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ORIGINAL PAPER

The effect of peripheral blood values on prognosis of patients with locally advanced gastric cancer before treatment

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Abstract We aimed to investigate the prognostic significance of neutrophil, lymphocyte, platelet, mean platelet value (MPV), platelet-lymphocyte ratio (PLR) and neutrophil–lymphocyte ratio (NLR) in patients with locally advanced gastric cancer (LAGC). One hundred sixty-eight patients with LAGC who had been followed-up between 2004 and 2008 were included in present study. The results of hematological (platelet, lymphocyte, neutrophil and MPV) and biochemical (uric acid and LDH) parameters were evaluated before treatment. NLR was divided into two groups as <2.56 and ≥2.57 and PLR was also divided into two groups as ≤160 and >160. Platelet counts and lymphocyte counts were also divided into two groups; ≤300.000/mm3 and >300.000/mm3, and <1,500/mm3 and ≥1,500/mm3, respectively. Results were evaluated with Kaplan–Meier and Long-rank tests. The mean age of patients at diagnosis was 60.1 ± 12.1 and 114 of patients (67.8%) were male. For 168 patients, 48 months overall survival (OS) rate was 45.2% and the median OS was 39 months (range 33–44). In patients whose PLR was less than 160 ($n = 54$), the median OS was 45 months (range 38–52) and also for cases whose PRL was greater than 160 ($n = 114$), the median OS was 27 months (range 22–32) ($p = 0.006$). While for fifty patients whose lymphocyte counts were less than 1,500, the median OS was 27 months (range 21–33), in cases with high lymphocyte counts (≥1,500) ($n = 118$), it was 41 months (range 35–48) ($p = 0.03$). The median OS was 41 (range 34–48) and 30 (range 23–37) months in two platelets groups, respectively ($p = 0.24$). However, in the patients whose NLR was less than 2.56 ($n = 107$), median OS was better than with cases whose NLR was greater than or equal to 2.56 (42 vs. 27 months). Routine peripheral blood counts may be useful prognostic factor for evaluating the accuracy of risk stratification in patients with radically resected gastric cancer Our results need to be confirmed by study including larger sample size in future.

Keywords Neutrophil · Platelet · Lymphocyte · Platelet-lymphocyte ratio · Neutrophil–lymphocyte ratio · Gastric cancer

Introduction

Assessment of the inflammatory response to the tumor may be easier and more-cost effective in clinical practice. Therefore, the role of immune system on disease cessation or progression has been recently investigated, and some hematological parameters including leukocyte counts have been shown as both a diagnostic and prognostic factors in various types of malignancies [1–5]. Furthermore, the neutrophil to lymphocyte ratio (NLR) has been documented as a simple index of systemic inflammatory response in critically ill patients with malignancy [6–9]. Similary, preoperative platelet to lymphocyte ratio (PLR) has been also suggested as an independent significant prognostic indicator in pancreatic cancer [10].

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Gastric cancer is one of the most common cancer and the leading cause of cancer death and mortality in both sexes [11]. Altered immune response to gastric cancer has been previously reported [12, 13]. Both NLR and thrombocytosis have seperately investigated as a prognostic factors in gastric cancer [7, 9, 14]. In this study, we aimed to assess the prognostic values of pretreatment lymphocyte, neutrophil, platelet counts, mean platelet volume (MPV), NLR and PLR in patients with gastric cancer.

Materials and methods

Between 2004 and 2008, a total of 168 patients with locally-advanced gastric cancer who followed-up in the Department of Medical Oncology outpatient clinics, were included in the study. Patients' hematological parameters (neutrophil, lymphocyte, thrombocyte, MPV were measured before treatment. The exclusion criteria were history of blood transfusion within the last two months, active bleeding, bleeding diathesis, hyper- or hypothyroidism, infections, disseminated intravascular coagulation, heparin treatment or connective tissue disease.

Venous blood samples taken from patients admitted to the oncology outpatient clinic for adjuvant chemotherapy, and were collected in ethylenediaminetetraacetic acid (EDTA)-containing tubes. Blood counts were analyzed on a Sysmex hemocounter before the initiation of chemotherapy. The results of these pretreatment blood counts were retrospectively evaluated. Patients were staged according to the American Joint Committee on Cancer (AJCC) Staging Manuel. Demographical data of the patients were recorded and survival data were extracted from patients' charts. The results of pretreatment hematologic tests consisting of neutrophil, lymphocyte and platelet counts and MPV and pretreatment clinical biochemical tests, including serum total and direct bilirubin, urea, creatinine, albumin and lactate dehydrogenase (LDH) and alkaline phosphatase (ALP) enzyme activities were also evaluated.

NLR

NLR was calculated as neutrophil count divided by lymphocyte count. The calculated values were defined at two categories as <2.56 and ≥ 2.56. [2].

PLR

PLR was calculated as platelet count divided by lymphocyte count. The calculated values were divided into two categories as ≤ 160 or >160 [3].

Lymphocyte, and platelet counts

Lymphocyte counts were divided into two categories as less than 1,500/mm^3 and equal or greater than 1,500/mm^3. Similarly platelet counts defined as less than or equal to 300,000/mm^3 and greater than 300,000/mm^3 [2, 4, 5].

Statistical analysis

Frequency, percent ratio, arithmetic mean, standard deviation, 95% confidence intervals and mean values were used for the description of the variables. The Kolmogorov–Smirnov test was used to test the fitness of the continuous variables to normal distribution. Variables following a standard normal distribution were compared by the Student's t-test and Mann–Whitney-U test was used for non-parametric independent group comparison. Survival analyses were performed by the Kaplan–Meier test. Overall survival (OS) was described as the time from diagnosis to the date of the patient's death or last known contact. The patient data available permitted the calculation of 12 months survival rates thus the overall survivals of the cases were defined for a period of one year. Survival rates of the subgroups were compared by the Log-Rank test. P-values less than or equal to 0.05 were considered to be statistically significant.

Results

Of the 168 patients in the study, 114 were males (67.8%) and 54 (32.2%) were females. The mean age of the patients at the time of diagnosis was 60.1 ± 12.1 years (ranges 28–83 years). For all patients, 48 months overall survival (OS) rate was 45.2% and the median OS time was 39 months (range 33–44 months). The pretreatment serological and hematological data of the patients are summarized in Table 1.

The median OS time was significantly higher for patients whose PLR was less than or equal to 160 ($n = 54, 32\%$), than the patients whose PRL was greater than 160 ($n = 114, 68\%$) [45 months (95% CI; 38–52) vs. 27 months (95% CI; 22–32), $p = 0.006$, Fig. 1.].

A total of 50 patients (30%) had a lymphocyte counts less than 1,500/mm^3, while others (70%) had lymphocyte counts were greater than or equal to 1,500/mm^3. The median OS interval was significantly higher in patients with lymphocyte counts which were greater than or equal to 1,500/mm^3 than those with $<$1,500/mm^3 [41 months (95% CI; 35–48) vs. 27 months (95% CI; 21–33), $p = 0.03$, Fig. 2].

In 40% of patients, thrombocyte count was detected as greater than 300.000/mm^3 and in 13% of patients, $>$400.000/mm^3. Three-years OS rate was 64% and the median survival time was 41 months (95% CI; 34–48 months) in patients whose platelets counts were less than or equal to

Table 1 Patients' hematological values before treatment

Variables	Mean ± SD	%95 CI.	Median	Range
Age	60.17 ± 12.15	58.32–62.02	60	28–83
Leukocyte	6,893.5 ± 2,750.7	6,474.5–7,312.5	6,640	2,400–16,320
Neutrophil	4,231.5 ± 2,476.2	3,854.3–4,608.7	3,850	365–14,200
Lymphocyte	1,911.3 ± 752.5	1,796.3–2,026.2	2,000	430–5,000
Thrombocyte	292.428 ± 123.946	274.107–312.011	279.000	75.000–877.000
NLR	2.64 ± 2.2	2.3–2.98	2	0.15–12
PLR	175.1 ± 101.6	159.6–190.6	152	60.1–668.0

NLR neutrophil–lymphocyte ratio, *PLR* platelet-lymphocyte ratio
SD Standard deviation

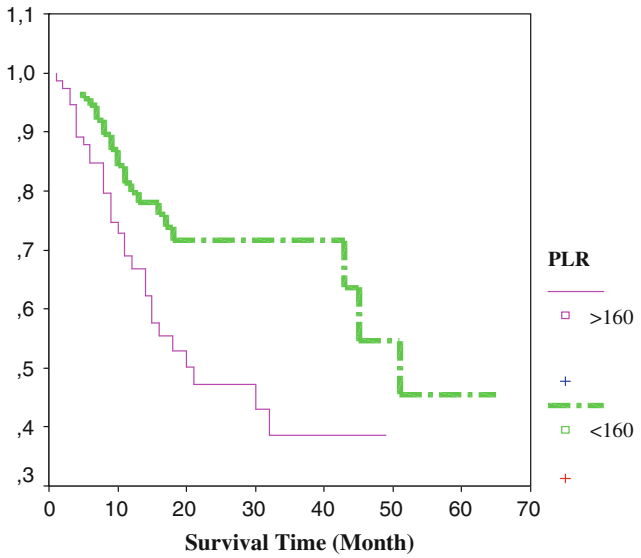

Fig. 1 Kaplan–Meier cumulative survival curves for locally advanced gastric cancer patients strafied by platelet-lymphocyte ratio (PLR)

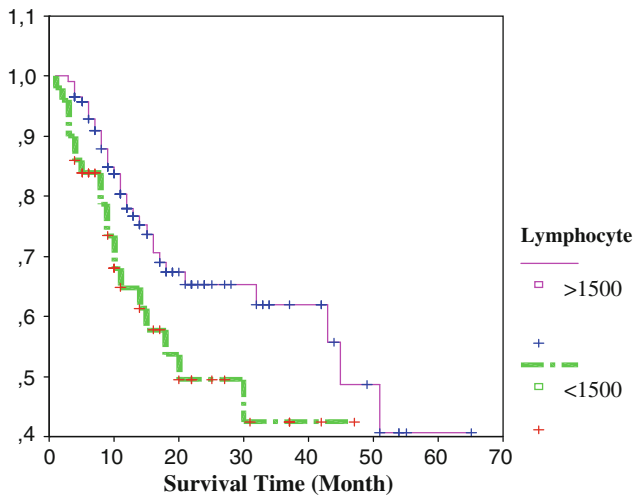

Fig. 2 Kaplan–Meier cumulative survival curves for locally advanced gastric cancer patients according to lymphocyte counts

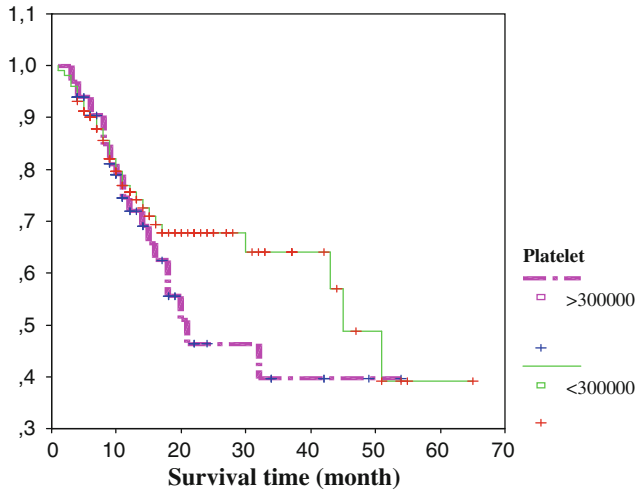

Fig. 3 Kaplan–Meier cumulative survival curves for locally advanced gastric cancer patients according to platelet counts

300.000/mm^3. On the other hand, for patients whose platelets counts were greater than 300.000/mm^3, three-years OS rate and the median survival interval were 40% and 30 months (95% CI; 23–37), respectively. These differences were not statistically significant ($p = 0.24$, Fig. 3). The association of hematological parameters with the median survival time is listed in Table 2.

One hundred and seven patients (63.6%) were detected whose NLR was less than 2.56, while there were 61 patients (36.4%) whose NLR was greater than or equal to 2.56. The median OS duration was significantly higher in patients with NLR < 2.56 than those with NLR ≥ 2.56 (42 months (95% CI; 36–49) vs. 27 months (95% CI; 21–34), $p = 0.001$). The relationship between NLR, PLR and lymph node involvement or tumor grade was not found significant ($p > 0.05$).

Discussion

Gastric cancer is often diagnosed at an advanced staged, because screening is not performed routinely in most of the

world, except for Japan [15, 16]. Infections, autoimmune diseases, benign and malign tumors are caused chronic inflammations [8]. Inflammatory cells can suppress or stimulate tumor growth. Moreover, inflammation plays a major role in the development and progress of various organ cancers [17–19]. Therefore, hematological markers including neutrophils, lymphocytes, NLR or PLR are recommended as diagnostic and prognostic factors in various types of cancers in recently published studies [1–5].

Firstly, Levin and Conley have been reported thrombocytosis in patients with gastric cancer, but the prognostic significance of thrombocytosis has not been investigated [20]. However, its' prognostic importance have been observed frequently in patients with gynecological cancers, renal cell carcinoma, and lung cancer [21–23]. The prevalence of thrombocytosis in patients with gynecological cancer was 9.5–38%, 13–60% with primary lung cancer, 56.8% with renal cell carcinoma, and 33% with colon cancer [4, 14, 24, 25]. We found that thrombocyte count was greater than 400.000/mm^3 in 13% of patients. Our results were similar to the study of Ikeda et al. [14].

Shimada et al. found that thrombocytosis was present in only 5.1% of patients with esophageal cancer. Furthermore, they showed that the patients with high platelet counts had significantly worse survival than the low platelet group [4]. Similarly, Ikeda et al., indicated that the patients without thrombocytosis had significantly better survival than those with thrombocytosis in gastric cancer patients [14]. In our study, we suggested that the patients whose platelet counts were less than or equal to 300.000/mm^3, had better the median survival time than those with platelet counts >300.000/mm^3. Although this difference was not statistically significant, it may be noteworthy for clinical practice.

Preoperative PLR has been defined as an independent significant prognostic marker by Smith et al. in resected pancreatic ductal adenocarcinoma [26]. In the same study, the median overall survival in patients with a PLR of 150 or less was 19.7 months, 13.7 months in those with a PLR of 151–300, and 5.8 months in patients with a value of greater than 300. Smith et al. showed elevated preoperative CA 19-9 levels and PLR were associated with poorer survival in patients underwent resection for ampullary adenocarcinoma [3]. In our study, for cases where PLR was less than or equal to 160 ($n = 54$), the median survival time was 45 months. Nonetheless, the median survival interval was 27 months in patients whose PLR was higher than 160. This difference was significant ($p = 0.006$).

Some studies indicated that a decreased lymphocyte count in the peripheral blood is a predictor of a poor prognosis in cancer patients [27–29]. Bruckner et al. suggested that a pretreatment absolute neutrophil count <6,000/mm3 and lymphocyte count >1,500/mm3 were independent prognostic indicators of a good prognosis for patients with metastatic gastric cancer [30]. Moreover, Elias et al. investigated mononuclear cell percentages in patients with head and neck cancer, and they showed that high percentages of lymphocytes (≥30%) and low monocyte percentages (<10%) related to a better prognosis [31]. The relation between low lymphocyte counts and poor prognosis has been reported in patients with various tumor types, including ovarian, pancreatic, renal and breast tumors [27, 28, 32]. In our study, we found that the median survival interval was significantly higher in patients with lymphocyte counts which were greater than or equal to 1,500/mm^3 ($n = 118$) than those with <1,500/mm^3 ($n = 50$) (41 months vs. 27 months, $p = 0.03$).

NLR is considered as a simple indicator of the systemic inflammatory response in critically ill patients [6]. Elevated NLR at the time of diagnosis accompanies low survival rates in ovarian cancer [8]. In addition, an elevated NLR is also a potentially poor prognostic predictor after curative resection for hepatocellular carcinoma [33]. Walsh et al. demonstrated that for patients with colorectal cancers, preoperative NLR value greater than 5 associated with a poor survival rates [34]. Yamanaka et al. found that in patients with NLR value less than 2.5, the median survival time was significantly higher than those with NLR of >2.5 in advanced gastric cancer (363 days vs. 239 days.) [2]. Similarly, in the present study, the patients with an NLR value lower than 2.56 had significantly higher median duration of survival than those with an NLR value of 2.56 or above (42 vs. 27 months, $p = 0.001$). The reports associated with the effect of peripheral blood values on prognosis of patients with locally advanced gastric cancer were shown in Table 3.

In conclusion, we found that pretreatment routine hematological parameters including lymphocyte, and NLR

Table 2 The association of hematological parameters with the median survival time

Parameter	Median survival time (month)	Range	*P* value
Lymphocyte count			
<1,500	27	21–33	0,03
≥1,500	41	35–48	
NLR			
<2.56	42	36–49	0,001
≥2.56	27	21–34	
Thrombocyte count			
≤300.000	41	34–48	0,24
>300.000	30	23–37	
PLR			
≤160	45	38–52	0,006
>160	27	22–32	

NLR neutrophil–lymphocyte ratio, *PLR* platelet-lymphocyte ratio

Table 3 The reports regarding the impact of peripheral blood values on prognosis of patients with locally advanced gastric cancer in the literature

Reference (no.)	Neutrophil count	Lymphocyte count	Thrombocyte count	NLR	PLR
Bruckner et al. [30]	<6,000 correlated favorable prognosis ($p < 0.001$)	>1,500 correlated favorable prognosis ($p < 0.001$)	–	–	–
Ikeda et al. [14]	–	–	Thrombocytosis correlated poor survival ($p < 0.0001$)	–	–
Yamanaka et al. [3]	NS	NS	–	–	<2.5 correlated good survival ($p = 0.019$)
Present study	–	>1,500 correlated good survival ($p = 0.03$)	NS	<2.56 correlated good survival ($p = 0.001$)	<160 correlated good survival ($p = 0.006$)

NLR neutrophil–lymphocyte ratio, *PLR* platelet-lymphocyte ratio, *NS* not significant

and PLR were correlated with prognosis in patients with gastric cancer who had undergone curative gastrectomy. Our finding may be useful for evaluating the accuracy of risk stratification and lead to more appropriate clinical management of patients with radically resected gastric cancer, but, our results need to be confirmed by study including larger sample size in future.

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