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Neutrophil to Lymphocyte Ratio, Platelet to Lymphocyte Ratio, and Lymphocyte to Monocyte Ratio in Gastric Cancer Patients Compared with the Control Group and Its Association with Pathological Factors of the Disease

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ABSTRACT

Background and Objective: Considering the prevalence of gastrointestinal cancers in the region and the importance of helpful criteria in the diagnosis of the disease, the present study was conducted to compare the blood parameters neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR) and lymphocyte to monocyte ratio (LMR) in gastric cancer patients in Mazandaran province and its comparison with non-affected people.

Methods: This cross-sectional study was conducted in 2019 and 2020 on 62 cancer patients referred to Imam Hospital in Sari in the case group and 124 non-patients from the community in the control group. Convenience sampling was used in the case group and random sampling was used in the control group from among the Tabari Cohort Population. The two groups were matched in terms of age and gender. The required data including age, gender, LMR, NLR and PLR for all subjects as well as pathological indices and chemotherapy status were recorded for the case group.

Findings: The gender ratio in both groups was 69.4% males and 30.6% females. The mean age of the examined subjects in the group of cancer patients and the control group was 62.3±12.53 and 51.7±9.02 years, respectively (p=0.105). The mean NLR (2.14 vs. 1.62, p=0.000) and PLR (9.48 vs. 6.27, p=0.000) in the group with gastric cancer were significantly higher than the healthy control group, and the mean LMR (3.42±2.12 vs. 10.9±2.99, p=0.000) was significantly lower than the healthy control group.

Conclusion: The results of high NLR and PLR and low LMR showed that these indices can be used in gastric cancer screening studies.

Keywords: *Leukocyte Count, Platelet Count, Lymphocyte Count, Gastric Cancer.*

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Introduction

Gastric cancer is the fifth most malignant cancer and the fourth most common cause of cancer-related deaths worldwide (1). However, this disease is often diagnosed in advanced stages (2, 3).

Inflammation, as a biological response of the body against adverse stimuli, plays a central role in cancer biology. Chronic inflammation caused by chemical and physical factors and autoimmune and inflammatory reactions caused by them are associated with increased risk of malignancy (4-6). Although the exact mechanism of systemic inflammation in cancer patients has not yet been clarified, it is generally accepted that cancer-related inflammation is related to the interaction between cancer cells and host defense cells (7). Many tumors, such as gastric cancer, cause systemic inflammatory response (SIR). SIR can be evaluated by the number or ratio of neutrophils, lymphocytes, monocytes and serum platelets (8). In addition to the mentioned parameters related to SIR, the combined parameters related to SIR are also presented, which include neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), mean platelet volume and distribution extent of red blood cells (9-14). Previous studies have shown that LMR (Lymphocyte to Monocyte Ratio) and PLR can play the same role as NLR in disorders such as gastric cancer (11, 14, 15-18). The role of tumor-associated macrophages, as well as peripheral blood-based surrogate parameters such as the lymphocyte to monocyte ratio, has been documented as a potential biomarker for prognostic clinical outcomes in patients with cancer, including colorectal cancer, sarcoma, and lymphoid neoplasms (9-11, 14-18).

Considering the prevalence of gastrointestinal cancers in the region and the fact that previous studies investigated the relationship between the combined parameters of SIR and the prognosis of the disease, this study aims to compare blood indices such as LMR, NLR, PLR of gastric cancer patients in the early stages of the disease and compare it with non-affected people.

Methods

This cross-sectional study was conducted in 2019 and 2020 with the code of ethics IR.MAZUMS.IMAMHOSPITAL.REC.1398.168 on gastric cancer patients and control group. The control group was also selected from Tabari cohort population. The number of samples was determined by considering the 95% confidence level and 90% power, and the mean and standard deviation (2±0.9 in gastrointestinal cancers and 1.6±0.5 in benign lesions) for NLR based on the study of Wu et al. in 2018 (19) and using STATA software and with a 2:1 ratio; 62 people were determined in the group of stomach cancer patients and 124 people in the control group. Convenience sampling was used in the case group and random sampling was used in the control group from among the Tabari Cohort Population. Tabari cohort profile has been published before (20). People in the case group, with a pathology report based on stomach cancer and having a CBC diff test, and in the control group, without a chronic disease such as diabetes, high blood pressure, thyroid disorders, cancer, cardiovascular diseases, smoking, and body mass index below 30 were included in the study. People in the case group with a metastatic cancer were excluded from the study. In the selection of the control group, by removing the influential variables and defining the inclusion criteria, we tried to select almost healthy samples. The two groups of case and control were matched based on age and gender, and according to the two-to-one ratio of case and control groups, for each case, two control subjects who were the same in terms of gender and were in the same decade of age were selected. Required information including age, gender, blood parameters, neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, and lymphocyte to monocyte ratio were recorded for all individuals. In addition, tumor-related indices such as tumor location, histology, stage, lymphovascular invasion, perineural invasion and history of

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receiving neoadjuvant chemotherapy were recorded in the cancer group. Tumor characteristics were extracted from the pathology report. To calculate the ratios, the percentage of neutrophils and lymphocytes and the number of platelets per 100,000 were taken from the CBC test sheet of the patients as the basis of calculations. The obtained data were analyzed by SPSS 20 statistical software and Fisher's exact test, T-test and Mann-Whitney statistical tests. One-Sample Kolmogorov Smirnov test was used to check the normality of data distribution. In order to eliminate the effect of neoadjuvant chemotherapy, sensitivity analysis was performed without considering people with a history of neoadjuvant to compare the parameters between case and control groups, and $p<0.05$ was considered significant.

Results

This study was conducted on 62 patients with gastric cancer and 124 non-affected people as a control group. In the cancer group, 43 people (69.4%) were men and 38 people (30.6%) were women, and in the control group, 86 people (69.4%) were men and 38 people (30.6%) were women (p=0.57). The mean age of the examined subjects in the group of cancer patients and the control group was 62.3±12.53 and 51.7±9.02 years, respectively (p=0.105). The level of NLR and PLR in gastric cancer patients was significantly higher than the control group, but LMR in gastric cancer patients was significantly lower than the control group (Table 1).

In terms of histological status, 28.6% of the investigated cancers were well to moderate and 71.4% were poor. There was no significant difference between the mean NLR and PLR and the mean LMR in the two groups (Table 2). In terms of disease stage, 72.7% were in stage 1 or 2 and 27.3% were in stage 3. The mean NLR and PLR and the mean LMR were not significantly different in the two groups of grades 1 or 2 and grade 3 (Table 2). Lymphovascular invasion was present in 53.3% of the examined patients. The mean NLR and PLR and the mean LMR were not significantly different in terms of the presence and absence of lymphovascular invasion (Table 2). Perineural invasion was observed in 46.7% of investigated cases. The mean NLR and PLR and the mean LMR were not significantly different according to the presence and absence of perineural invasion involvement (Table 2).

In 43.5% of cases, the site of involvement was in the cardia area and in 56.5% in other areas of the stomach. The mean NLR and PLR and the mean LMR were not significantly different in the cases where the tumor was located in the cardia area compared to the cases where the tumor was located in other areas (Table 2). There was a history of receiving neoadjuvant chemotherapy in 16.4% of cases. The mean NLR and PLR in people who had a history of receiving neoadjuvant was significantly lower than the others, but the mean LMR was not significantly different in people with and without a history of receiving neoadjuvant (Table 2).

Table 1. Examining the difference between NLR, PLR and LMR in the two gastric cancer and control groups

Group	NLR			PLR			LMR	
	Median	Interquartile range	p-value	Median	Interquartile range	p-value	Mean±SD	p-value
Control (124 patients)	1.62	1.15-1.96	0.000	6.27	5.23-7.83	0.000	10.9±2.99	0.000
Case (62 patients)	2.14	1.55-3.56		9.48	6.61-13.19		3.42±2.12	

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In addition, the results of the sensitivity analysis showed that the median and interquartile range of NLR (1.63-3.74: 2.34 vs. 1.15-1.96: 1.62, p=0.000) and PLR (7.55-15.44: 9.8 vs. 5.23-7.83: 6.27, p=0.000) in the group with gastric cancer without a history of chemotherapy was also significantly more than the healthy control group. The mean and standard deviation of LMR (3.21±1.96 vs. 10.9±2.99, p=0.000) in the gastric cancer group without history of chemotherapy was also significantly lower than the healthy control group.

Table 2. The level of NLR, PLR and LMR in the gastric cancer group according to tumor characteristics

Tumor characteristics	NLR		PLR		LMR	
	Median (interquartile range)	p-value	Median (interquartile range)	p-value	Mean±SD	p-value
Histological status						
Well to moderate	2.33 (1.24-3.35)	0.959	10.27 (8.51-14.68)	0.5	3.59±2.03	0.946
Poor	1.95 (1.5-3.65)		9.36 (6.85-12.94)		3.66±2.59	
Stage of the disease						
1 or 2	1.41 (1-2.24)	0.683	6.13 (4.53-7.88)	0.066	4.48±2.52	0.915
3	2.03 (1.05-2.24)		9.23 (9.22-9.45)		4.68±3.07	
Lymphovascular invasion						
Yes	2.14 (1.13-3.28)	0.725	9.22 (7.05-10.72)	0.247	4.13±3.07	0.538
No	1.46 (1.16-3.75)		6.44 (4.5-11.44)		3.26±2.26	
Perineural invasion						
Yes	1.36 (0.95-2.24)	0.105	6.64 (4.5-9.44)	0.355	4.3±3.06	0.398
No	2.23 (1.51-3.71)		8.74 (6.52-11.37)		3.11±2.2	
Cardia involvement						
Yes	2.07 (1.63-3.37)	0.973	9.20 (5.17-10.81)	0.445	3.23±1.35	0.266
No	2.08 (1.34-3.6)		9.22 (7.06-13.6)		3.89±2.55	
Neoadjuvant history						
Yes	1.41 (1.02-2.13)	0.009	6.59 (4.59-9.22)	0.008	4.5±2.65	0.087
No	2.24 (1.63-3.75)		9.7 (7.47-15.52)		3.24±1.97	

Discussion

In the present study, the level of NLR in gastric cancer patients was significantly higher than the healthy control group. Similar to the present study, in a study by Han et al., the results showed higher preoperative NLR values in patients with primary esophageal cancer, compared to the healthy control group (21). Furthermore, in a study by Wu et al., the serum level of NLR was higher than the control group (19). In our study, the mean level of NLR in the cases that received chemotherapy was significantly lower than the cases that did not receive chemotherapy, which is not consistent with the results of the study by Aldemir et al. (in which patients receiving chemotherapy did not show a significant difference in the level of NLR compared with the group that did not receive chemotherapy) (22). Successful chemotherapy can reduce the production of inflammatory factors by suppressing part of the tumor tissue and thus reducing its activity. Therefore, the difference between our study and the study of Aldemir et al. could be the result of receiving an inappropriate

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dose of chemotherapy in patients or an inappropriate treatment protocol. The decrease in NLR level after chemotherapy can confirm the relationship between increased neutrophils and tumor activity (23). In our study, the NLR level was not significantly related to the stage, but in the study of Wu et al., a significant relationship between high NLR levels and tumor stage was observed, which was inconsistent with our study (19). It seems that the increase in NLR is more related to the tumor activity than the amount of its expansion and the difference in the results of the two studies can be related to the heterogeneity of the type of treatments received by the patients of the two studies to suppress the tumor activity. Therefore, in the study of Wu et al., the increase in NLR with the stage of the disease can be due to the failure of chemotherapy treatment in controlling the tumor and as a result of the increase in the production of inflammatory factors, which has caused the activation of the myelocyte line in the bone marrow.

In the study of Aldemir et al., there was no correlation between NLR and the prognosis of low-stage gastric cancer patients, but significant effects of this factor on prognosis were seen in patients with advanced gastric cancer (22). In this study, high NLR was introduced as an inappropriate prognosis factor in advanced stages of gastric cancer. High NLR can itself be caused by high tumor activity and increase in more aggressive tumors, and conversely, by increasing the production of neutrophils and attacking the tumor tissue, it causes an increase in systemic inflammatory reactions, and worsens the patient's prognosis. In our study, there was no significant difference between the mean NLR in the well to moderate and poor groups, but in the study of Wu et al., the serum level of NLR in malignant lesions was significantly higher than in benign lesions or the control group, which was not consistent with our study (19). According to our initial assumptions, we expected to have a higher level of NLR in more malignant (poorly differentiated) tumors due to more activity and higher systemic inflammation in malignant tumors compared to benign tumors. The reason for the difference in our results with the study of Wu et al. and the initial assumptions of the research can be related to the time from the onset of the disease until its detection, the difference in the type of treatment received, and also the difference in the co-morbidities of the two groups, which caused false negative results. Our study did not show a significant difference in the median level of NLR in the presence or absence of lymphovascular invasion, which was consistent with the study of Wu et al. (19). Before the tumor enters the vascular system, the inflammatory factors released from the tumor into the bloodstream exert their effects, and probably the entry of the tumor into the lymphovascular system does not exert a double stimulatory effect on the bone marrow. In the study of Ghahremanfard et al., NLR was performed in three groups of patients with gastric cancer, colorectal cancer, and the control group, the ratio of neutrophils to lymphocytes in patients with gastric and colorectal cancer was significantly higher than the normal population. The ratio of neutrophils to lymphocytes had no effect on the mortality rate, nor did it show a difference in metastatic and non-metastatic malignant patients (24).

In this study, the level of PLR in gastric cancer patients was significantly higher than the control group. Wu et al. also found that people with gastric cancer have higher levels of PLR than healthy people (19), which was consistent with our study, and could indicate increased platelet production in patients with gastric cancer. The increase in platelet production can depend on the stimulating effect of inflammatory factors released from the tumor on the megakaryocyte line in the bone marrow. In the study of Fang et al., it was found that the systemic inflammatory markers NLR and PLR are even more valuable for the diagnosis of gastric cancer than the traditional tumor markers CEA and CA19-9 (25). The mean level of PLR in the cases that received chemotherapy in our study was significantly lower than that in the cases that did not receive chemotherapy, which was inconsistent with the results of the study by Aldemir et al. As mentioned in regard with the relationship between NLR and chemotherapy, the difference between the results of our study and the study of Aldemir et al. could be due to receiving an inappropriate dose of chemotherapy or an inappropriate treatment protocol in the patients of this study (22). In our study, the mean level of PLR in the

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two groups of stage 1 and 2 was not significantly different from stage 3, but in the study of Wu et al., the increase in PLR was significantly related to the increase in stage, which was inconsistent with our study (19). The difference in the results of the two studies can be related to the heterogeneity of the type of treatments received in the patients of the two studies to suppress tumor activity. In our study, there was no significant difference between the mean PLR in "well to moderate" and "poor" groups. However, in the study of Wu et al., the serum levels of NLR and PLR in malignant lesions were significantly higher than benign lesions or the control group (19). We expected to have a higher level of PLR in poorly differentiated tumors than in benign tumors due to higher systemic inflammation. The mean level of PLR was not significantly different according to the presence or absence of lymphovascular invasion, which was consistent with the study of Wu et al. (19). It seems that lymphovascular invasion cannot cause a higher level of immune stimulation than the situation before lymphovascular invasion. The reason for this could be that the inflammatory factors released from the tumor have already exerted their effects by reaching the vascular system.

The results of our study showed that LMR in patients with gastric cancer is lower than healthy control group, which was consistent with the study of Lin et al. (26). These results can indicate the strong role of this index in helping to screen gastric cancer. Monocytes are considered as pro-tumor cells because they facilitate the development and dissemination of tumor cells. Monocytes can be recruited to the tumor microenvironment using tumor-derived CCL5 and enhance tumor cell growth and survival. On the other hand, tumor cells induce the differentiation of monocytes into tumor-associated macrophages, which in turn weakens the antitumor immune response and stimulates the migration and metastatic spread of tumor cells (27). In this study, the mean level of LMR in cases that received chemotherapy was not significantly different compared to cases that did not receive chemotherapy. Similar results were obtained by Zhou et al., and their study showed that a lower LMR, regardless of receiving or not receiving chemotherapy, decreases the prognosis in patients (28). It is possible that the effects exerted by the tumor on the cells that produce lymphocytes and monocytes have more lasting effects and a longer period of time is needed after chemotherapy to observe LMR changes. In our study, the mean level of LMR in the two groups of stage 1 and 2 was not significantly different from stage 3, but the study of Lin et al. and Deng et al. showed that LMR decreases as the stage of the disease increases (26, 29). The difference in the results of the mentioned studies requires the need for more studies in this field. There was no significant difference between the mean level of LMR in the two groups of well to moderate and poor differentiation. In the study of Deng et al., there was no significant correlation between tumor grade and LMR, which was consistent with our study (29). It is possible that the difference in the histological characteristics of the tumor does not have much effect on the agranulocyte precursors. In our study, the mean level of LMR was not significantly different according to the presence or absence of lymphovascular invasion. But in the study of Lin et al. and Deng et al., lower LMR was associated with more lymph node metastasis (26, 29), which was inconsistent with our study. Since the cells responsible for immunity in the lymphatic tissues are mainly lymphocytes, we expected that, as in the study of Lin et al., lymphatic involvement would cause the entry of lymphocytes from the blood into the lymphatic tissues and, as a result, a lower LMR ratio in the patients' blood. Due to the difference in results, understanding this factor needs further investigations.

One of the limitations of the present study was the presence of patients who received neoadjuvant treatment. Although sensitivity analysis was used to compare the parameters in two groups and this effect was removed, but this issue affects the stage.

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Our study showed that the indices of NLR, PLR in gastric cancer patients are higher compared to healthy subjects and LMR is lower compared to healthy subjects. Therefore, the results of high NLR and PLR and low LMR can be used in gastric cancer screening studies.

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