

# Preoperative Neutrophil-Lymphocyte Ratio, Platelet-Lymphocyte Ratio and Lymphocyte-Monocyte Ratio in Peripheral Blood of Patients with Gastrointestinal Malignant Lesions

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**ABSTRACT:** Local inflammation plays a very important role in the apparition and development of tumors and metastasis. The objective of this study was to investigate the significance of neutrophil to lymphocyte ratio (NLR), lymphocyte to monocyte ratio (LMR) and platelet to lymphocyte ratio (PLR) in peripheral blood of patients with gastrointestinal malignant tumors. Methods: Medical records of 145 patients diagnosed with gastrointestinal malignant tumor between January 2017 and December 2017 were analyzed retrospectively. Pretreatment neutrophil, lymphocyte, platelet and monocyte counts and NLR, LMR and PLR were investigated. Results: The mean for NLR, PLR and LMR in patients with gastrointestinal cancer were determined. Conclusions: Determination of NLR, PLR and LMR can be easily done with a simple blood test and may be useful inflammatory markers as in our study we have observed the presence of increased inflammatory response in patients with gastrointestinal cancer.

**KEYWORDS:** Lymphocyte to monocyte ratio (LMR), neutrophil to lymphocyte ratio (NLR), and platelet to lymphocyte ratio (PLR), cancer, malign lesions, gastrointestinal

## Introduction

Colorectal cancer has remained the third most common cancer in the world in the last 17 years, ranging from 9.4% of total cases in 2002 [1] to 9.7% in 2008 and 2012 [2-4], reaching 10.20% in 2018 [5].

The gastric cancer occupied the fourth place in 2002 (8.6% of total cases) and 2008 (7.8%) [1,2] reaching the fifth place by 2012 (6.8%) and 2018 (5.7%) [4,5].

Gastric cancer was the second leading cause of death from 2002 to 2008 (9.7%) and the third in 2012 (8.5%) and 2018 (8.1%) [4,5].

Local inflammation plays a very important role in the development and progression of local tumors and metastasis.

Inflammation promotes carcinogenesis, primary tumor growth, stimulating the proliferation of tumor cells, inhibiting cellular apoptosis and increasing mitotic rates [6].

Inflammation is a very complex biological response to cellular damage, where the immune system tries to start the regenerative processes and neutralize or eliminate the infection.

It is a normal response process to an infection or an injury and whether the tumor promoting inflammation precedes or follows the tumor's

onset, it can help the cancer cells in their progression [7].

Chronic inflammation and infections are known to cause angiogenesis and therefore they contribute to cancer initiation and progression.

Also, chronic infections are considered etiological factors for: Hepatitis B, Hepatitis C, hepatomas, oral and cervical cancers, Helicobacter pylori and gastric cancer [8].

One such example of a connection between inflammation and gastrointestinal cancer is the increased risk of developing colorectal cancer in patients with inflammatory bowel disease [9].

Neutrophil to lymphocyte ratio (NLR) is a marker for systemic inflammation that can be obtained with a simple complete blood count (CBC) and it is effective in predicting the prognosis of many cancer treatments.

Mean NLR values in healthy adult people that had no cancer or other known medical history was shown in several studies to be 1.65 with  $\pm 1.96$  standard deviation (SD): 0.78-3.53 [95% confidence intervals (CI) 0.75-0.81]; [10] with 1.63 (0.76) NLR mean for men and 1.66 (0.82) NLR mean for women [11].

A high NLR can guide us towards suspecting an advanced or aggressive tumor with the presence of systemic inflammation that can help the tumor to develop and spread.

An elevated NLR may be a consequence of low lymphocyte count who are known to have tumor suppressing effects and/or a high neutrophil count which can promote tumor metastases by causing angiogenesis [6].

It has also been shown in several studies that NLR can be a good indicator of the prognosis for colorectal cancer [12-14].

Lymphocytes are usually involved in chronic infections while neutrophils are the most numerous cells found at the onset of acute inflammation.

Neutrophils and lymphocytes have opposite effects in malign tumor development, with neutrophils releasing tumor growth factors and causing angiogenesis, while T-lymphocytes can inhibit the spread of tumor cells.

Thus, neutrophilia and/or lymphopenia, causing a high NLR, are commonly observed in malign tumors [15].

Regarding the lymphocyte to monocyte ratio (LMR), high monocyte count associated or not with low lymphocyte count causing a low LMR, is known to be a poor prognostic indicator in cancer.

The association between high monocytes and poor cancer prognostic is still unclear.

Monocyte can create proinflammatory cytokines and thus promote angiogenesis and metastasis in patients with malign tumors [16].

The study aimed to correlate the value of neutrophil to lymphocyte ratio, platelet to lymphocyte ratio and lymphocyte to monocyte ratio in peripheral blood with the occurrence of gastrointestinal malignant tumors.

## Material and methods

Information was collected from patients with gastrointestinal lesions admitted to the Surgery Clinic I of the Craiova County University Hospital between January 2017 and December

2017 that had a CBC and histopathological examination, after obtaining clearance from the Ethics Committee of the University of Medicine and Pharmacy of Craiova, Romania.

A positive diagnosis of benign or malign lesion has been established based on incisional and/or excisional biopsy followed by histopathological examination.

A total number of 150 cases resulted in the research.

The exclusion criteria were: patients without histopathological confirmation of malignant tumor or without recorded neutrophil, lymphocyte, platelets and monocyte counts and those having acute or chronic systemic inflammatory condition (5 cases) resulting in a total of 145 patients meeting the inclusion criteria.

The data collected included: gender, age, histopathological data, histopathological confirmed malign tumor, monocytes, neutrophils, platelets, lymphocytes.

The neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR) and lymphocyte to monocyte ratio (LMR) were calculated and a statistical analysis was performed using MedCalc 18.11.3 and Microsoft Excel 2016 v1809.

Statistical analysis was assessed from the perspective of: NLR, PLR, LMR, gender, age, tumor location and histopathological differentiation using independent samples t test.

## Results

From 145 patients available with preoperative CBC record and histopathological malign confirmation, in gender distribution we found 53 women (36.55%) and 92 men (63.45%), with an average age of 66.6 years (Table 1).

**Table 1. Mean age by gender in the study group**

	Women	Men
Sample size	53	92
Mean age	68.09±2.86	65.77±2.04
Standard deviation	10.38	9.89
95% CI for the mean	65.23-70.95	63.72-67.82

Mean NLR for the study group was 4.61 (3.93-5.28) with a SD 4.11, while PLR was

185.96 (168.54-203.38; SD: 106.13) and LMR was 3.08 (2.81-3.36; SD: 1.64); (Table 2).

**Table 2. NLR, PLR and LMR in all patients**

	NLR	PLR	LMR
Sample size	145	145	145
Arithmetic mean	4.6119	185.9665	3.0866
95% CI for the mean	3.9361 to 5.2877	168.5448 to 203.3882	2.8112 to 3.3619
Variance	16.9508	11264.7391	2.6953
Standard deviation	4.1171	106.1355	1.6417
Standard error of the mean	0.3419	8.8141	0.1393

From 145 patients with malignant lesions, the mean NLR, PLR and LMR for women were 5.02 (3.97-6.06; SD: 3.79), 214.46 (180.02-248.91; SD: 124.96) and 3.25 (2.76-3.73; SD: 1.74); (Table 3), while for men the mean was 4.37 (3.48-5.26; SD: 4.29), 169.54

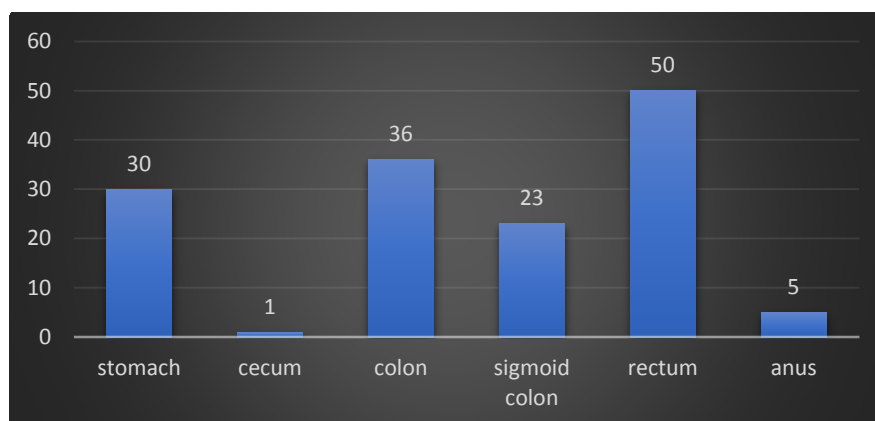
(150.84-188.25; SD: 90.3) and 2.97 (2.65-3.29; SD: 1.56); (Table 4), showing an increased inflammatory response in NLR (P=0.329) and PLR (P=0.007) for women and a higher response in LMR (P=0.359) for men.

**Table 3. NLR, PLR and LMR in the women's group**

Women	NLR	PLR	LMR
Sample size	53	53	48
Arithmetic mean	5.0244	214.4667	3.2503
95% CI for the mean	3.9793 to 6.0695	180.0232 to 248.9103	2.7699 to 3.7307
Variance	14.3759	15615.2664	3.0376
Standard deviation	3.7916	124.9611	1.7429
Standard error of the mean	0.5208	17.1647	0.2394

**Table 4. NLR, PLR and LMR in the men's group**

Men	NLR	PLR	LMR
Sample size	92	92	92
Arithmetic mean	4.3743	169.5479	2.9744
95% CI for the mean	3.4847 to 5.2639	150.8441 to 188.2518	2.6509 to 3.2979
Variance	18.4523	8156.9042	2.4404
Standard deviation	4.2956	90.3156	1.5622
Standard error of the mean	0.4478	9.4161	0.1629



**Fig.1. The distribution of malignant lesions in the study group**

The following malignant lesions were found in our study: 30 patients had stomach cancer, 1 patient with cecum cancer, 36 patients with colon cancer, 23 patients with sigmoid

colon cancer, 50 patients with rectum cancer and 5 patients with anus malignant lesion (Fig.1, Table 5).

**Table 5. NLR, PLR and LMR values in accordance with lesions distribution in the study group**

	Cases	Mean NLR	Mean PLR	Mean LMR
stomach	30	4.11	192.81	3.12
cecum	1	4.99	185.31	3.79
colon	36	3.99	151.27	3.27
sigmoid colon	23	6.09	189.53	2.71
rectum	50	4.48	191.77	3.09
anus	5	6.41	320.32	2.61

In our study group, 80 patients had a precise differentiation grade according to the histopathological results: 4 patients with G1, 19 patients with G1-G2, 42 patients with G2, 5 patients with G2-G3 and 10 patients with G3.

In our study we have found no relevant association between the histopathological differentiation grade and the mean value for NLR, PLR and LMR (Table 6).

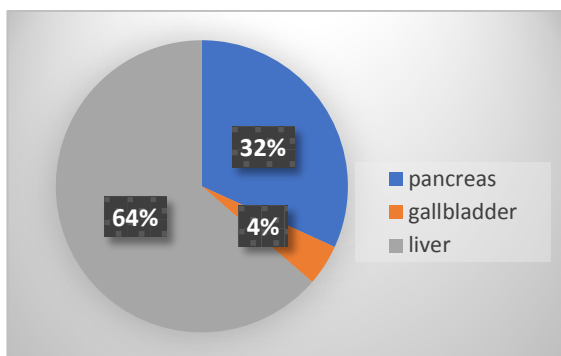
**Table 6. Histopathological differentiation grade in the study group**

Differentiation grade	Mucinous	Non-mucinous	Total	NLR	PLR	LMR
IHC	10	5	15			
G1-well	0	4	4	2.71	141.32	3.69
G1-G2	3	16	19	4.23	177.76	3.27
G2-moderate	2	40	42	4.27	173.64	3.09
G2-G3	0	5	5	2.89	138.89	3.98
G3-poor	1	9	10	3.91	175.35	2.82
in situ	0	2	2	3.87	221.60	2.41

From 145 cases, only 16 patients (11%) were histopathological confirmed to have mucinous adenocarcinoma (Table 7), while the majority (89%) had non-mucinous adenocarcinoma.

**Table 7. Mucinous vs non-mucinous**

Mucinous adenocarcinoma	16	11%
Non-mucinous adenocarcinoma	129	89%



**Fig.2. Local advanced invasion in the accessory organs**

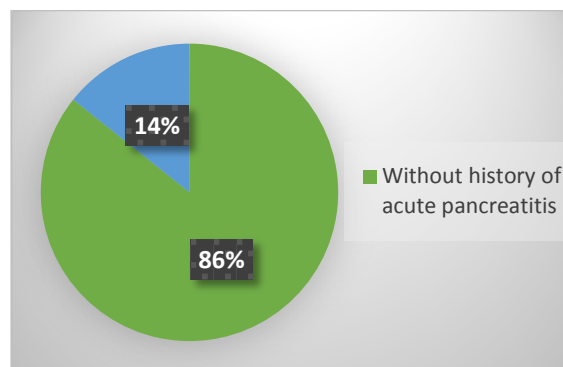
Invasion in the accessory organs was found only in 22 patients (15.17%): 7 cases (32%) were found to have cancer extended to the pancreas, 1 case (4%) of gallbladder invasion and 14 cases (64%) with liver invasion (Fig.2).

Local invasion was present in 22 patients, while 123 patients had no local invasion. There

was no significant statistical difference based on the mean value of NLR and PLR between the two lots. The mean LMR was slightly lower in patients with local invasion compared with patients with no local invasion (Table 8).

**Table 8. Mean NLR, PLR and LMR for patients with and without local invasion**

	NLR	PLR	LMR
With local invasion	4.61	164.53	2.58
Without local invasion	4.58	180.75	3.16



**Fig.3. History of acute pancreatitis**

From the 7 patients with pancreatic cancer invasion, only 1 case (14.28%) was known to have had a history of acute pancreatitis (Fig.3).

## Discussion

Recent data have shown that inflammation is a critical component in cancer. Many cancers appear in sites of chronic irritation, inflammation and infection, reason why inflammatory cells are considered to be crucial in the neoplastic process. In response to tissue damage, neutrophils and monocytes, along with platelets, are directed to the site of the lesion, thus explaining their increased number in inflammations [17].

This is also found in this present study as mean NLR, PLR and LMR suggested higher inflammatory response.

In chronic inflammation repeated damage and regeneration of tissue occurs and it can lead to p53 mutations which is known to take part in the pathogenesis of many cancers [18].

Approximately 20% of all cancers are linked to infectious agents [19]. Several studies show the contribution of hepatitis B virus (HBV) and/or hepatitis C virus (HCV) in liver cancer [20,21]. The presence of Human papillomavirus (HPV) infection is known to be a major cause of many cancers. Recent studies show that cells modified by HPV promote chronic inflammation and carcinogenesis [22]. Epstein-Barr virus is known for its oncogenic potential and its association with several human cancers, including gastric carcinoma [23].

Also, one study highlights the risk of developing acute pancreatitis in patients undergoing FOLFOX6 chemotherapy following colorectal cancer [24].

Even though there is a small difference in the age-related variance between the two groups the data analyzed is relevant.

In recent years there is a growing interest in finding the correlation between inflammation and cancer as it has been shown in several studies a direct connection between inflammation markers such as NLR, PLR, LMR and cancer. In our study, we found 16 cases (11%) were histopathological confirmed to be mucinous adenocarcinoma while other studies report a 10%. In this study on gastrointestinal cancers, 11% of cases (n=16) were histopathological confirmed as mucinous adenocarcinoma, which is similarly to what is reported in other studies [25].

Mean NLR in healthy adult people was shown in several studies to be 1.65 [ $\pm$ 1.96 SD: 0.78-3.53]; [10,11] while other reported normal NLR to be between 1.76 and 2.24 [26]. In our analysis on 145 patients, 53 women and 92 men, with gastrointestinal malign tumors we found

NLR mean to be 4.61 (3.93-5.28; SD: 4.11) resulting in a significant difference emphasizing the presence of systemic inflammation in patients with gastrointestinal cancer.

Mean PLR in healthy adult people is 132.4 [11] while in our study we found a mean PLR of 185.96 (168.54-203.38; SD: 106.13) further suggesting the presence of inflammation in patients with gastrointestinal cancer.

The mean LMR was 3.08 (2.81-3.36; SD: 1.64) in our patients with gastrointestinal cancer while LMR in healthy people was reported to be 5.31 [11], thus suggesting an increased inflammatory response in patients with gastrointestinal malignancies which is in consonance with other studies that suggest a low LMR to be an indicative of poor prognosis [27].

In our study we have found no relevant association between the histopathological differentiation grade and the mean value for NLR, PLR and LMR. There was no significant statistical difference based on the mean value of NLR and PLR between the two lots. The mean LMR was slightly lower in patients with local invasion compared with patients with no local invasion.

From 145 patients with gastrointestinal cancer, in 7 cases the cancer extended to the pancreas from which one case (14.28%) was known to have had acute pancreatitis in their medical history, that is related to the result 14.8% of Syed et al. study. This is in accordance with the literature which states that acute pancreatitis is a risk factor for pancreatic cancer development [28].

## Conclusion

Determining NLR, PLR and LMR can easily be done with a simple blood test and can be useful inflammatory markers which are known to be related to the prognosis of patients with gastrointestinal cancer.

In this study, we found a high NLR and PLR and a low LMR in patients with gastrointestinal cancer suggesting an increased inflammatory response in patients with malignancies in this area.

The limitation of our study includes a low number of enrolled cases, which can be corrected in further study by continuing the enrollment.

## Abbreviations

NLR=neutrophil-lymphocyte ratio; SD=standard deviations; 95% CI=confidence intervals of 95%; LMR=lymphocyte-monocyte ratio; PLR=platelet-lymphocyte ratio; CBC=complete blood count.

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