

## **Abstract**

**Introduction:** Gastrointestinal cancers are among the most prevalent cancers in various societies. In the last years, different factors such as Neutrophil-to-Lymphocyte Ratio (NLR) and Platelet-to-Lymphocyte Ratio (PLR) have been used to examine the prognosis of patients. In this study, we aimed to research the NLR and PLR levels as prognostic factors in patients with gastrointestinal cancer.

**Materials and methods:** This study was an analytical study type, which was done in a Cross-Sectional way. Number of 210 patients with advanced gastrointestinal cancer (rectal, gastric, pancreatic and colon cancer) were studied. Information such as age, gender, smoking history, grade, disease stage, etc. were obtained from file of patients. NLR and PLR were calculated. Patients were divided into two groups, Progressive and Non-Progressive, based on RECIST<sup>1</sup> criteria, and then the relationship between PLR and NLR levels and disease prognosis were assessed. Data were entered into SPSS version 20 software after collecting and analyzed using statistical tests.

**Results:** The results of the study showed that there is a statistically significant difference among the average of neutrophil count, lymphocyte count, platelet count, NLR, and PLR variables between the two investigated groups in patients with colon, gastric, pancreas, and rectal cancer. The results of the study by using the ROC curve showed that, the area under the ROC curve (AUC) was above 0.9 for both the NLR and PLR indicators in all four investigated cancers, which indicates the high validity of the NLR and PLR indicators when the progressive status of the tumor was prognosticated in patients with advanced gastrointestinal cancer.

**Conclusion:** According to the findings of this research, we can conclude that NLR and PLR indicators can be used as a prognostic factor in patients with advanced gastrointestinal cancer.

**Keywords:** neutrophil, lymphocyte, platelet, prognosis, gastrointestinal cancers

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<sup>1</sup> A standard way to measure how well a cancer patient responds to treatment.

## **Introduction:**

Cancers are as one of the main causes of death in the world. The incidence <sup>2</sup> of cancers is increasing compared to cardiovascular diseases in developed countries (1, 2). Cancer is the third cause of death in Iran, and about 100,000 people get this disease in the country every year (3). In the meantime, gastrointestinal cancers are increasing and are one of the important causes of mortality among patients. Also, gastrointestinal cancer is one of the important causes of morbidity and mortality among patients in our country and has a relatively high prevalence (4,5). This cancer was not prevalent in other European countries, however, the incidence of this cancer is increasing in Asian and developing countries. Unlike advanced countries, the incidence rate of gastrointestinal cancer is increasing in Iran (6, 7).

Gastrointestinal cancers are one of the important causes of mortality among patients in the world. Gastric cancer is the second cause of death caused by cancerous tumors in the world, and esophageal cancer ranks fifth in this regard.

Although the abundance of colorectal cancers is lower than the esophagus and gastric in Iran, it is still one of the prevalent cancers and one of the important causes of death caused by cancer (4). The incidence risk of this cancer is largely dependent on many factors such as old age, male gender, inappropriate nutritional habits such as consuming a lot of salty foods, pickles, smoked foods, and not consuming vegetables and fruits, sedentary lifestyle, smoking and alcohol consumption, positive family history, as well as dietary factors and *Helicobacter pylori* infection. On the other hand, change in lifestyle and urbanization are factors whose their relationship with gastrointestinal cancers has been proven during studies (4). On the other hand, the presence of inflammation has been proven in the development and progression of many cancers. Parameters such as selectin, fibrin, troponin, tissue factors and blood parameters such as white blood cell, platelets, neutrophil, lymphocyte and neutrophil to lymphocyte ratio (NLR) and gamma glutamyl transferase are among the most important parameters that have been considered their prognostic importance in many malignities(2).

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<sup>2</sup> Outbreak

Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) have been recently investigated as a new marker for inflammation (2). Recently, some studies showed that the PLR, NLR ratio are as potential markers in many malignities, including gastrointestinal cancer. So that the survival of patients with cancer decreases when NLR and PLR levels increases. (8-13). Also, the combination of NLR and PLR alone has the ability to prognosticate the prognosis of patients more than any of these parameters.

Since, the early diagnosis of gastrointestinal cancers has led to an increasing the life expectancy of patients and significant reduction in their costs (4), so far, limited studies have investigated the neutrophil to lymphocyte ratio and neutrophil to platelet ratio as a prognostic factor in patients with gastrointestinal cancer and the role of these biomarkers as a prognostic factor is not clear in patients with gastrointestinal cancer. The purpose of this study is to investigate the neutrophil to lymphocyte ratio and neutrophil to platelet ratio as a prognostic factor in patients with gastrointestinal cancer.

## **Materials and methods:**

This study was a cross-sectional analytical type and was performed on all patients with advanced gastrointestinal cancer (locally advanced cancer or metastatic conditions, according to the definition) in a period of one year (from April 2019 to 29 March, 2019).

Inclusion criteria include people with advanced gastrointestinal cancer (rectal, gastric <sup>3</sup>, pancreas, and colon cancer) and the exclusion criteria include people who did not want to take part in the study and people whose file information was incomplete. The sampling method of our study is convenience or accessible sampling among all eligible <sup>4</sup> patients.

Information such as age, gender, smoking history, grade, disease stage, etc. were obtained from the patients' file. Also, preliminary findings such as CT scan results, pancreatic EUS, and primary pathology after surgery were obtained from the patients' file. The NLR and PLR levels were calculated after taking the CBC test of the patients during the initial diagnosis of the disease, and then the correlation

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<sup>3</sup> Stomach

<sup>4</sup> Qualified, Favorable

between levels of the two mentioned indicators and the prognosis of the disease was evaluated. CT scan and EUS were used for disease follow-up. Then, the patients were divided into two groups, Progressive and Non-Progressive, based on the RECIST<sup>5</sup> criterion, according to the para-clinical findings (14).

## **Results:**

In this study, 210 patients with advanced gastrointestinal cancer were investigated. Among these investigated patients, 66 people had colon cancer, 73 people had gastric cancer, 20 people had pancreatic cancer, and 51 people had rectal cancer.

Analysis of the study results on the comparison of variables frequency distribution: gender and smoking (using the Fisher Exact test) and the variables average of age, BMI, neutrophil count, lymphocyte count, platelet count, NLR and PLR indicators (using the Wilcoxon test) in the two investigated groups (progressive, non-progressive) in patients with advanced colon cancer showed that there is a statistically significant difference among the variables average of neutrophil count, lymphocyte count, platelet count, NLR and PLR indicators between the two investigated groups; so that the average of neutrophil count, platelet count, NLR and PLR indicators were significantly higher in the progressive group than in the non-progressive group in patients with advanced colon cancer (Table 1).

The analysis of the study results on the comparison of the frequency distribution and the average of the studied variables in the two investigated groups in patients with advanced gastric cancer showed that there is a statistically significant difference among the variables average of neutrophil count, lymphocyte count, platelet count, NLR and PLR and the frequency distribution of smoking and gender between the two investigated groups; so that the average of neutrophil count, platelet count, NLR and PLR indicators were significantly higher in the progressive group than in the non-progressive group in patients with advanced gastric cancer. Other information has been given in Table 2.

The results of the study on the comparison of the frequency distribution and average of the studied variables in the two investigated groups in patients with advanced pancreatic cancer have been shown in Table 3. The analysis of the table

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<sup>5</sup> Response Evaluation Criteria in Solid Tumors

using relevant statistical tests showed that there is a statistically significant difference among the variables average of neutrophil count, lymphocyte count, NLR and PLR between the two investigated groups.

The analysis of the study results on the comparison of the frequency distribution and the average of the studied variables in the two investigated groups in patients with advanced rectal cancer showed that there is a statistically significant difference among the variables average of age, neutrophil count, lymphocyte count, platelet count, NLR and PLR between the two investigated groups; so that the average of neutrophil count, platelet count, NLR and PLR indicators were significantly higher in the progressive group than in the non-progressive group in patients with advanced rectal cancer (Table 4).

The study results on the validity of NLR and PLR indicators in prognosis of the progressive status of the tumor in patients with advanced gastrointestinal cancer using the ROC curve showed that the AUC <sup>6</sup> was greater than 0.9 for both NLR and PLR indicators in all four investigated cancers, which shows the high validity of NLR and PLR indicators in prognosis of the progressive status of the tumor in patients with advanced gastrointestinal cancer (Table 5 and Diagrams 1-4).

## **Discussion:**

Neutrophils to lymphocytes ratio has recently been investigated as a new marker for inflammation (2). Some studies have shown that the PLR, NLR ratio are as potential markers in many malignities including gastrointestinal cancer. So that, the survival of patients with cancer decreases when NLR and PLR levels increases (8-13). The results of the present study showed that the average of neutrophil count, platelet count, NLR and PLR indicators were significantly higher in the progressive group than in the non-progressive group in patients with all four advanced gastrointestinal cancers (colon, rectum, gastric and pancreas). The results of YU's study showed that the NLR level before surgery can be a prognostic factor for patients with gastric cancer. The results also showed that high NLR level is related to poor prognosis in these patients (15); that the results of the above study on gastric cancer were consistent with the results of the Mori's study, in which the increase of NLR level during chemotherapy may be a useful prognostic indicator

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<sup>6</sup> Area Under the ROC Curve

in patients with stage II or III of gastric cancer (16). In another study that was done in 2019 on patients with gastric cancer, the NLR level was higher in patients who had metastases in comparison with patients who did not have metastases, and besides the NLR level was inversely related to the survival period (17). This issue was also proven for pancreatic cancer in the study of Gemenetzis. The results of this study showed that the NLR, PLR levels increase in patients with pancreatic cancer(18).

In the present study regarding the cutoff value, the 3.98, 4.56, 3.92 and 2.16 values were proposed as the cutoff of the NLR indicator and the 176, 199, 280 and 96 values as the cutoff of the PLR indicator for colon, gastric, pancreas and rectal cancers, respectively. In Goh's study, the cutoff values for NLR 3 and PLR 275 were determined to prognosticate gastrointestinal cancers (19). In another study which was done in 2015, NLR above 5 was associated <sup>7</sup> with poor prognosis and reduced survival in patients with gallbladder and pancreatic cancer (20); It was consistent with the results of the present study, which a cutoff 3.92 had been considered for NLR in patients with pancreatic cancer. In YU's study, 3.5 was considered as the NLR cutoff in patients with gastric cancer (15); which is similar to the results of the present study. Also, a cutoff 2.83 was considered for NLR in patients with advanced gastrointestinal cancer in Murakan's study (17); Overall, the cutoff values seem to be slightly different depending on the type of investigated gastrointestinal cancer in the investigated population, but in general, the values are close to each other in the aforementioned studies.

The results of the present study showed that the specificity of the NLR indicator is higher than its sensitivity during prognosis of the disease progress in patients with advanced gastrointestinal cancers except the rectum, This shows that the value of NLR indicator is higher in non-progressive group patients than in progressive group patients when it is diagnosed. But in patients with rectum cancer, the value of the mentioned indicator is higher in diagnosing real patients with progressive cancer due to the 100% sensitivity of the NLR indicator. Considering that the NPV of the NLR indicator is also higher than its PPV in patients with rectum cancer; It can be said that the diagnostic value of NLR as a prognostic factor is higher in patients with rectum cancer. In Nora's study, NLR was generally reported with

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<sup>7</sup> Dependent

high sensitivity and negative predictive value in advanced gastrointestinal cancers (21).

**Conclusion:**

According to the results of the study, it can be concluded that the NLR and PLR indicators levels have increased in advanced gastrointestinal cancer and they can be used as a prognostic factor in patients with advanced gastrointestinal cancer (rectal, gastric, pancreas and colon cancer).