Scientific Research Publishing

Journal of Cancer Therapy, 2023, 14, 6-24
https://www.scirp.org/journal/jct
ISSN Online: 2151-1942
ISSN Print: 2151-1934

# Pretreatment Neutrophil/Lymphocytes Ratio in Non-Metastatic Colon Cancer as a Prognostic and Predictive Factor: A Retrospective Study

**Manar Muhammed Muhammed, Ahmed Mustafa Elzawawy, Mohamed Abozeid, Sharehan Hassan Soliman***

Clinical Oncology and Nuclear Medicine Department, Faculty of Medicine, Suez Canal University, Ismaïlia, Egypt
Email: *Sharyhan_hassan@med.suez.edu.eg

**How to cite this paper:** Muhammed, M.M., Elzawawy, A.M., Abozeid, M. and Soliman, S.H. (2023) Pretreatment Neutrophil/Lymphocytes Ratio in Non-Metastatic Colon Cancer as a Prognostic and Predictive Factor: A Retrospective Study. *Journal of Cancer Therapy*, **14**, 6-24.
https://doi.org/10.4236/jct.2023.141002

**Received:** December 10, 2022
**Accepted:** January 9, 2023
**Published:** January 12, 2023



## Abstract

**Background:** In developed countries, colon cancer is the second most prevalent cancer, only exceeded by prostate cancer in men and breast cancer in women. After Hepatocellular carcinoma, breast cancer, bladder cancer, lung cancer, Non-Hodgkin Lymphoma and brain tumors, colon cancer is the 7th most common cancer in Egypt, in both sexes, representing 3.47% and 3%, in both male and female cancers, respectively. **Aim of the Work:** The aim of this study was to evaluate the prognostic and predictive significance of pretreatment Neutrophil/lymphocytes ratio (NLR), in terms of disease-free survival (DFS) and recurrence, in high-risk stage II and stage III Colorectal cancer patients who underwent curative resection. **Patients and Methods:** We retrospectively evaluated 103 patients, who were submitted to upfront surgery as first therapeutic option in curative intent, between January 2017 and December 2018. Pretreatment Neutrophil/lymphocytes ratio (NLR), as well as demographics, clinical, histopathologic, and laboratory data were analyzed. Univariate and multivariate analyses were conducted to identify prognostic factors associated with disease free survival (DFS) and recurrence. **Results:** The cutoff point of Neutrophils/lymphocytes ratio (NLR) was calculated with Kaplan-Meier curves and log-rank test to 3. This study revealed that neutrophils/lymphocytes ratio (NLR) was significantly associated with disease free survival ($p < 0.001$*). Also, there was no difference in efficacy between both chemotherapy regimens FOLFOX and XELOX in both high-risk stage II and stage III colon cancer regarding disease free survival & the toxicity profile associated with each regimen and its grades between patients. **Conclusion:** Our study suggests that preoperative Neutrophils/lymphocytes ratio (NLR) more than 3 may be an independent prognostic marker for TTR (time to recurrence) in high-risk stage II and stage III colon cancer patients.

**Keywords**

Pretreatment Neutrophil/Lymphocytes Ratio-Non-Metastatic Cancer Colon

## 1. Introduction

Many risk factors for colon cancer exist. They are caused by old age, genetic variables, and behaviors, including diet, obesity, smoking and lack of physical activity [1].

Red meat, processed meat, and alcohol are dietary factors that increase the risk. Inflammatory bowel disorder, which involves Crohn's disease and ulcerative colitis, is another risk factor. Familial adenomatous polyposis and hereditary non-polyposis colon cancer are some of the inherited genetic conditions that may cause colon cancer, but these represent less than 5% of cases. It usually begins as a benign tumor, often in the form of a polyp, which over time becomes cancerous [2].

Colon Cancer is diagnosed after the onset of symptoms, or through screening colonoscopy in most patients.

Popular clinical presentations include abdominal pain, alteration of bowel habits, and perforation or intestinal obstruction. Bleeding and diarrhea are more likely to occur in right-sided lesions, while left-sided tumors are typically later identified and can occur as bowel obstruction [2].

A suspicion of diagnosis of colon cancer warrants colonoscopy with a biopsy of any suspected lesions, laboratory tests are conducted to confirm diagnosis, to test tumor markers (CEA) and organ function (liver, kidneys) of patients in preparation of diagnostic and therapeutic procedures and to estimate tumor burden [3].

A baseline CEA level that was obtained post operatively as it carries prognostic value and when highly elevated may indicate more advanced, disseminated disease.

For staging purposes, sufficient imaging of the chest and abdomen should be obtained, preferably preoperatively, by computed chest, abdomen, and pelvis tomography (CT scan). An abdominal barium analysis to delineate the primary lesion better preoperatively, if available [2].

Positron emission tomography (PET) scanning is emerging as a very useful modality for staging and assessment of colon cancers.

Despite the importance of molecular and biological characteristics in determining cancer patients' prognosis, some studies indicate the contribution of the host-driven inflammatory response to the actions of tumors and the outcome of treatment [4].

Tumor growth and metastatic spread are the result of many tumor-stromal interactions, including blood vessels, inflammatory cells, and the immune system, leading to chronic inflammation [4].

Systematic inflammatory response laboratory markers, such as C-reactive protein (CRP), hypoalbuminemia, Glasgow Prognostic Score (combining CRP and albumin), white blood cell count, neutrophil/lymphocyte ratio (NLR) or platelet/lymphocyte ratio (PLR), have been examined in many tumors as prognostic and predictive variables [5].

NLR, defined as the absolute neutrophils count divided by the absolute lymphocytes count, has been reported as a prognostic factor in several neoplastic diseases, such as breast cancer, stomach, pancreatic cancer and HCC [6].

In radically resected patients, the role of inflammation markers in predicting prognosis of colon cancer patients has been clearly demonstrated and more recently suggested in the metastatic setting as well [7].

In selecting colon cancer therapy, the identification of prognostic and predictive factors for chemotherapy and biological treatment is important, considering the schedules available and the goal of personalizing the treatment as much as possible. As a result of a chronic inflammatory state, there is rising evidence of stroma-tumor interaction, its role in the carcinogenesis process and tumor progression [4].

The mechanism underlying the correlation between high neutrophils/lymphocytes ratio (NLR) and worse outcomes has not been explained, but it may be due to the association between inflammation and Neutrophils/lymphocytes ratio (NLR). Neutrophilia may, therefore, suppress the immune system, eliminating immune cell cytolytic activity [8].

At the same time, both tumor cells and host cell, including neutrophils, can produce chemokines and cytokines, thus contributing to tumor progression.

The aim of this study was to evaluate the prognostic significance of pretreatment Neutrophils/lymphocytes ratio (NLR), in terms of disease-free survival (DFS) and recurrence in high-risk stage II and stage III Colorectal cancer patients, who underwent curative resection, without neoadjuvant treatment.

## 2. Patients and Methods

### 2.1. Study Design

A retrospective study was conducted to evaluate the prognostic and predictive value of pretreatment NLR in colon cancer patients attending Clinical Oncology Department, Suez Canal University Hospital, Ismailia, Egypt during the period from January 2017 to December 2018 with follow up period of 2 years (till December 2020).

### 2.2. Study Population

Study population included high risk stage II (T3 T4 N0 M0) and stage III Colon cancer patients attending Clinical Oncology Department, Suez Canal University Hospital, Ismailia, Egypt.

### 2.3. Inclusion Criteria

- Patients diagnosed with colon adenocarcinoma.

- Patients who underwent curative surgical resection that revealed colonic carcinoma (high risk Stage *II disease with pathology T*3 *T*4 *NO & stage III disease*).
- Performance *status* ≤ 2 according to the Eastern Cooperative Oncology Group system [9], age group (20 - 60).

### 2.4. Exclusion Criteria

- Patients with other pathological subtypes as gastrointestinal stromal tumor (GIST) and neuroendocrine tumor (NET).
- Patients with hematological disorders, systemic inflammation or severe chronic illness as cardiopulmonary disease, uncontrolled diabetes, or hypertension unstable hepatic disease or renal disease who can't tolerate chemotherapy.
- Patients with performance status > 2 according to the Eastern Cooperative Oncology Group.
- Patients with uncompleted data.
- Patients who were histologically classified as Tis or stage IV, even though a curative resection was achieved.
- Patients who suffered from multiple distant metastases.

### 2.5. Enrollment of Participants

From January 2017 till December 2018, a list of all eligible patients diagnosed with colorectal cancer were retrieved from the patient's records and traced to record disease outcome, Clinico-pathological parameters and response to different lines of treatment.

The data required for this study was collected from the files recording system in clinical oncology unit.

In this system, personal, clinical, laboratory, radiological, pathological, treatment received, and follow up data for every patient are recorded in separate files.

The following information was obtained from files about each patient:

- Personal data; name, age at diagnosis (20 - 60), sex (male or female).
- First presentation of disease (screening, intestinal obstruction, perforation).
- All patients underwent a complete clinical examination and colonoscopy result if was done.
- Staging; TNM staging system at diagnosis.
- Performance status.
- Co-morbidities (DM, HTN, Cardiac).
- Tumoral variables; tumor site (right colon, left colon), histological type, differentiation, lympho-vascular invasion (LVI), perineural invasion (PNI), and lymph node (LN) involvement.
- Baseline examinations and investigations: colonoscopy, CEA, a chest X-ray, an abdominal pelvic computed tomography (CT).
- The received treatment, assessment of treatment response and outcome by computed tomography (CT).

### 2.6. Clinico-Pathological Assessment

Laboratory Studies should include the following:

- Complete blood cell count with differential (for pretreatment NLR).
- Serum chemistries.
- Liver function tests.
- Renal function tests.
- Serum carcinoembryonic antigen (CEA) level.

Adequate imaging of the chest and abdomen should be obtained ideally preoperatively.

- Abdominal/pelvic computed tomography (CT scan).
- Chest computed tomography (CT scan).
- An abdominal barium study to better delineate the primary lesion preoperatively if was available.

The TNM staging system has become the international standard for staging of colon cancer. It uses the following three descriptors:

- T for primary tumor.
- N for lymph nodal involvement.
- M for metastasis.

Patient prognosis is a function of the clinical and histopathologic stage of colon cancer at diagnosis. In addition to the well-established significance of standard pathologic features such as,

- Depth of bowel wall penetration (T).
- Number of loco regional lymph nodes involved (N).
- Presence of extra-colonic metastases (M).
- Histologic grade.
- Evidence of lymph vascular invasion.
- Perineural invasion.
- Hematological tests

All blood samples were taken within two to three days before surgery. In this way, any kind of infection and co-existing inflammatory disease could be reliably excluded. NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count.

### 2.7. Optimal Cut-Off Value for NLR

In literature, there is an increasing interest in finding the optimal threshold value above which NLR significantly increases the likelihood of death or recurrence [10] [11] [12] [13] [14]. This has been typically carried out using ROC curves, which visually represent the sensitivity (*i.e.*, probability of correctly identifying an event e.g., a death) and the specificity (*i.e.*, probability of correctly identifying a nonevent) of various cutoffs.

In the present study, we used a method [14] based on Kaplan-Meier curves and the log rank test, which do account for censoring. For a range of potential threshold values of NLR, we calculated the Kaplan-Meier curves and the log rank

test, selecting the threshold giving the greatest separation of curves in terms of the lowest p-value.

Sample size

The sample size was determined using the following equation [15]:

$$n = \frac{\left(Z_{1-\frac{\alpha}{2}}\right)^2 * p(1-p)}{d^2}$$

where:

- $n$ = the sample size.
- $Z_{1-\frac{\alpha}{2}}$ = the confidence interval which equals to 1.96 when type 1 error is 5%.
- $p$ = prevalence of elevated neutrophil lymphocyte ratio (NLR) among colonic cancer patients equals to 43.1% based on previous literature [16].
- $d$ = Absolute error or precision, usually equals 10%.

The calculated sample size is 94 participants; however, after adding the expected (drop-out) rate (10%), the final sample size was 103 participants.

## 2.8. Treatment Regimens

XELOX consisted of a 2-h intravenous infusion of oxaliplatin 130 mg/m$^2$ on day 1 plus oral capecitabine 1000 mg/m$^2$ twice daily for 2 weeks as a 3-week cycle. The first dose of capecitabine was given in the evening of day 1 and the last dose on the morning of day 15.

FOLFOX 4 consists of a 2-hour infusion of LV (200 mg/m$^2$/d) followed by a 5FU bolus (400 mg/m$^2$/d) and 22-hour infusion (600 mg/m$^2$/d) for 2 consecutive days every 2 weeks with oxaliplatin 85 mg/m$^2$ as a 2-hour infusion on day 1.

## 2.9. Ethical Consideration

- Approval of the research ethics committee of Faculty of Medicine Suez Canal University (FOMSCU) to the final protocol.
- The research data was collected from the patients' files. Confidentiality of the information and patient privacy, no personal data was published.
- Data was used only in this research; this is beside that patients' contact was required to minimize the problems of inaccurate recording and follow up.

## 2.10. Data Management

All analyses were performed using statistical package for social sciences (SPSS) for windows version 22.0 (SPSS, Chicago, IL, USA). Descriptive data was presented as mean ± SD or percentages. Fisher's exact test and chi-square test were used for statistical analysis of categorical variables. Analysis of continuous variables was performed by independent t-test or non-parametric Mann-Whitney U-test according to the normality of the distributions. Correlation between numerical variables was assessed using Pearson's correlation coefficient or non-parametric Spearman's correlation coefficient according to the normality of the dis-

tributions. For all tests a probability value of less than 0.05 was considered statistically significant.

## 3. Results

Between January 1, 2017, to December 31, 2018, 103 patients were enrolled. There were 48 female patients (46.6%) and 55 male patients (53.4%). there were 27 patients between the age of 20 - 40 years (26.2%) and 76 patients between 40 - 60 years old (73.8%) with mean Age 46.29 (±8.49) SD and range (24.0 - 60.0). Median Follow up period (months) was 29.28 range (24.0 - 46.0). The clinicopathologic characteristics of the enrolled patients are presented in Table 1.

All patients received adjuvant 4 to 6 cycles of chemotherapy, with average treatment period from 6 to 8 months. 54 patients received FOLFOX regimen (52.4%) and 49 patients received XELOX regimen (47.6%). Regarding Post chemotherapy assessment, there were 95 patients developed complete response to chemotherapy according to RESICT criteria (92.2%) and 8 patients developed Progressive disease coarse (7.8%) with mean time to progression (months) 13.25 (±9.19) SD. Upon assessment of adverse events, 55.3% developed hand & foot syndrome and 58.3% developed neutropenia. Other adverse events include hepatotoxicity and neurotoxicity (Table 2).

The median value of NLR for the whole study population was 3.3 and range (1.0 - 7.0). 52 patients had NLR ≤ 3 (50.5%) and 51 patients had NLR > 3 (49.5%). Statistically significant decreased median values of NLR were found among patients presented with intestinal obstruction presentation (p value 0.015*). There was a significant difference between NLR and Post chemotherapy assessment with decreased median NLR highly associated with better response rate according to RECIST criteria and less progression and recurrence rates (p value 0.029*).

All patients receive four to six cycles of Folfox/Xelox regimen. Upon assessment of adverse events, there was a highly significant difference between both Chemotherapy regimens. Hand & foot syndrome toxicity and neurotoxicity were more prominent with XELOX regimen. There is no significant difference between chemotherapy regimens regarding Neutropenia, Hepatotoxicity.

Kaplan-Meier survival curve were used to analyze whether NLR influenced the prognostic value of disease-free survival. One year Disease free survival for NLR less than and more than 3 were 94.1% and 17.1%, respectively. Two years Disease free survival for NLR less than and more than 3 were 13.7% and 0.0%, respectively. An association analysis was performed and demonstrated that NLR was significantly associated with disease free survival ($p < 0.001$*). The results confirmed that the NLR score was an independent prognostic factor for survival rate (Figure 1).

Kaplan-Meier survival curve for disease free survival with chemotherapy regimen show that there was no statistically significance in disease free survival between chemotherapy regimens (Figure 2). Results show that there was a significant difference between Disease free survival with NLR (in high risk stage II

Table 1. Clinicopathological characteristics of the enrolled patients (n = 103).

| Demographic data | No. | % |
|---|---|---|
| **Sex** | | |
| Male | 55 | 53.4 |
| Female | 48 | 46.6 |
| **Age (years)** | | |
| 20 - 40 | 27 | 26.2 |
| >40 - 60 | 76 | 73.8 |
| Min. - Max. | 24.0 - 60.0 | |
| Mean ± SD. | 46.29 ± 8.49 | |
| Median (IQR) | 47.0 (39.0 - 54.0) | |
| Follow up period (months) | | |
| Min. - Max. | 24.0 - 46.0 | |
| Median | 29.28 | |
| **Performance status** | **No.** | **%** |
| 0 | 73 | 70.9 |
| 1 | 28 | 27.2 |
| 2 | 2 | 1.9 |
| **Comorbidities** | **No.** | **%** |
| No | 63 | 61.2 |
| **Yes** | **40** | **38.8** |
| DM | 14 | 13.6 |
| HTN | 18 | 17.5 |
| HCV | 6 | 5.8 |
| AF | 2 | 1.9 |
| **Smoking** | | |
| Non-smoker | 68 | 66.0 |
| Smoker | 35 | 34.0 |
| **Family history** | **No.** | **%** |
| Negative | 92 | 89.3 |
| **Positive** | **11** | **10.7** |
| FAP | 3 | 2.9 |
| Colon cancer | 8 | 7.8 |
| **Site** | **No.** | **%** |
| Right side | 45 | 43.7 |
| left side | 58 | 56.3 |

**Continued**

| Presentation | No. | % |
|---|---|---|
| Intestinal obstruction | 20 | 19.4 |
| Perforation | 10 | 9.7 |
| FBPR | 20 | 19.4 |
| Alternation of bowel habits | 16 | 15.5 |
| Abdominal pain | 23 | 22.3 |
| Constipation | 8 | 7.8 |
| Chronic anemia | 6 | 5.8 |
| **Pathology** | **No.** | **%** |
| Non mucinous | 50 | 48.5 |
| Mucinous | 29 | 28.2 |
| Signet ring ca | 24 | 23.3 |
| **LN dissected** | **No.** | **%** |
| <12 | 15 | 14.6 |
| ≥12 | 88 | 85.4 |
| Min. - Max. | 4.0 - 30.0 | |
| Mean ± SD. | 16.66 ± 6.10 | |
| Median (IQR) | 15.0 (12.0 - 20.0) | |
| **TNM staging** | **No.** | **%** |
| **T stage** | | |
| T2 | 13 | 12.6 |
| T3 | 65 | 63.1 |
| T4 | 25 | 24.3 |
| **N stage** | | |
| N0 | 43 | 41.7 |
| N1 | 36 | 35.0 |
| N2 | 24 | 23.3 |
| **M stage** | | |
| M0 | 103 | 100.0 |
| **Stage** | | |
| II | 43 | 41.7 |
| III | 60 | 58.3 |
| **Grade** | | |
| I | 14 | 13.6 |
| II | 76 | 73.8 |
| III | 13 | 12.6 |

**Continued**

| Tumor marker | No | % |
|---|---|---|
| Normal | 19 | 18.4 |
| Elevated | 79 | 76.7 |
| Not assessed | 5 | 4.9 |
| **Postoperative assessment** | **No.** | **%** |
| Free | 103 | 100 |

IQR: Inter Quartile Range; SD: Standard Deviation.

Table 2. Distribution of the studied cases according to administrated chemotherapy (n = 103).

| Chemotherapy (6 months) | No. | |
|---|---|---|
| Folfox | 54 | |
| Xelox | 49 | |
| **Post chemotherapy assessment** | | |
| CR | 95 | |
| Progression | 8 | |
| **Time to progression (months)** | | |
| Min. - Max. | 3.0 - 36.0 | |
| Mean ± SD. | 13.25 ± 9.19 | |
| Median (IQR) | 12.0 (6.0 - 24.0) | |
| **Toxicity** | **No** | |
| | **No.** | **%** |
| **Hand & foots syndrome** | 57 | 55.3 |
| Grade 1 | 46 | 44.7% |
| Grade 2 | 0 | 0 |
| Grade 3 | 0 | 0 |
| Grade 4 | 0 | 0 |
| **Neutropenia** | 60 | 58.3 |
| Grade 1 | 40 | 38.8 |
| Grade 2 | 3 | 2.9 |
| Grade 3 | 0 | 0 |
| Grade 4 | 0 | 0 |
| **Hepatotoxicity** | 58 | 56.3 |
| Grade 1 | 45 | 43.7 |
| Grade 2 | 0 | 0 |
| Grade 3 | 0 | 0 |
| Grade 4 | 0 | 0 |

**Continued**

| | | |
|---|---|---|
| **Neurotoxicity** | 42 | 40.8 |
| Grade 1 | 29 | 28.2 |
| Grade 2 | 32 | 31.1 |
| Grade 3 | 0 | 0 |
| Grade 4 | 0 | 0 |
| **GIT symptoms (diarrhea & vomiting)** | | |
| Grade 1 | 25 | 24.3 |
| Grade 2 | 22 | 21.4 |
| Grade 3 | 8 | 7.8 |
| Grade 4 | 0 | 0 |

IQR: Inter Quartile Range; SD: Standard Deviation.

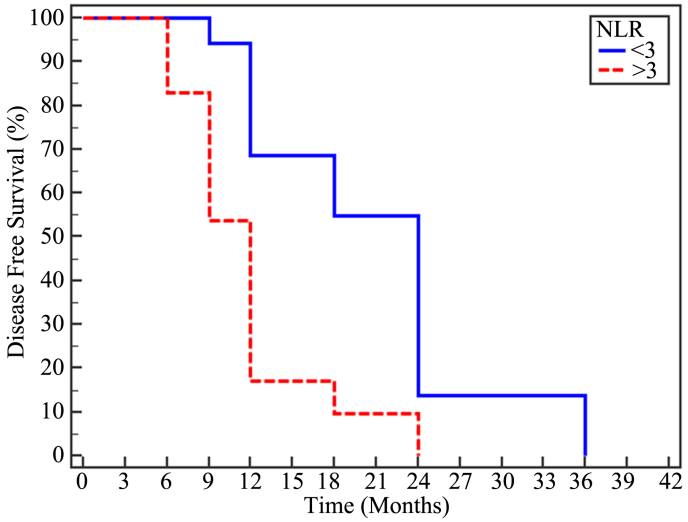


**Figure 1.** Kaplan-Meier survival curve for disease free survival with NLR.

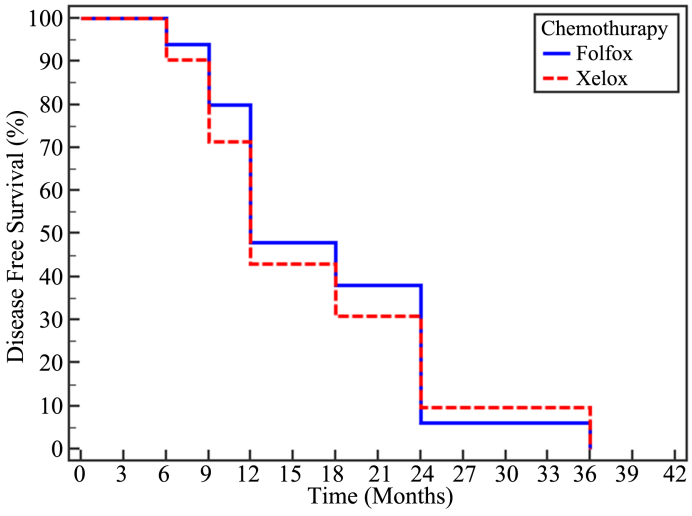


**Figure 2.** Kaplan-Meier survival curve for disease free survival with chemotherapy.

disease) (Table 3 and Figure 3). Results also show that there is highly significant difference between Disease free survival and NLR (in stage III disease) (Table 4 and Figure 4).

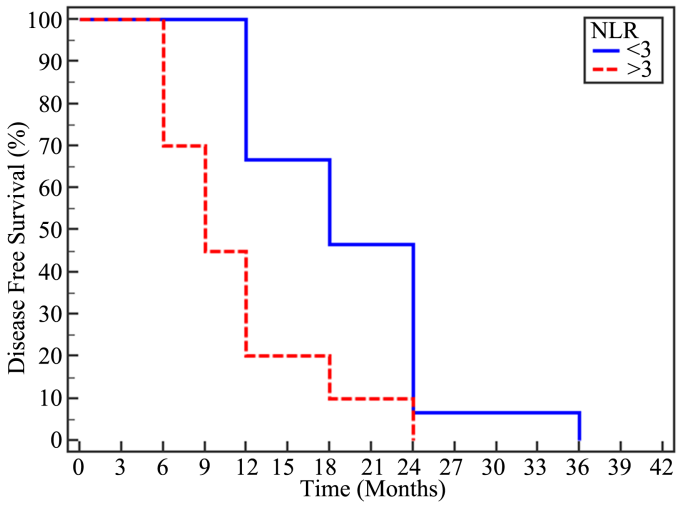


Figure 3. Kaplan-Meier survival curve for disease free survival with NLR (in stage II cases).

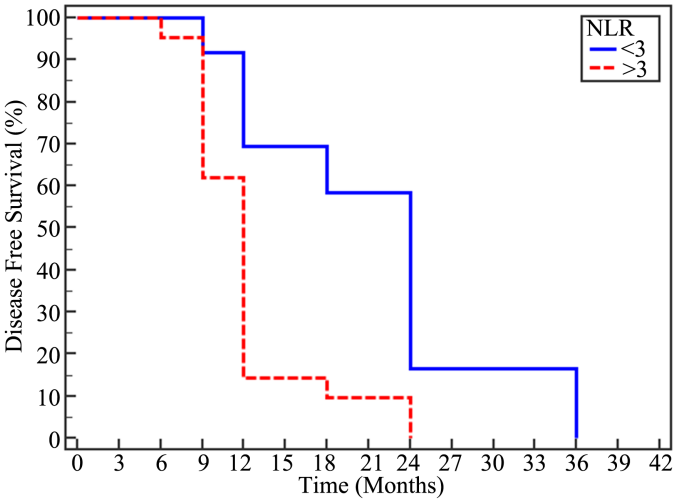


Figure 4. Kaplan-Meier survival curve for disease free survival with NLR (in stage III cases).

Table 3. Disease free survival with NLR (in high risk stage II disease).

| NLR | Mean | Median | % 1 year | % 2 year | % End of study | Log rank | |
|---|---|---|---|---|---|---|---|
| | | | | | | $\chi^2$ | p |
| <3 | 19.60 | 18.0 | 66.7 | 6.7 | 0.0 | 11.202* | 0.001* |
| >3 | 11.3 | 9.0 | 20.0 | 0.0 | 0.0 | | |

This table shows that there is significant difference between Disease free survival with NLR (in high risk stage II disease). *statistically significant p value (p value is considered significant less than/equal to 0.05).

**Table 4.** Disease free survival with NLR (in stage III cases).

| NLR | Mean | Median | % 1 year | % 2 year | % End of study | Log rank | |
|---|---|---|---|---|---|---|---|
| | | | | | | $\chi^2$ | p |
| <3 | 21.4 | 24.0 | 69.4 | 16.7 | 0.0 | 19.077* | <0.001* |
| >3 | 12.1 | 12.0 | 14.3 | 0.0 | 0.0 | | |

This table shows that there is highly significant difference between disease free survival and NLR (in stage III cases). *Statistically significant p value (p value is considered significant less than/equal to 0.05).

## 4. Discussion

NLR, defined as the absolute neutrophils count divided by the absolute lymphocytes count, has been reported as a prognostic factor in several neoplastic diseases, such as breast cancer, gastric, pancreatic cancer and hepatocellular carcinoma [6].

In radically resected patients, the role of inflammation markers in predicting prognosis of colon cancer patients has been clearly demonstrated and more recently suggested in the metastatic setting as well [7].

Risk stratification strategies are currently guided by patient characteristics (e.g. age, sex) and tumor-specific features. The European Society for Medical Oncology (ESMO) highlights the Eastern Cooperative Oncology Group (ECOG) performance status and the presence of comorbidities as relevant patient-level prognostic traits. On the other hand, TNM stage, mismatch repair, microsatellite instability, invasion status and carcinoembryonic antigen (CEA) levels are established tumor-specific prognostic factors [17].

In addition, it is increasingly recognized that inflammation and immune cells play an important role in tumorigenesis, therefore several inflammatory markers are being extensively investigated for their prognostic and predictive values. For example the modified Glasgow Prognostic Score (mGPS), which combines plasma albumin and C-reactive protein levels, reflects systemic inflammatory status and has shown potential as a useful tool in colon cancer prognosis. Moreover, the Immunoscore assay that assesses the tumor immune infiltrate has recently been endorsed by ESMO [18].

Recent data indicate that inflammatory cells that accumulate around neoplasms play a crucial role in tumor progression. Patients with a high density of lymphocytes in the stroma of tumors were reported to have increased clinical outcome compared to those with low density of lymphocytes, whereas high density of neutrophils was associated with decreased clinical outcome [19].

In this study we aimed to monitor the outcome of high risk stage II and stage III colon cancer who underwent curative resection by evaluating the prognostic and predictive role of pretreatment NLR in term of disease free survival.

In 2013, study done by Absenger *et al.* [20], to evaluate the effect of NLR on time-to-recurrence (TTR) and overall survival in stage II-III colon cancer enrolled 504 patients. Study revealed that the median age at the time of diagnosis was 65

years (range 27 - 95 years). There were 293 (85.1%) male and 211 (41.9%) female. Results showed that NLR > 4 was significantly associated with T4 tumors (p = 0.03). None of the other clinicopathological parameters were associated with NLR > 4. In univariate analysis, the elevated NLR was significantly associated with decreased TTR (HR = 2.27; 95% CI = 1.42 - 3.62; p = 0.001) and remained significant in multivariate analysis including the factors of sex, tumor size, number of resected lymph nodes, histological grade, clinical stage and adjuvant chemotherapy (HR = 1.95; 95% CI = 1.21 3.13, p = 0.006). Patients with NLR < 4 had a median TTR of 92.6 months. In contrast, patients with NLR > 4 showed a median TTR of 62.2 months. In univariate analysis, the elevated NLR was also significantly associated with decreased OS (HR = 2.05, 95% CI = 1.06 - 3.95, p = 0.033). Patients with preoperative NLR ≤ 4 had a median OS of 101.3 months, whereas patients with NLR > 4 showed a median OS of 83.4 months. This study suggests that preoperative NLR may be an independent prognostic marker for TTR in stage II and III colon cancer patients.

In 2010, a Chinese study by Liu *et al.* [21] done to determine the prognostic implications of the N/L ratio in the peripheral blood of rectal cancer patients. Study included 123 patients. Median NLR was 2.41 ± 2.206 (range, 0.76 - 20.45). Results showed that N/L ratio was significantly associated with tumor size (p = 0.003) and level of cancer antigen 125 (p = 0.027). A multivariate Cox model established a significant relationship between the N/L ratio and survival (adjusted hazard ratio, 2.615; 95% confidence interval, 1.152 - 5.933; p = 0.021).

In 2012, Carruthers *et al.* [22], in UK performed a retrospective study on 115 patients. This study aimed to investigate the association between the inflammatory markers and the outcome of treatment. patients with locally advanced rectal cancer undergoing preoperative chemoradiation had full blood count and neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratios (PLR) were collected. Results show that elevated NLR is a valuable prognostic marker in patients undergoing chemoradiation for locally advanced rectal carcinoma. Elevated NLR were associated with worse Overall survival and disease-free survival. [22]

Another Korean study in 2014 by Kim *et al.*, enrolled One hundred two patients with rectal cancer. Patients treated by preoperative Concomitant chemoradiotherapy followed by surgery were enrolled. A NLR ≥ 3 were considered elevated. Results showed 24.5% had elevated NLR, also elevated tumor markers (p = 0.001), large tumor size (p = 0.03), and elevated NLR (p = 0.04) were significant predictors for a poor response [23].

Shen *et al.*, in 2017 investigated the association between the NLR and prognoses in locally advanced rectal cancer. 202 patients with rectal cancer were enrolled. Patients received neoadjuvant concurrent chemoradiotherapy and underwent surgical resection thereafter. NLR cutoff point was 3. In this cohort study, the NLR did not correlate with survival outcomes [24].

In 2015, Nagasaki *et al.*, evaluated the prognostic role of NLR in patients with locally advanced rectal cancer. Patients were treated with neoadjuvant concomi-

tant chemoradiotherapy followed by surgery. NLRs were calculated using a cut-off value of 3.0. Results show that a high NLR was significantly associated with elevated carcinoembryonic antigen levels before NACRT (p = 0.0154). Also, high NLR was associated with worse overall survival (hazard ratio (HR) 3.38, p = 0.012) but not significantly associated with relapse-free survival (HR 1.073, p = 0.8438) [25].

Vallard *et al.*, in 2018 aimed to evaluate the prognostic significance of the inflammatory markers in locally advanced rectal cancer patients. From 2004 to 2015, 257 rectal cancer patients were enrolled with NLR cutoff point 2.8. Results show that Elevated NLR was marginally associated with incomplete pathological response in multivariate analysis, suggesting a possible value as a biomarker of radio-sensitivity [26].

Ward *et al.* 2018, included 146 patients with stage II and III rectal cancer. Low NLR (<4.47) was associated with decreased OS. Study concluded that NLR, and PLR values are accurate predictors of 5-y OS in patients with locally advanced rectal adenocarcinoma [27].

Ki *et al.*, 2020, investigated the prognostic value of neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in rectal cancer patients receiving neoadjuvant concurrent chemoradiotherapy (CCRT). 184 patients with newly diagnosed rectal cancer receiving neoadjuvant CCRT were enrolled. Results showed that that patients with stage II and III rectal cancer with high NLR had a worse 5-year DFS (p = 0.018) and OS (p = 0.015). Study revealed that Pre-CCRT NLR and PLR are independent prognostic factors for rectal cancer patients and could be used as a potential biomarker to identify high-risk patients for more intense treatment and care [28].

In this study, the median value of NLR for the whole study population was 3.3 and range (1.0 - 7.0). 52 patients had NLR ≤ 3 (50.5%) and 51 patients had NLR > 3 (49.5%). Statistically significant decreased median values of NLR were found among patients presented with intestinal obstruction presentation (p value 0.015*). There was a significant difference between NLR and Post chemotherapy assessment with decreased median NLR highly associated with better response rate according to RECIST criteria and less progression and recurrence rates (p value 0.029*). Therefore, our study suggests that preoperative NLR more than 3 may be an independent prognostic marker for TTR (Time to recurrence) in high-risk stage II and stage III colon cancer patients.

## 5. Conclusion

In conclusion, our study suggests that preoperative NLR may be an independent prognostic marker for TTR in high risk stage II and III colon cancer patients.

## 6. Study Limitations

Some limitations of our study must be considered, due to its retrospective design, a selection bias cannot be fully excluded. We also took into consideration that it was a single center-based study with a small number of patients, with a

relatively small sample size, which precluded the accurate matching of both groups, in term of comparable staging, hence their proper comparison.

A major limitation in the current study was the incompliance of some patients to regular follow ups and unavailability of some information. So, we recommend later research with a larger number of patients and longer period of follow up.

## Acknowledgements

I would like to thank all authors for their contribution in the design of the work. Any opinions, findings, and conclusions expressed in this material are those of the authors.

## Authors' Contributions

SHS, MMM contributed to the conception and design of the work. SHS, MMM contributed to the acquisition, analysis, and interpretation of the data. SHS, MMM, MA, AME revised and supervised the work. SHS wrote the initial draft of the manuscript. All authors contributed to manuscript revision. All authors approved the final version of the manuscript.

## Availability of Data and Materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Ethics Approval and Consent to Participate

The study was approved by the Research Ethics Committee of Suez canal University Department of Clinical Oncology & Nuclear medicine, Suez Canal University, and informed consent was waived being a retrospective medical record review study.

- Approval of the research ethics committee of FOMSCU to the final protocol.
- Clinical data will be collected after approval of the research ethics committee of (FOMSCU).
- The research data was collected from the patients' files. Confidentiality of the information and patient privacy, no personal data was published. Data will be used only in that research, this is beside that patients' contact was required in order to minimize the problems of inaccurate recording and follow up.
- Analysis of data was demonstrated in a secret way without mentioning patients' names.

## Conflicts of Interest

The authors declare that they have no competing interests.

## References

[1] Ibrahim, A.S., Khaled, H.M., Mikhail, N.N., Baraka, H. and Kamel, H. (2014) Cancer Incidence in Egypt: Results of the National Population-Based Cancer Registry

Program. *Journal of Cancer Epidemiology*, **2014**, Article ID: 437971. https://doi.org/10.1155/2014/437971

[2] Forman, D., *et al.* (2014) Colorectal Cancer. In: Stewart, B.W. and Wild, C.P., Eds., *World Cancer Report*, The International Agency for Research on Cancer, World Health Organization, IARC Press, Lyon.

[3] Altman, J. (2019) Colorectal Cancer: Diagnosis. ASCO, Alexandria.

[4] Balkwill, F. and Mantovani, A. (2010) Cancer and Inflammation: Implications for Pharmacology and Therapeutics. *Clinical Pharmacology & Therapeutics*, **87**, 401-406. https://doi.org/10.1038/clpt.2009.312

[5] Roxburgh, C.S. and McMillan, D.C. (2010) Role of Systemic Inflammatory Response in Predicting Survival in Patients with Primary Operable Cancer. *Future Oncology*, **6**, 149-163. https://doi.org/10.2217/fon.09.136

[6] McMillan, D.C. (2009) Systemic Inflammation, Nutritional Status and Survival in Patients with Cancer. *Current Opinion in Clinical Nutrition & Metabolic Care*, **12**, 223-226. https://doi.org/10.1097/MCO.0b013e32832a7902

[7] Diakos, C.I., *et al.* (2016) Is Baseline Neutrophil to Lymphocyte Ratio (NLR) an Independent Prognostic Biomarker for Progression Free Survival (PFS) and Overall Survival (OS) in Metastatic Colorectal Cancer (mCRC)? Analysis of the AGITG MAX Study. *Annals of Oncology*, **27**, Article No. vi197. https://doi.org/10.1093/annonc/mdw370.137

[8] Petrie, H.T., Klassen, L.W. and Kay, H.D. (1985) Inhibition of Human Cytotoxic T Lymphocyte Activity in Vitro by Autologous Peripheral Blood Granulocytes. *The Journal of Immunology*, **134**, 230-234. https://doi.org/10.4049/jimmunol.134.1.230

[9] Oken, M.M., *et al.* (1982) Toxicity and Response Criteria Of The Eastern Cooperative Oncology Group. *American Journal of Clinical Oncology*, **5**, 649-655. https://doi.org/10.1097/00000421-198212000-00014

[10] Malietzis, G., *et al.* (2014) A Preoperative Neutrophil to Lymphocyte Ratio of 3 Predicts Disease-Free Survival after Curative Elective Colorectal Cancer Surgery. *Annals of Surgery*, **260**, 287-292. https://doi.org/10.1097/SLA.0000000000000216

[11] Chiang, S.-F., *et al.* (2012) Can Neutrophil-to-Lymphocyte Ratio Predict the Survival of Colorectal Cancer Patients Who Have Received Curative Surgery Electively? *International Journal of Colorectal Disease*, **27**, 1347-1357. https://doi.org/10.1007/s00384-012-1459-x

[12] Ozdemir, Y., Akin, M.L., Sucullu, I., Balta, A.Z. and Yucel, E. (2014) Pretreatment Neutrophil/Lymphocyte Ratio as a Prognostic Aid in Colorectal Cancer. *Asian Pacific Journal of Cancer Prevention*, **15**, 2647-2650. https://doi.org/10.7314/APJCP.2014.15.6.2647

[13] Shin, J.S., Suh, K.W. and Oh, S.Y. (2015) Preoperative Neutrophil to Lymphocyte Ratio Predicts Survival in Patients with T1-2N0 Colorectal Cancer. *Journal of Surgical Oncology*, **112**, 654-657.https://doi.org/10.1002/jso.24061

[14] Jankova, L., Dent, O.F., Chan, C., Chapuis, P. and Clarke, S.J. (2013) Preoperative Neutrophil/Lymphocyte Ratio Predicts Overall Survival but Does Not Predict Recurrence or Cancer-Specific Survival after Curative Resection of Node-Positive Colorectal. *BMC Cancer*, **13**, Article No. 442. https://doi.org/10.1186/1471-2407-13-442

[15] Charan, J. and Biswas, J. (2013) How to Calculate Sample Size for Different Study Designs in Medical Research? *Indian Journal of Psychological Medicine*, **35**, 121-126. https://doi.org/10.4103/0253-7176.116232

[16] Dell'Aquila, E., *et al.* (2018) Prognostic and Predictive role of Neutrophil/Lymphocytes Ratio in Metastatic Colorectal Cancer: A Retrospective Analysis of the TRIBE Study by GONO. *Annals of Oncology*, **29**, 924-930. https://doi.org/10.1093/annonc/mdy004

[17] Yamamoto, T., Kawada, K. and Obama, K. (2021) Inflammation-Related Biomarkers for the Prediction of Prognosis in Colorectal Cancer Patients. *International Journal of Molecular Sciences*, **22**, Article No. 8002. https://doi.org/10.3390/ijms22158002

[18] Sunakawa, Y., *et al.* (2018) Immune-Related Genes to Dominate Neutrophil-Lymphocyte Ratio (NLR) Associated with Survival of Cetuximab Treatment in Metastatic Colorectal Cancer. *Clinical Colorectal Cancer*, **17**, e741-e749. https://doi.org/10.1016/j.clcc.2018.08.002

[19] Bhattacharjee, D. and Quirke, P. (2021) What Is the Role of the Neutrophil: Lymphocyte Ratio in Colorectal Cancer? *Turkish Journal of Colorectal Disease*, **31**, 1-12. https://doi.org/10.4274/tjcd.galenos.2020.2020-9-3

[20] Absenger, G., *et al.* (2013) Preoperative Neutrophil-to-Lymphocyte Ratio Predicts Clinical Outcome in Patients with Stage II and III Colon Cancer. *Anticancer Research*, **33**, 4591-4594.

[21] Liu, H., *et al.* (2010) The Baseline Ratio of Neutrophils to Lymphocytes Is Associated with Patient Prognosis in Rectal Carcinoma. *Journal of Gastrointestinal Cancer*, **41**, 116-120. https://doi.org/10.1007/s12029-009-9125-4

[22] Carruthers, R., *et al.* (2012) Systemic Inflammatory Response Is a Predictor of Outcome in Patients Undergoing Preoperative Chemoradiation for Locally Advanced Rectal Cancer. *Colorectal Disease*, **14**, e701-e707. https://doi.org/10.1111/j.1463-1318.2012.03147.x

[23] Kim, I.Y., You, S.H. and Kim, Y.W. (2014) Neutrophil-Lymphocyte Ratio Predicts Pathologic Tumor Response and Survival after Preoperative Chemoradiation for Rectal Cancer. *BMC Surgery*, **14**, Article No. 94. https://doi.org/10.1186/1471-2482-14-94

[24] Shen, J., *et al.* (2017) Prognostic Role of Neutrophilto Lymphocyte Ratio in Locally Advanced Rectal Cancer Treated with Neoadjuvant Chemoradiotherapy. *Medical Science Monitor*, **23**, 315-324. https://doi.org/10.12659/MSM.902752

[25] Nagasaki, T., *et al.* (2015) Prognostic Impact of Neutrophil-to-Lymphocyte Ratio in Patients with Advanced Low Rectal Cancer Treated with Preoperative Chemoradiotherapy. *Digestive Surgery*, **32**, 496-503. https://doi.org/10.1159/000441396

[26] Vallard, A., *et al.* (2018) Outcomes Prediction in Pre-Operative Radiotherapy Locally Advanced Rectal Cancer: Leucocyte Assessment as Immune Biomarker. *Oncotarget*, **9**, 22368-22382. https://doi.org/10.18632/oncotarget.25023

[27] Ward, W.H., *et al.* (2018) Predictive Value of Leukocyte- and Platelet-Derived Ratios in Rectal Adenocarcinoma. *Journal of Surgical Research*, **232**, 275-282. https://doi.org/10.1016/j.jss.2018.06.060

[28] Ke, T.-M., *et al.* (2020) High Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio Predict Poor Survival in Rectal Cancer Patients Receiving Neoadjuvant Concurrent Chemoradiotherapy. *Medicine*, **99**, e19877. https://doi.org/10.1097/MD.0000000000019877

## List of Abbreviations

AF: Atrial Fibrillation; CEA: Carcinoembryonic Antigen; CRC: Colorectal Cancer; CRP: C-Reactive Protein; CT: Computed Tomography; DFS: Disease Free Survival; DM: Diabetes Miletus; ECOG PS: Eastern Cooperative Oncology Group (ECOG) Performance Status; ESMO: European Society for Medical Oncology; FAP: Familial Adenomatous Polyposis; FBPR: Fresh Bleeding Per Rectum; FOMSCU: Faculty of Medicine Suez Canal University; GIST: Gastrointestinal Stromal Tumor; GIT: Gastrointestinal; HCV: Hepatitis C Virus; HCC: Hepatocellular Carcinoma; HTN: Hypertension; LN: Lymph Node; LVI: Lymphovascular Invasion; mCRC: metastatic Colorectal Cancer; Mgps: Modified Glasgow Prognostic Score; NACCRT: Neoadjuvant Concurrent Chemoradiotherapy; NET: Neuroendocrine Tumor; NLR: Neutrophil/Lymphocytes Ratio; OS: Overall Survival; PET CT: Positron Emission Tomography; PLR: Platelet/Lymphocyte Ratio; PNI: Perineural Invasion; PS: Performance Status; TTR: Time to Recurrence.