# The Impact of Neutrophil to Lymphocytic Ratio (NLR) as a Predictor of Treatment Outcomes in Rectal Carcinomas: A Retrospective Cohort Study

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## Abstract

**Background and aim**: The prognostic role of neutrophil to lymphocyte ratio (NLR) has been shown in many solid tumors included in a recent meta-analysis of one hundred studies. We aimed to evaluate the prognostic value of neutrophil to lymphocyte ratio in treatment outcomes; response and survival of patients with different stages of rectal cancers. **Patients and methods**: All patients with pathologically confirmed cancer rectum presented to our department during the period from January 2012 to the end of 2014 were included in this retrospective study, these recruited patients were evaluated through their files to determine different objectives of our study. **Results**: The median overall survival was $31 \pm 4.676$ months while disease free survival was $40 \pm 2.346$ for the whole study group; neutrophil to lymphocyte ratio was negatively correlated with overall survival with $r = -0.743$, $P < 0.001$, also with disease free survival with $r = -0.717$, $P < 0.0001$. Neutrophil to lymphocyte ratio was positively correlated with the number of positive lymph nodes dissected to total number of lymph nodes dissected ratio with $r = +0.254$, $P = 0.028$. Roc curve was used to find the accurate cut point of NLR for these patients and was found to be of 4.5. **Conclusion**: Elevated pre-treatment NLR is an independent predictor of shorter survival in patients with rectal cancer. This parameter is a simple, easily accessible laboratory test for identifying patients with poorer prognosis.

## Keywords

Neutrophil to Lymphocyte Ratio, Overall Survival, Disease Free Survival, Rectal Carcinomas

## 1. Introduction

Colorectal cancer (CRC) incidence and mortality rates vary markedly around the world. Globally, CRC is the third most commonly diagnosed cancer in males and the second in females, with 1.8 million new cases and almost 861,000 deaths in 2018 according to the World Health Organization GLOBOCAN database. Rates are substantially higher in males than in females.

Colorectal cancer exhibits a great geographic variation over 10-fold worldwide, with the highest incidence rates which are in Europe, North America, and Australia, and the lowest incidence rates are in Africa and central Asia [1]. This may be attributable to differences in dietary and environmental exposures that are imposed upon a background of genetically determined susceptibility.

Low socioeconomic status (SES) is also associated with an increased risk for the development of CRC; one study estimated the CRC risk to be approximately 30 percent increased in the lowest as compared with the highest SES quintile [2].

Egypt is among low SES which was lacking incidence rates at national level. Available statistics were proportions derived from single or multicenter hospital registries that could not be used for calculation of incidence rates, the most recent data for colorectal cancer incidence in Egypt came from that published at 2014 by Amal S. *et al.* [3] and collected their data during the period from 2009-2011 from 3 geographical regions; lower Egypt, middle Egypt, and upper Egypt. The crude incidence rates for cancer colon were 3/100,000 (2.3%), 2.2/100,000 (2.31%), and 2.4/100,000 (2.08%) respectively, and for cancer rectum; 0.9/100,000 (0.65%), 1/100,000 (1.01%), and 0.7/100,000 (0.64%) respectively.

It is now well established that inflammatory response has an important role in tumor development and progression, markers like C-reactive protein, certain cytokines, leukocytosis, hypoalbuminemia, thrombocytosis and others have been incorporated in the prognostic scores for several cancers.

When we talk about a type of cancer; we prefer to determine the prognosis of this cancer based on the available prognostic information that simply included neutrophil to lymphocyte ratio (NLR).

Elevated neutrophil lymphocytic ratio in the peripheral blood is found to have a prognostic impact in various cancers like non-small cell lung cancer, hepatocellular carcinoma, mesothelioma, cholangiocarcinoma, breast cancer, and gastroesophageal cancers, but the magnitude of this impact is unclear.

The prognostic role of NLR has been shown in many solid tumors included in a recent meta-analysis of one hundred studies [4]. It was incorporated into a simple score for metastatic castration resistant cancer prostate that established four risk categories with 0, 1, 2, 3 - 5 points that included NLR > 3 [5].

We aimed to evaluate the prognostic value of NLR in treatment outcomes; response and survival of patients with different stages of rectal cancers.

## 2. Patients and Methods

This is a retrospective cohort study to evaluate the impact of neutrophil lym-

phocytic ratio as a predictor of treatment outcomes in rectal carcinomas. All patients with pathologically confirmed cancer rectum presented to our department during the period from January 2012 to the end of 2014 were included in this retrospective study, these recruited patients were evaluated through their files to determine different objectives of our study; patients with colonic cancers, previous chemotherapy treatments, inflammatory bowel disease were excluded, in addition, patients underwent emergent surgery for obstruction or perforation without preoperative blood pictures were also excluded. The protocol of the study was approved by the ethic committee of Assiut University before data collection with an ethical approval ID: 171006231.

## 3. Data Collection

A variety of data were collected from patients' files including: Age, Sex, Performance status according to ECOG scale, Histological subtype of the tumor (adenocarcinoma, signet ring carcinoma, and mucinous carcinoma), Grading, and stage.

Type of response in the study groups was determined according to response evaluation criteria in solid tumors (RECIST criteria) [6], where at least one measurable lesion should be measured in at least one dimension with the longest diameter ≥ 20 mm using conventional techniques or ≥10 mm using MSCT, all lesions were measured at baseline evaluations then at regular intervals of at least 3 monthly intervals with CT or MRI to measure target lesions with cuts ≥ 10 mm or 5 mm using spiral CT. all measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total to represent all involved organs (target lesions were selected based on their sizes *i.e.* longest diameter, and their suitability for accurate repeated measurements).

Different prognostic factors were also evaluated including number of pathological LN and number of excised LNs if done. The presence of obstruction or perforation at time of presentation, metastatic at presentation, perineural invasion and lymphovascular emboli, pretreatment carcinoembryonic antigen (CEA) levels were also determined. Detailed data about the lines of treatments the patients received were collected either concurrent chemoradiation (neo adjuvent or adjuvant) and systemic chemo therapy for adjuvant basis or metastatic cases.

Relapsing patterns whether local relapse and/or distant relapse and their sites were recorded.

*Blood sample analysis.* Peripheral blood samples obtained at the time of diagnosis before surgery were determined. The NLR was calculated from the preoperative blood sample by dividing the absolute neutrophil count by the absolute lymphocyte count.

The overall survival (OS), and disease free survival (DFS) were calculated.

## 4. Statistics

G power 3.1 program was used to calculate sample size, descriptive statistics in

the form of mean, standard deviation, median, standard error, were used, the relation between two scale variables was tested using Spearman correlation with r is the correlation coefficient, for the relations between scale and categorical variables non parametric tests were used in the form of Mann Whitney-U test and Kruskal Wallis test were used, Kaplan-Meier test used for calculation of survivals and for comparison between survival curves according different prognostic factors Log-Rank test was mainly used, Z-test was used for homogeneity of data. Roc curve was used for determination of NLR cut point, all data were analyzed using SPSS ver. 20 program, and any variable attained P value of ≤0.05 was considered significant.

## 5. Results

This study was a retrospective cohort one done in clinical oncology department, Assiut University Hospital and involved patients with pathologically confirmed cancer rectum presented to our department during the period from January 2012 to the end of 2014, these recruited patients were evaluated through their files to determine different objectives of our study. 123 patients were collected from our patients' files registry system, but only 100 patients were included because of incomplete files detected and subsequently omitted from our study, they were possibly referred to us for palliative RT only.

These patients' files were followed up for a period of 5 years, G power program was used to calculate the sample size for Bivariate correlation tests (the main test was correlation between OS, DFS and NLR) was 83 patients to detect correlation pH1 of 0.3 with $\alpha$ error of 0.05 and a power of 80% with P value of 0.05 and confidence interval of 95%, however our study power was 86.5% a little bit better than expected as described in the curve Figure 1.

The mean age for 100 patients with rectal carcinoma was 45 ± 43 years with slight female predominance as male to female ratio was 1:1.17, most patients had a good performance status ranging from PS1-2, however 18% of patients had PS3 who were included within the group of being metastatic at presentation, Table 1.
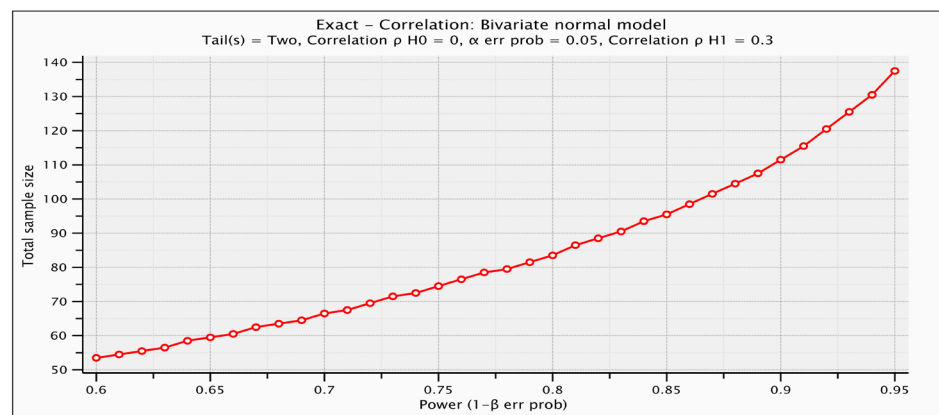


**Figure 1.** G power curve for our study.

Table 1. Demographic data of 100 patients with rectal carcinoma.

| Data | N = 100% |
|---|---|
| Age (mean ± SD) | 45.43 ± 16.39 |
| Min-max | 17 - 80 |
| Gender | |
| Male | 46 46% |
| female | 54 54% |
| Male: female ratio | 1:1.17 |
| ECOG-PS | |
| PS1 | 38 38% |
| PS2 | 44 44% |
| PS3 | 18 18% |

Data expressed as mean, SD, percentages.

As expected, the most common pathologic subtype was conventional adenocarcinoma with variable grades of differentiation with 56%, 11%, and 6% of our patients had G2, G1, and G3. Mucinous carcinoma with ≥50% of the tumor containing mucin was considered as G3 according to updated pathologic classification (ESMO, 2019) represented 10% of our patients, most patients were presented as locally advanced where T3, and T4a were elucidated in 44% and 32%, 55% of our patients were found to have positive LN while N0 was found in 19%, and Nx in 26% of patients due to absence of LN to be detected in postoperative specimens implicating that total mesorectal excision was not done, Table 2.

19 patients were presented to surgical oncology department by intestinal obstruction, CEA was done preoperatively in 42% of patients with a mean value of 37.18 ± 70.73, the diagnosis of rectal carcinoma was done through endoscopic biopsy in 74% of patients, followed by excisional biopsy in 17% of them, 54%, 15%, 8% of patients underwent low anterior resection (LAR), Rectosigmoidectomy, abdominoperineal resection (APR) ± metastatectomy respectively.

37% of patients received neoadjuvant chemoradiation with capecitabine mainly with a dose of radiation varied from 50.4 - 54 Gy while 35% of patients received adjuvant chemoradiation with a dose of radiation varied from 45 - 50.4 Gy, Table 3.

Hematologic parameters of 100 patients with rectal carcinoma were illustrated in the next table with mean value of NLR ratio was 4.488 ± 3.065, Table 4.

**Outcomes of treatments among 100 patients with rectal carcinoma:**

38% of patients achieved CR, 25% achieved PR, 15% achieved SD, and 22% of our patients achieved PD, Figure 2, the median and mean OS for different response groups were tabulated in Table 5, and graphed in Figure 3 to prove a significantly better OS among patients achieved CR.

1) - Response
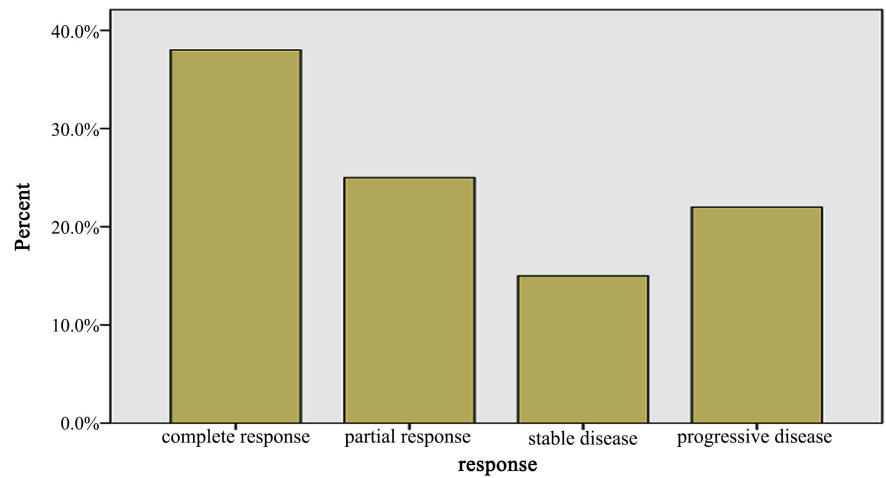
Relation between response and OS.
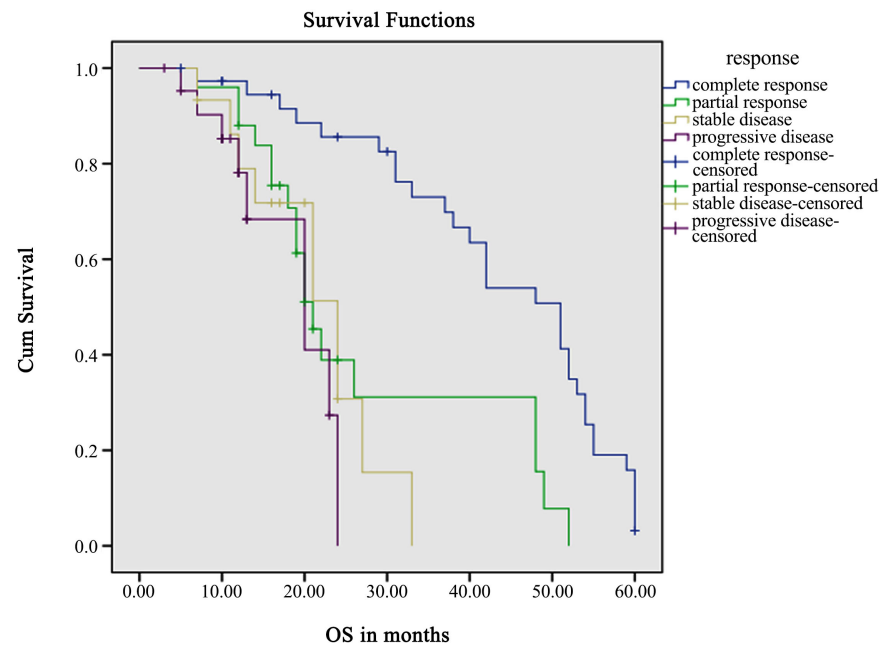
2) - Relapse

*Local relapse.*

Local relapse was developed in 39% of patients, with no significant difference in OS among those relapsed locally and those with no local relapse, (P = 0.518), **Figure 4** and **Figure 5**.



**Figure 2.** Distribution of response among patients showed that 38% of them achieved CR, 25% achieved PR, 15% achieved SD, and 22% of our patients achieved PD.



**Figure 3.** Overall survival according to different response patterns among 100 patients with rectal carcinoma with log-rank = 29.357, P < 0.0001.

| Overall Comparisons | | | |
|---|---|---|---|
| | Chi-Square | df | Sig. |
| Log Rank (Mantel-Cox) | 29.357 | 3 | 0.0001 |
| Breslow (Generalized Wilcoxon) | 20.826 | 3 | 0.005 |
| Tarone-Ware | 25.131 | 3 | 0.0005 |
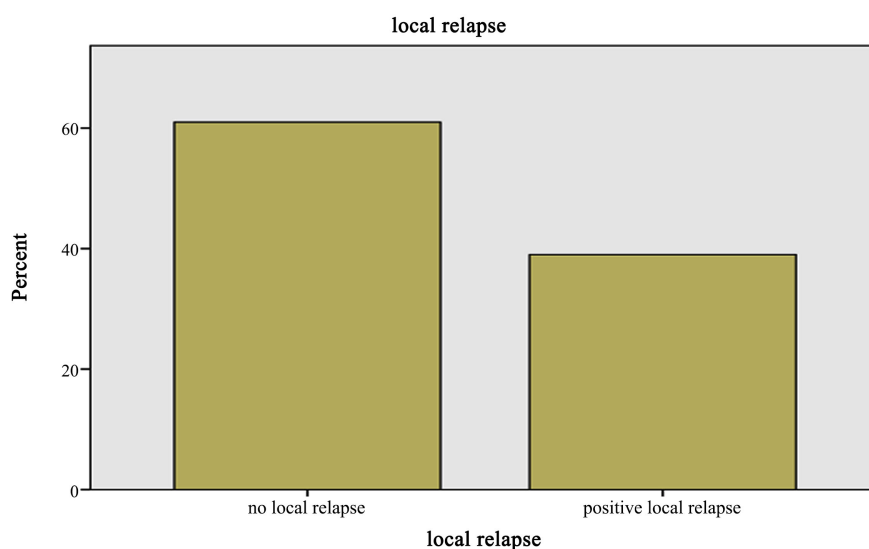
**Figure 4.** 61% of our patients did not develop local relapse while 39% developed local relapse.
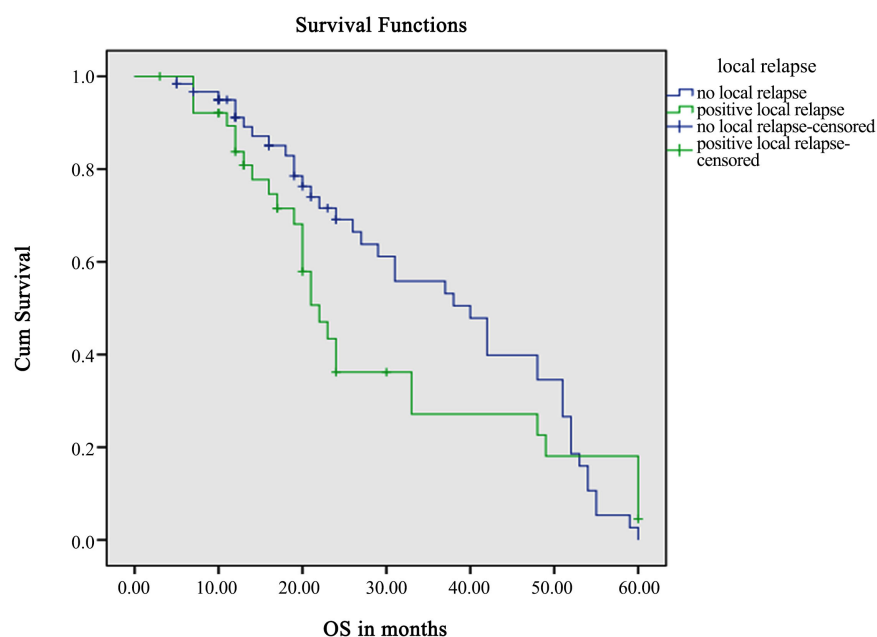


**Figure 5.** The median OS for patients without local relapse was 40 ± 5.387 (95% CI = 29.442 - 50.558), while the mean was 36.399 ± 2.427 (95% CI = 31.581 - 41.097), while for those relapsed locally; the median was 22 ± 1.88 (95% CI = 8.316 - 25.684), and the mean OS was 29.169 ± 3.358 (95% CI = 22.587 - 35.752), log rank = 0.417, P = 0.518.

| Overall Comparisons | | | |
|---|---|---|---|
| | Chi-Square | df | Sig. |
| Log Rank (Mantel Cox) | 0.417 | 1 | 0.518 |
| Breslow (Generalized Wilcoxon) | 3.434 | 1 | 0.064 |
| Tarone-Ware | 2.355 | 1 | 0.125 |

**Table 2.** Pathologic criteria of rectal carcinoma in our study patients.

| Pathological data | N% | |
|---|---|---|
| Pathological type | | |
| Conventional adenocarcinoma | 73 | 73% |
| Mucinous carcinoma | 10 | 10% |
| Signet ring carcinoma | 17 | 17% |
| Grade | | |
| G1 | 11 | 11% |
| G2 | 56 | 56% |
| G3 | 16 | 16% |
| G4 | 17 | 17% |
| T stage | | |
| Tx | 8 | 8% |
| T1 | 3 | 3% |
| T2 | 12 | 12% |
| T3 | 44 | 44% |
| T4a | 32 | 32% |
| T4b | 1 | 1% |
| N stage | | |
| N0 | 19 | 19% |
| Nx | 26 | 26% |
| N1a | 3 | 3% |
| N1b | 11 | 11% |
| N1c | 3 | 3% |
| N2a | 15 | 15% |
| N2b | 23 | 23% |
| Positive LN excised (mean ± SD) | 4.782 ± 5.096 | |
| Dissected LN (mean ± SD) | 13.584 ± 7.138 | |
| Positive LN to total LN dissected ratio (mean ± SD) | 0.313 ± 0.276 | |
| M stage | | |
| M0 | 65 | 65% |
| M1 (at presentation) | 35 | 35% |
| Positive LVI | 6 | 6% |
| Positive PNI | 5 | 5% |

Data expressed as number and percentage, mean ± SD.

**Table 3.** Clinical data of 100 patients with rectal carcinoma.

| Clinical data | N% | |
|---|---|---|
| *Obstruction at presentation* | 19 | 19% |
| *CEA* | | |
| Not done | 58 | 58% |
| Done | 42 | 42% |
| Mean ± SD | 37.18 ± 70.73 | |
| Range | 0.16 - 262 | |
| *Type of biopsy* | | |
| Endoscopic | 74 | 74% |
| Incisional | 3 | 3% |
| Excisional | 17 | 17% |
| Punch biopsy | 6 | 6% |

Continued

| | | |
|---|---|---|
| *Colostomy* | 36 | 36% |
| *Type of surgery* | | |
| No surgery | 18 | 18% |
| LAR | 54 | 54% |
| APR | 4 | 4% |
| APR with metastatectomy | 4 | 4% |
| Rectosigmoidectomy | 15 | 15% |
| Posterior pelvic exentration | 4 | 4% |
| Proctectomy | 1 | 1% |
| *Neoadjuvant chemoradiation* | 37 | 37% |
| *Adjuvant chemoradiation* | 35 | 35% |
| *Site of metastasis* | | |
| Liver | 32 | 32% |
| Lung | 7 | 7% |
| Brain | 3 | 3% |
| Multiple sites | 7 | 7% |

Data expressed as number, percentage, mean, and SD. LAR; low anterior resection, APR; abdominoperineal resection, SD; standard deviation.

**Table 4.** Hematologic parameters of 100 studied patients with rectal carcinoma at time of presentation.

| Hematologic parameter | Mean ± SD |
|---|---|
| HB | 11.062 ± 1.59 |
| WBCs | 6.39 ± 3.26 |
| Plt | 304.38 ± 143.91 |
| NLR ratio | 4.488 ± 3.065 |

Data expressed as mean ± SD, Plt; platelet, HB; hemoglobin, WBCs; white blood cells.

**Table 5.** Differences in OS according to response pattern.

| OS | CR | PR | SD | PD |
|---|---|---|---|---|
| **Median ± SE** | 51 ± 4.317 | 21 ± 1.471 | 24 ± 3.504 | 20 ± 4.295 |
| **95% CI** | 42.538 - 59.462 | 18.118 - 23.882 | 17.132 - 30.868 | 11.581 - 28.419 |
| **Mean ± SE** | 43.502 ± 2.584 | 27.823 ± 3.561 | 21.585 ± 2.286 | 18.385 ± 1.664 |
| **95% CI** | 38.437 - 48.567 | 20.844 - 34.803 | 17.105 - 26.065 | 15.123 - 21.647 |

Data expressed as mean ± SE, median ± SE, tests for calculation of survival was Kaplan-Meier, log-rank for comparison.

### Relation of overall survival to local relapse
### *Distant relapse*

Distant metastases developed in 38% of patients, and those patients had a significantly lower OS P < 0.001, Figure 6 and Figure 7.
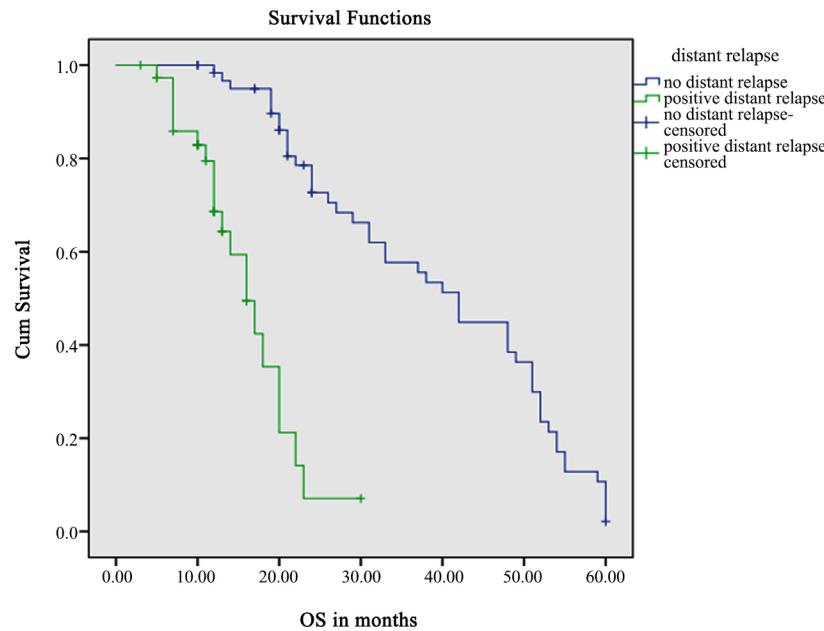
### *Relation between distant relapse and OS*
### 3) - Survival functions of the whole study patients
### *Overall survival*

The mean OS in our patients was 33.439 ± 1.996 months with 95% CI = 29.527 - 37.351, while the median OS was 31 ± 4.676 months with 95% CI = 21.836 - 40.164, Figure 8.
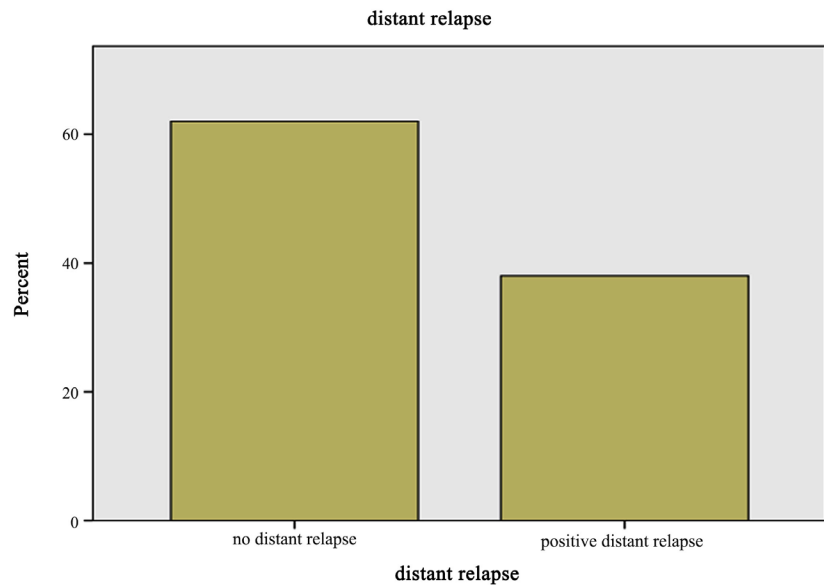
**Figure 6.** 62% of patients did not develop distant relapse while 38% developed distant relapse.



**Figure 7.** Showed the mean OS for those without distant relapse was 34.145 ± 2.049 with 95% CI = 30.130 - 38.161, while the median OS was 29 ± 3.028 with 95% CI = 23.064 - 34.936. The mean OS for those with distant relapse was 12.632 ± 0.916 with 95% CI = 10.835 - 14.428, while the median OS was 12 ± 0.507 with 95% CI = 11.006 - 12.994, log-rank = 75.429, P < 0.001.

| Overall comparisons | | | |
| --- | --- | --- | --- |
| | Chi-Square | df | Sig. |
| Log Rank (Mantel-Cox) | 44.413 | 1 | 0.001 |
| Breslow (Generalized Wilcoxon) | 40.237 | 1 | 0.005 |
| Tarone-Ware | 42.764 | 1 | 0.0005 |
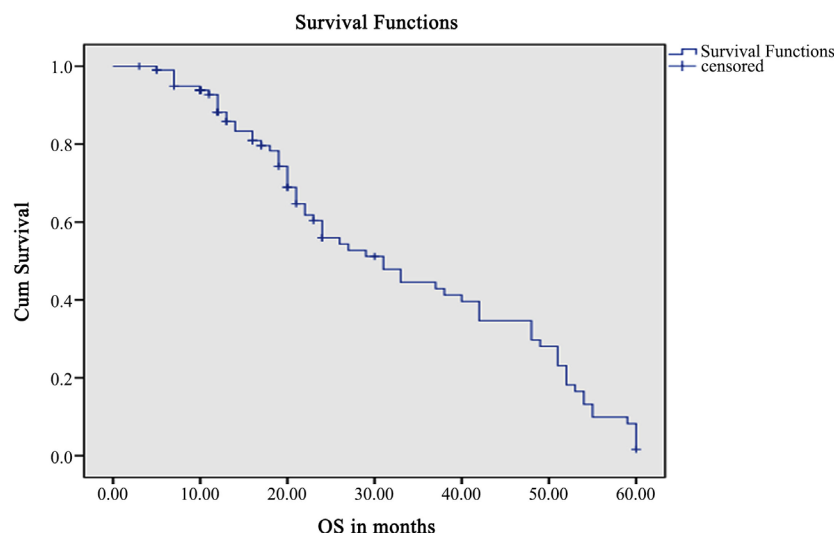
**Figure 8.** The mean OS was 33.439 ± 1.996 months with 95% CI = 29.527 - 37.351, while the median OS was 31 ± 4.676 months with 95% CI = 21.836 - 40.164.

### Disease free survival

The mean DFS of 100 patients with rectal carcinomas was 35.704 ± 2.328 with 95% CI = 31.141 - 40.268, while the median DFS was 40 ± 2.346 with 95% CI = 35.402 - 44.598, Figure 9.

### Prognostic factors for OS

Upon analyzing the possible prognostic factors for overall survival, we found significant negative correlations between OS and CEA (r = −0.394, P = 0.01), number of positive LN dissected (r = −0.399, P < 0.0001), positive LN/total LN dissected ratio (r = −0.374, P < 0.001), and NLR (r = −0.743, P < 0.0001) Table 6, Figures 10-12, also significant negative correlation between DFS and NLR as shown in Figure 13.

Furthermore, significant impact of ECOG-PS (P < 0.0001), N stage (P = 0.002), absence of metastasis (P < 0.0001), receiving adjuvant chemoradiation (P = 0.003), and absence of distant metastasis (P < 0.0001) on OS as illustrated in Table 6.

Roc curve was constructed to reach to a cut point for NLR and was calculated from this curve using its coordinates of sensitivity and 1-specificity to be around 4.5 then NLR values were separated into two groups NLR < 4.5 and >4.5 and survival data of our patients were compared accordingly, Figure 14.

### Roc curve and cutoff point for NLR
### OS and DFS according to NLR

Significantly patients with NLR < 4.5 had a better OS than those with NLR > 4.5 (*log-rank* = 49.231, *P* < 0.0001), in addition, patients with NLR < 4.5 had a significantly better DFS than those with NLR > 4.5 (*log-rank* = 24.900, *P* < 0.0001), Figure 15 and Figure 16, Table 7.

### Relation between NLR and response

Patients with complete response had a mean NLR of 2.811 ± 1.51, while those with partial response had a mean NLR of 4.959 ± 3.314, patients with stable dis-

ease achieved a mean NLR of 5.189 ± 3.353 and those with progressive disease attained a mean NLR of 6.364 ± 3.302, P value < 0.001, Figure 17. No significant differences in the mean NLR among patients with or without local relapse with mean NLR for those without relapse = 4.331 ± 3.197, while it was 4.735 ± 2.871 for those with local relapse, P value = 0.513, Figure 18. Significant differences in the mean NLR among patients with or without distant relapse with mean NLR for those without distant relapse = 3.367 ± 2.257, while it was 6.317 ± 3.347 for those with distant relapse, P value < 0.001, Figure 19.

**Table 6.** Different prognostic factors for OS detected in 100 studied patients with rectal carcinoma.

| Prognostic factor | r | Mean ± SD | P value |
|---|---|---|---|
| Age | −0.045 | | 0.664 |
| CEA | −0.394 | | 0.01 (s.) |
| NO of dissected LN | −0.178 | | 0.121 |
| NO of +ve LN | −0.399 | | 0.0001 (s.) |
| +ve LN/total LN dissected ratio | −0.374 | | 0.001 (s.) |
| NLR | −0.743 | | 0.0001 (s.) |
| Gender | | | |
| Female | NA | 24.389 ± 16.941 | 0.310 (n.s.) |
| Male | | 27.826 ± 16.636 | |
| ECOG-PS | | | |
| PS1 | | 36.289 ± 16.421 | |
| PS2 | NA | 20.114 ± 13.868 | 0.0001 (s.) |
| PS3 | | 18.500 ± 13.613 | |
| Pathologic subtype | | | |
| Conventional adenocarcinoma | | 26.068 ± 16.696 | |
| Mucinous carcinoma | NA | 28.300 ± 16.145 | 0.826 (n.s.) |
| Signet ring carcinoma | | 24.176 ± 18.625 | |
| Grade | | | |
| G1 | | 23.272 ± 15.640 | |
| G2 | NA | 25.642 ± 16.172 | |
| G3 | | 30.875 ± 18.351 | 0.608 (n.s.) |
| G4 | | 24.176 ± 18.625 | |
| T stage | | | |
| Tx | | 17.5 ± 17.163 | |
| T1 | | 11 ± 6.557 | |
| T2 | | 25.833 ± 20.341 | |
| T3 | NA | 28.250 ± 16.966 | 0.309 (n.s.) |
| T4a | | 26.843 ± 15.225 | |
| T4b | | 12 ± 0 | |
| N stage | | | |
| N0 | | 28.894 ± 18.719 | |
| Nx | | 22.961 ± 17.831 | |
| N1a | | 38.333 ± 29.143 | |
| N1b | | 26.454 ± 11.792 | |
| N1c | NA | 30 ± 19.697 | 0.002 (s.) |
| N2a | | 22.80 ± 12.689 | |
| N2b | | 18.391 ± 9.981 | |
| M stage | | | |
| M 0 | NA | 31.431 ± 18.154 | 0.0001 (s.) |
| M1 | | 15.828 ± 6.247 | |

Continued

| | | | |
|---|---|---|---|
| **Neoadjuvant chemoradiation** | | | |
| No | NA | 27.571 ± 17.097 | 0.209 (n.s.) |
| Yes | | 23.243 ± 16.157 | |
| **Adjuvant chemoradiation** | | | |
| No | NA | 22.123 ± 15.248 | 0.003 (s.) |
| Yes | | 33.114 ± 17.430 | |
| **Local relapse** | | | |
| No | NA | 27.787 ± 12.225 | 0.171 (n.s.) |
| Yes | | 23.128 ± 15.927 | |
| **Distant relapse** | | | |
| No | | 34.145 ± 16.131 | 0.0001 (s.) |
| Yes | | 12.631 ± 5.649 | |

Data expressed as mean ± SD, r = Spearman correlation coefficient, P value considered significant at level < 0.05, tests of significance included Mann-Whitney test, Kruskal-Wallis test, NA; not applicable, s.; significant, n.s.; non significant, LN; lymph node.

**Table 7.** OS and DFS among patients with NLR < 4.5 versus those with NLR > 4.5.

| Survival | OS | | DFS | |
|---|---|---|---|---|
| | NLR < 4.5 | NLR > 4.5 | NLR < 4.5 | NLR > 4.5 |
| Median ± SE | 31 ± 5.931 | 13 ± 1.085 | 39 ± 5.212 | 12 ± 0.756 |
| *95% CI | 19.375 - 42.625 | 10.872 - 15.128 | 28.785 - 49.215 | 10.518 - 13.482 |
| Mean ± SE | 34.544 ± 2.225 | 14.605 ± 1.155 | 35.795 ± 2.534 | 15.857 ± 2.631 |
| *95% CI | 30.183 ± 38.905 | 12.340 - 16.869 | 30.829 - 40.762 | 10.701 - 21.013 |
| Log-Rank | 49.231 | | 24.900 | |
| P-value | P < 0.0001 | | P < 0.0001 | |

Data expressed median, standard error, mean, tests for comparison through log-rank test using Kaplan-Meier methods for calculating and graphing OS and DFS.
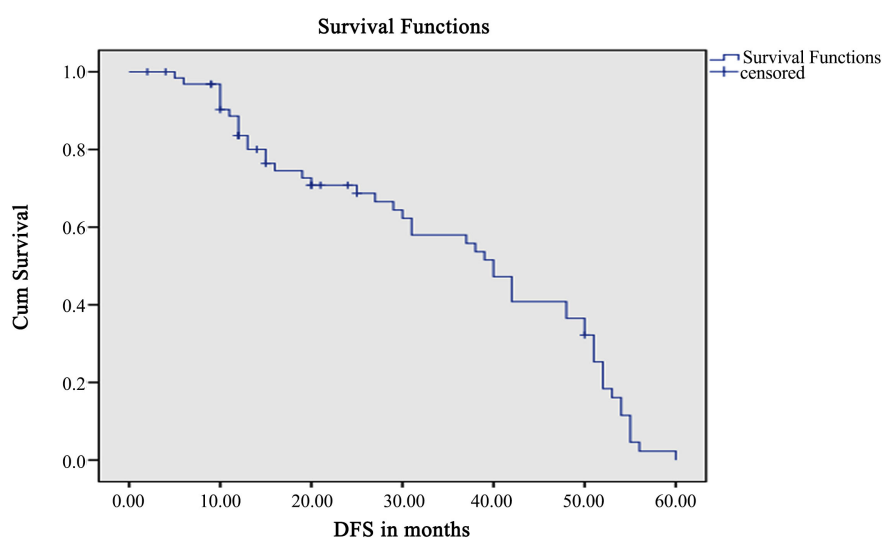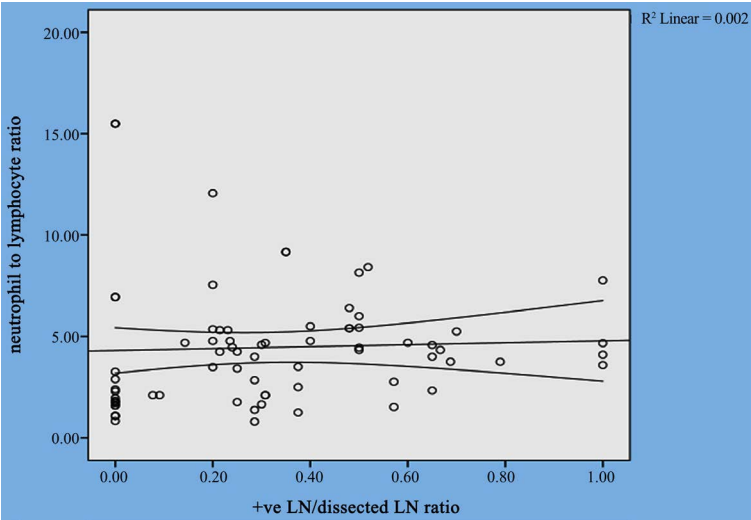


**Figure 9.** The mean DFS was 35.704 ± 2.328 with 95% CI = 31.141 - 40.268, while the median DFS was 40 ± 2.346 with 95% CI = 35.402 - 44.598.
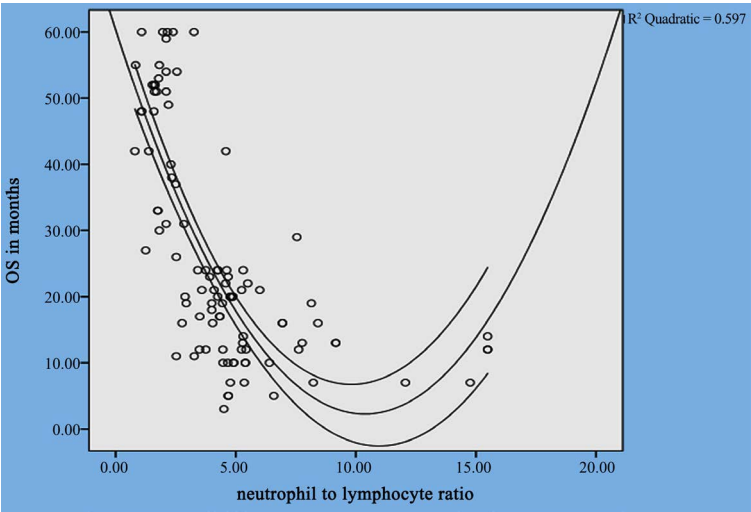
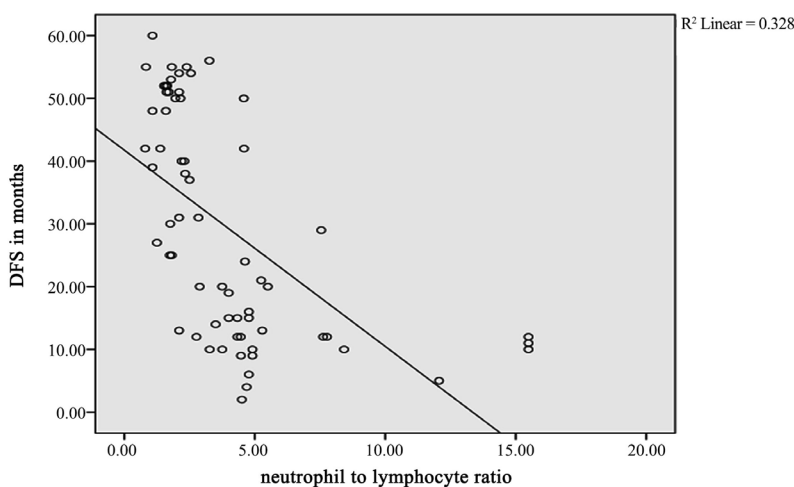**Figure 10.** Spearman correlation curve between NLR and OS with r = −0.743, P < 0.0001.
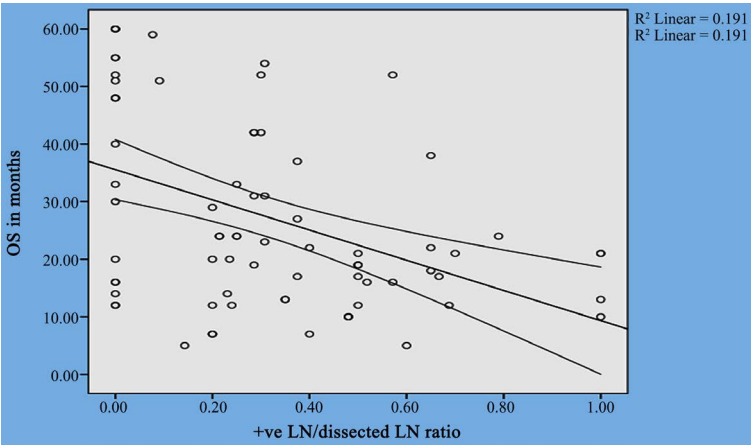


**Figure 11.** Spearman correlation between +veLN/total LN dissected ratio and OS with r = −0.374, P < 0.001.



**Figure 12.** Spearman correlation curve between NLR and +ve LN/total LN dissected showed mild positive correlation with r coefficient = +0.254 and P < 0.028.

### Hazard ratios of different prognostic factors of survival

Increasing NLR was associated with increasing the hazard of death by 1.186 over time but this effect was not significant (P = 0.248), however increasing the NO of positive LNs dissected increasing the hazard of death by 5.319 times for each year the patients had lived, for the ratio; the hazard was 0.000 (<1) this meant that the hazard of death decreased markedly by (100% − (100% × 0.180) = 82%) decreasing the ratio for each year the patient had lived (P = 0.037), **Figure 20**.



**Figure 13.** Spearman correlation curve between DFS and NLR showed negative significant correlation with r = −0.717, P < 0.0001.
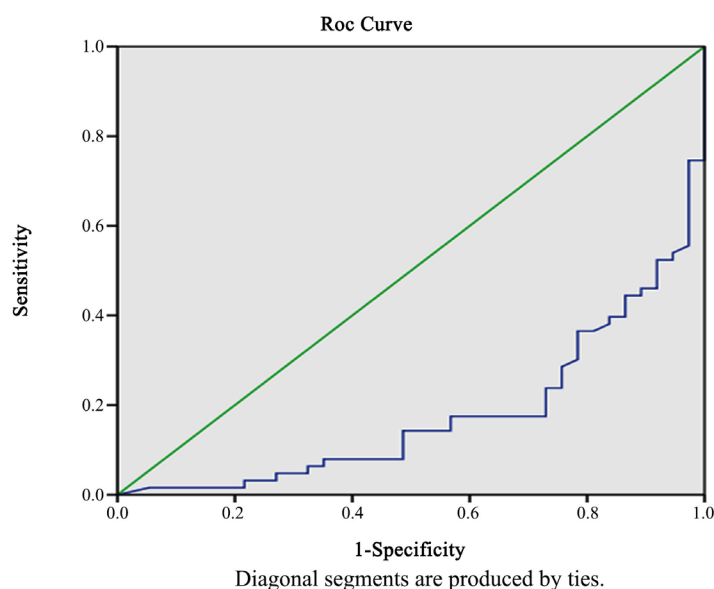


**Figure 14.** ROC curve with area under the curve equals 0.178 ± 0.042 with 95% CI = 0.096 - 0.260 and P < 0.0001, the point with highest sensitivity and specificity as determined from their related coordinates to be about 4.5 and this point was taken as cutoff point for NLR to stratify OS into two groups those with NLR < 4.5, and those with NLR > 4.5.
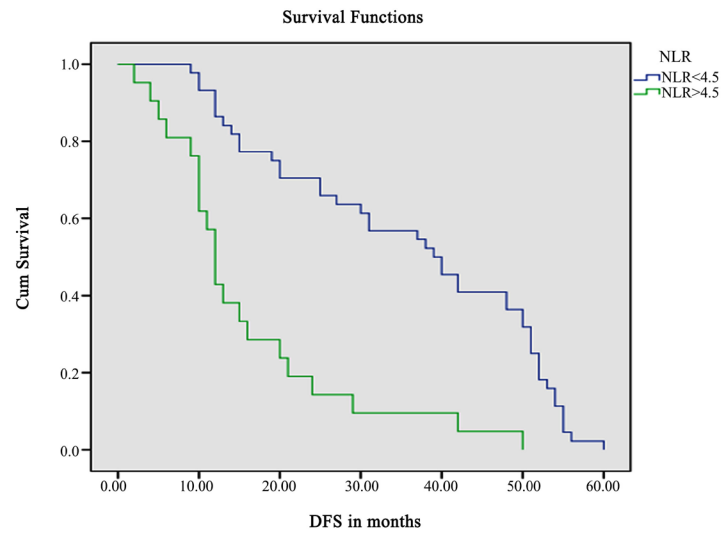
**Figure 15.** DFS curves for patients with NLR < 4.5 versus those with NLR > 4.5, P < 0.0001.
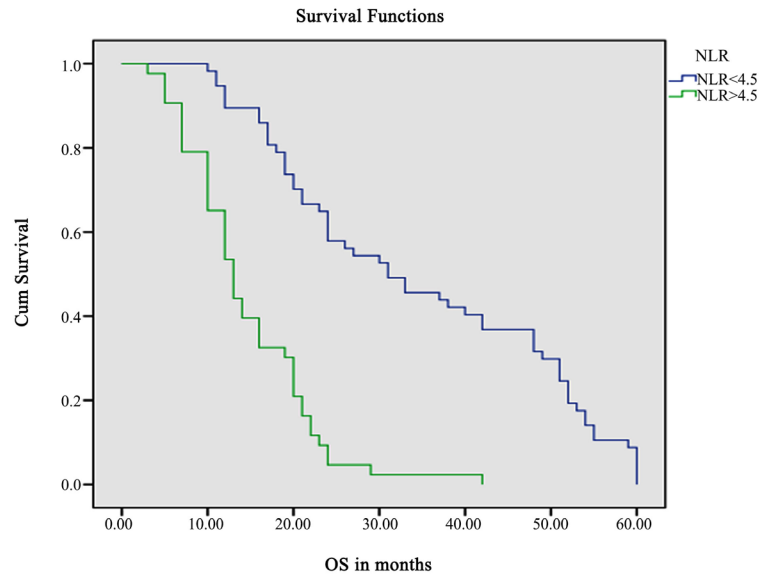


**Figure 16.** OS curve for patients with NLR < 4.5 versus those with NLR > 4.5, P < 0.0001.
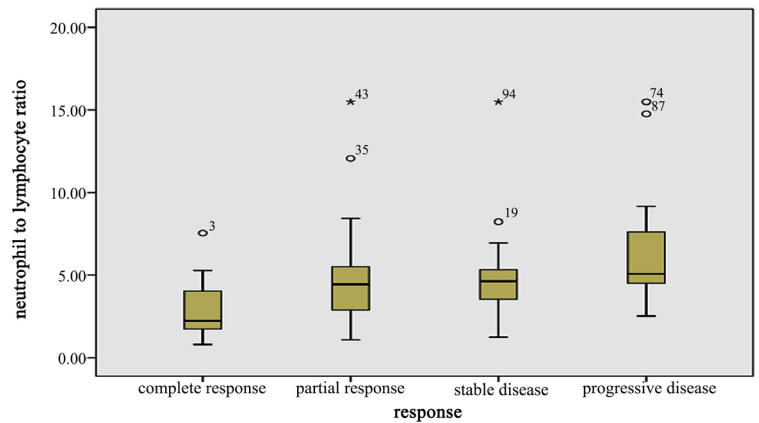


**Figure 17.** Boxplot of NLR according to pattern of response, test of significance was by Kruskal-Wallis test.
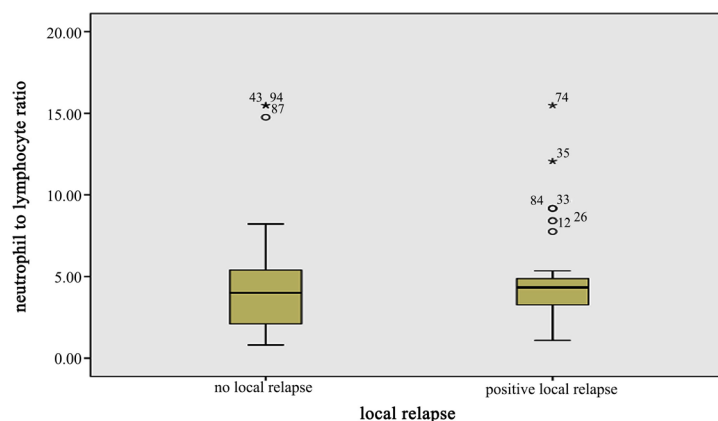
**Figure 18.** Boxplot for NLR according to local relapse, test of significance was Mann-Whitney P = 0.513.



**Figure 19.** Boxplot for NLR according to distant relapse, test of significance was Mann-Whitney P < 0.001.



**Figure 20.** Forest plot of hazard ratios for different prognostic factors of OS.

## 6. Discussion

Collectively, inflammatory responses play principal roles in tumor development, progression, immune surveillance, and response to therapy; this is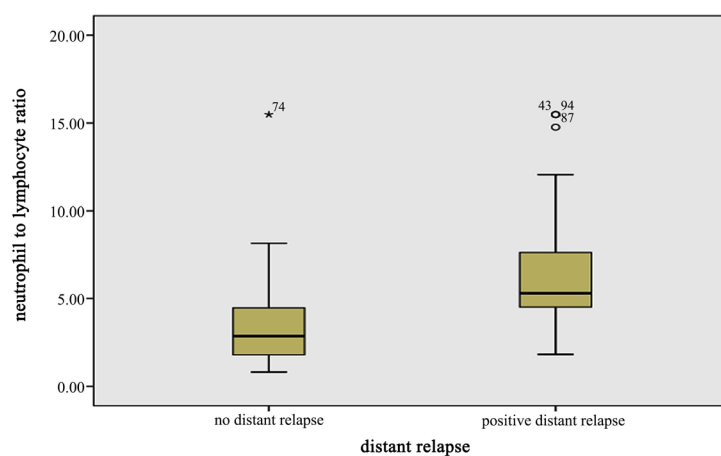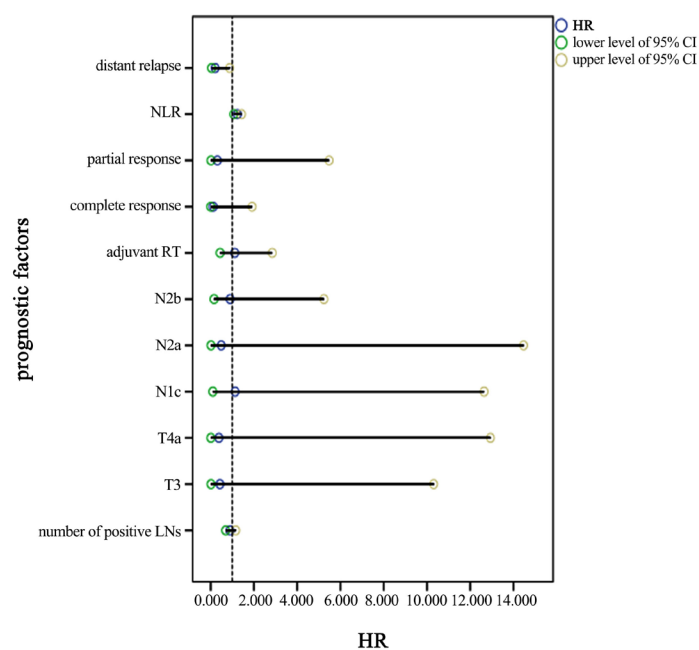 true for NLR where an elevated level of this inflammatory index has been reported as a worse predictor for many cancers (breast cancer, RCC, GC, HCC) including rectal carcinomas. This study was carried out at our department to accurately define the prognostic role of NLR in patients with rectal cancers.

Our results elucidated that the mean NLR for 100 patients with rectal carcinomas involved in this study was $4.488 \pm 3.065$ and was proved to be of 4.5 after doing Roc curve, NLR was negatively correlated with poor OS and DFS with r = −0.734, P < 0.0001 for the former and r = −0.717, P < 0.0001 for the later, in addition, it was correlated positively with positive LNs/total LNs dissected ratio with r = +0.254, P = 0.028. Increased NLR was associated with poor response to different lines of treatment (P < 0.0001), although increased NLR was not associated with local relapse but it was related to increased risk of distant metastases (P < 0.001).

The mechanism underlying the association between elevated NLR and poor outcome in rectal cancer still isn't fully understood. The first potential mechanism may lie in that inflammation contributes to the construction of "tumor microenvironment" by supplying different cytokines that active some tumor signaling pathways, such as nuclear factor kB (NF-kB), transducer and activator of transcription 3 (STAT3) [7]. These transcription factors possibly induce genes in premalignant cells to stimulate cell proliferation and survival, as well as angiogenesis, invasiveness, motility, chemokine, and cytokine production [8] particularly, interleukin 6 (IL-6) which is an important tumor-promoting cytokine and its tumor-promoting effect is mainly exerted via STAT3 [9].

Serum concentration of IL-6 has been reported to be increased in colorectal cancer and other 12 different cancer types and has been associated with tumor stage and adverse prognosis [10]. This is why NLR was associated mainly with distant metastases as detected in our study.

Second mechanism, lymphocytes can reduce tumor infiltration via a series of lymphocytes, activated T-cells, and natural killer cells, which have been shown to improve the survival for patients with cancer [11]. The dysfunction of T-lymphocyte, as one of the commonest kinds of tumor infiltrating lymphocyte, could result in immune escape of tumor cells [11]. In addition, inflammation promotes the accumulation of myeloid-derived suppressor cells and regulatory T-cells (Tregs), both of which down regulate the immune surveillance and anti-tumor immunity [12].

In general, elevated NLR caused by neutrophlia or lymphopenia, indicates enhanced inflammatory response and suppression of immunity. As tumorigenesis and tumor progression often take decades, NLR as a predictor can be used to tailor the personalized treatment strategy.

In a study of 200 patients undergoing curative resection for rectal cancer, NLR

was shown to be a prognostic biomarker of OS [13]. Toiyama *et al.*, proved in their study that NLR was significantly correlated with poor OS [14]. Our results completely agreed with the previous two studies.

The study of Carruthers reported that higher NLR was found to be correlated with all treatment outcomes including OS, DFS, and time to local relapse [15], our study was partially comparable to Carruthers in that NLR was not associated with local relapse.

However, NLR is a sensitive parameter with low specificity. An elevated NLR could be induced by many non-malignant conditions, such as infections and medications. So these factors might be considered as a confounding factor for accurate interpretation of our results.

A total of six trials comprising 857 patients were evaluated in a meta-analysis to report HR of NLR for OS and found that a pooled HR of 13.408 (95% CI: 4.896 - 36.715) for NLR [16], HR of NLR for OS in the present study was 1.186 (95% CI = 0.888 - 1.582) although it was much lower than the previous analysis but more than one implicating that elevated NLR was associated with poor OS, in addition, the cut off values for different studies in this meta-analysis varied from 2 - 5.

Jinwen Shen *et al.* [17] defined the cutoff value of NLR in their study to be 2.7 ± 1.5 and they found that it didn't correlate with any clinico-pathologic characteristics except age; furthermore it didn't correlate with any survival outcomes, our results didn't come into alignment with that of Jinwen Shen possibly as this study dealt with those patients with locally advanced cancer rectum only who were decided to be treated with neoadjuvant CRT.

The cutoff value for NLR in Corrado Pedrazzani *et al.* was 3.5 ± 1.8 and high NLR (>3.5) was correlated with increased age (p = 0.026), advanced pT (p < 0.001), TNM stage (p < 0.001), metastatic disease at presentation (p < 0.001), elevated CEA (p = 0.017), and lower 5-year OS (p < 0.001), but no impact of high NLR on tumor grade, PNI, LVI, furthermore, high NLR was found to be independant predictor of 5-year survival in Cox regression model [18], we couldn't say that we were through with this study as high NLR was not correlated with age, pT, TNM stage, but correlated significantly with OS, however this impact on the OS lost when compared to the number of positive LNs, and positive LNs/dissected LNs ratio in multivariate Cox regression hazard model in our study.

The meta-analysis of Xuan *et al.* [19] that evaluated the relation between NLR and response to neoadjuvant treatment in solid tumors including rectal cancer where lower NLR was associated with higher odds of pCR (OR = 2.01, 95% CI, 1.14 - 3.55, $I^2$ = 55%) after neoadjuvant chemoradiation with statistical significance, in addition, The pooled results of the NLRs for OS among different tumor subgroups in this analysis showed a statistical association with OS in rectal cancer (HR = 1.93, 95% CI, 1.17 - 3.19), in the current study; we didn't correlate between NLR and the response to different lines of treatment, instead, we tried

to find a relation between chemoradiation given pre-, or post-operative and this hematologic parameter, and we found a statistical association between adjuvant chemoradiation but not with neoadjuvant chemoradiation (P = 0.032).

In a systematic review including over 10,000 patients with advanced rectal cancer, an elevated pretreatment NLR has been found to correlate with poor cancer-specific and overall survival [20], Accordingly, in our study cohort, patients with an elevated pretreatment NLR (>4.5) showed an inferior OS than those with NLR < 4.5 (P < 0.0001). This cut-off was in line with the previously reported cut-off values for NLR in different studies and meta-analyses [15] [20] [21].

In Egypt, colorectal cancer ranked the 7th commonest one to represent about 3.47% of all male cancers, and 3% of all female cancers [22], colorectal cancer was diagnosed at a mean age of 53 ± 14.326 years which was a decade younger than the corresponding age in USA. Slight female predominance was evident in a recent Egyptian study [23]. The estimated median OS in Islam *et al.* was 24 months with 44 months in stage I versus 8 months in stage IV, while DFS was 12 months that varied from 24 months in stage I to zero in stage IV [23]. Consistent with the previous study the mean age of our study was 45.43 ± 16.39 with female predominance (m/f = 1.17:1), 35% of our patients presented as stage IV versus 22% of the previous study, the median OS of our study was better than Islam *et al.* (31 ± 4.676 months), subsequently, DFS was obviously better than the previous study (40 ± 2.346) implicating adherence of our department to standardized treatment guidelines.

According to Chau *et al.* [24], NLR is unlikely to have any prognostic significance in metastatic patients and may have predictive importance for the outcomes from chemotherapy in such patients and this was justified for further investigation, however, we didn't fall in with Chau *et al.* because higher prevalence of cancer associated inflammation in metastatic patients was evident simply as a result of widespread nature of the disease, so it is likely for NLR to be correlated with the outcomes in these patients (P = 0.019).

We detected a negative association between NLR and the number of patients received adjuvant chemoradiation and indirectly with favorable OS, subsequently NLR levels might assist in defining patients more likely to benefit from adjuvant treatment in those with non metastatic cancers (P = 0.032), an issue needs further investigation, and this was contrary to Lucy Jankova *et al.* [25].

CEA mediates metastasis by binding to its receptor, hnRNP, in the liver, A meta-analysis showed that low preoperative CEA level (less than 50 ng/mL) was associated with a significantly better OS following resection of liver metastasis. Another meta-analysis using a cut-off of 200 ng/mL for CEA to stratify patients into 2 groups, also demonstrated improved survival time with lower CEA level [26]. Consistent with the previous study we declared a negative correlation between OS and high level of CEA.

Hyunjung Kim *et al.* [26] found positive association between high NLR

(>1.98) with tumor grade (P = 0.048), and high CEA (≥100 ng/ml, P = 0.005) in patients with CRLM, we agreed with the previous study in that positive correlation between high NLR and high CEA (P = 0.037) was evident in our study.

The cutoff value of NLR in our cohort study was higher than that reported in many studies (around 2.5), possibly due to heterogeneity of our patients (early, locally advanced, metastatic, with and without surgery, heterogeneity of treatments), and small sample size, so it is better to be validated in a large scale prospective study.

In summary, high pretreatment NLR correlated with poor response to treatment, poor pathologic features, and poor OS and DFS. Further it may allow optimization for selecting patients who will need further treatment, such as inflammatory and immune modulation, which could improve their long-term outcomes.

## 7. Conclusion

Elevated pre-treatment NLR is a significant independent predictor of shorter survival in patients with rectal cancer. This parameter is a simple, easily accessible laboratory test for identifying patients with poorer prognosis.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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