results need to be prospectively confirmed in laparoscopically staged patients.

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