

## ORIGINAL ARTICLE

## NEUTROPHIL TO LYMPHOCYTE RATIO AS A PREDICTOR OF SEVERITY IN COLORECTAL ADENOCARCINOMA

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**Background:** Colorectal cancers are slowly developing cancers of which more than 95% are adenocarcinomas, beginning in the mucus-producing glands lining the colon and rectum. In Pakistan, colorectal carcinoma is ranked as the seventh most common malignancy in men and the ninth most common in women with a male to female ratio of 9 to 1. This study aimed at investigating Neutrophil to Lymphocyte Ratio (NLR) as a potential marker for predicting severity of disease in terms of tumour histological grade in patients with pre-operative colorectal adenocarcinoma. **Methods:** Retrospective cross-sectional study design was adopted and this study was conducted at the Department of Pathology, Pakistan Institute of Medical Sciences Islamabad. Sixty patients of all age-groups and both genders, diagnosed as colorectal adenocarcinoma on histopathological examination of resected specimens, were selected by consecutive non-probability sampling. Separately, 60 healthy subjects, age and sex-matched, were selected as control. **Results:** Results revealed that the most common age group was 41–60 years showing 29 cases (48%) followed by the age group 61–80 years with 17 cases (28%). The most common site was the rectum having 24 cases (40%) followed by the right hemicolon with 13 cases (21.7%). The mean of neutrophil to lymphocyte ratio rose in direct proportion to the grade of colorectal carcinoma, showing a mean value of 4.5 in well differentiated low grade carcinoma, 5.0 in moderately differentiated and 6.0 in high grade poorly differentiated carcinoma. All patients had higher total leukocyte count, higher absolute neutrophil count, higher total neutrophil percentage and higher NLR as compared to their normal healthy counterparts. **Conclusion:** It is concluded that the NLR is directly proportional to tumour grade so it can be used preoperatively to assess whether the tumour is advanced so that it can be dealt with accordingly. This ratio can also be used as an independent screening marker for colorectal carcinoma since it shows very low levels in normal colonic epithelium.

**Keywords:** Colorectal carcinoma; Neutrophil to lymphocyte ratio; Absolute neutrophil count

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## INTRODUCTION

Colorectal Cancers (CRC) are slowly developing cancers of which more than 95% are adenocarcinomas, beginning in the mucus-producing glands lining the colon and rectum.<sup>1</sup> It accounts for approximately 10% of cancer-related fatality in the West.<sup>2</sup> In 2018, the incidence was approximately 1,096,000 new cases of colon cancer and about 704,000 new cases of rectal cancer.<sup>1</sup> A meta-analysis from Pakistan showed the prevalence ranged from 4 to 6% with an overall prevalence of 5%.<sup>3</sup> In Pakistan, colorectal CA is ranked as the seventh most common malignancy in men and the ninth most common in women with a male to female ratio of 1.9:1. A study from Karachi from 1995 to 1997 showed that incidence of CRC was 3.9% of all the cancers diagnosed in this period.<sup>4</sup>

Risk factors include frequent consumption of red and processed meat, reduced dietary fiber intake, alcoholism, obesity, high sugar intake, high saturated fat intake, cigarette smoking, sedentary lifestyle, and presence of pre-existing pathological conditions such as inflammatory bowel disease<sup>5</sup>. Prognostic factors associated with CRC include TNM staging and morphological characteristics e.g., tumour grade, histological type, depth of invasion, perineural invasion, venous invasion, tumour budding, immunological response of host and molecular markers, among others<sup>6</sup>.

Tumour grade is usually considered as a prognostic variable independent of stage, and higher grade is linked with greater disease severity and poor patient survival. Several studies have established that a 2-tiered grading system, in which well and moderately differentiated tumours (up to 50% gland formation) are classified as low grade

and poorly differentiated (<50% gland formation) as high grade improves prognostic implication.<sup>7</sup>

Complete blood count (CBC) is a routine, inexpensive laboratory test giving useful information about the patient's formed blood elements that may be employed in diagnosis and prognosis of many diseases.<sup>8</sup> Neutrophil to Lymphocyte Ratio (NLR), the quotient of the absolute counts of neutrophils and lymphocytes, is a marker of systemic inflammation readily obtained from CBC. Neutrophilia is a feature of cancer-associated chronic inflammation and neutrophils are documented to have a role in tumour-promotion, immunosuppression, production of cytokines responsible for tumour progression and promoting metastasis by suppressing the activity of cytotoxic T cells. Neutrophilia is generally accompanied by relative lymphopenia, expressing a substantial deterioration in the cell-mediated adaptive immunity. Thus, NLR represents the unfavourable effects of neutrophilia and loss of lymphocyte-mediated adaptive immunity.<sup>9</sup>

Lymphocyte Ratio depicts a predictive role in the prognosis of acute and chronic inflammatory processes, even when the white blood cell count is within normal range. It has been concluded by a recent meta-analysis that a high NLR is an independent factor associated with poorer overall survival in solid tumours (colorectal, gastroesophageal, hepatocellular, ovarian, and pancreatic carcinoma), haematological malignancies and a wide range of non-malignant disorders like renal or hepatic dysfunction, metabolic syndrome, hypertension, diabetes mellitus, abnormal thyroid function, local or systemic infection and inflammatory diseases.<sup>8</sup>

The objective of our research is to investigate Neutrophil to Lymphocyte Ratio (NLR) as a potential marker for predicting severity of disease in terms of tumour grade in pre-operative patients with colorectal adenocarcinoma. Very few studies have been done in this regard in our country. The rationale of this study is to evaluate the utility of NLR as an adjunct tool to predict the histopathological grade in patients suffering from colorectal cancer, and indirectly its early or advanced nature, which may help the surgeon in preoperative prognostication of tumour, family counselling and management decisions.

## MATERIAL AND METHODS

It was a retrospective cross-sectional study conducted at the Department of Pathology, Pakistan Institute of Medical Sciences Islamabad. After approval from the Hospital Ethics

Committee, 60 patients of all age-groups and both genders diagnosed as colorectal adenocarcinoma on histopathological examination of resected specimens were selected by consecutive non-probability sampling. Similarly, 60 age and sex-matched healthy subjects were selected as control. The CRC patients were histologically graded as under:

Grade 1: Well differentiated tumour showing more than 95% gland formation

Grade 2: Moderately-differentiated tumour showing 50–95% gland formation

Grade 3: Poorly-differentiated tumour with less than 50% gland formation

Grade 4: Undifferentiated tumour showing no gland formation or mucin production, and no evidence of squamous or neuroendocrine differentiation

Histological grade of tumour was based on microscopic evaluation by consultant histopathologist. Severity of the disease was based on the tumour grade, and was directly related to it. Confidentiality of personal information was maintained. All malignancies not belonging to adenocarcinoma subtype and metastatic tumours from non-colorectal regions were excluded.

Patient's demographic data, registration number, site of tumour, grade of tumour and complete blood count findings including absolute counts of neutrophils and lymphocytes, and neutrophil-lymphocyte ratio (calculated as the ratio of absolute count of neutrophils (expressed per microliter) to the absolute count of lymphocytes (expressed per microliter) from the electronic laboratory records preceding the surgical biopsy procedure were noted down on a proforma. The data was entered and analyzed using SPSS version 20. Descriptive statistics were used to measure qualitative and quantitative variables. Categorical variables such as gender, site of tumour, histological grade of tumour was expressed in terms of frequency and percentage. Quantitative variables such as age of patient, TLC, ANC, ALC and NLR were measured as mean  $\pm$  standard deviation. Quantitative variables were represented as histogram and qualitative variables as bar or pie charts. Stratification was done based on age, gender and grade of tumour. Post-stratification, independent sample t test for age and gender; and ANOVA test for histological grade was applied to assess differences in haematological parameters studied. A *p*-value of <0.05 was taken as significant.

**RESULTS**

In our study, we had 60 patients, with a male to female ratio of 1.9:1, as shown in figure-1.

The ages of subjects ranged from 26 to 82 years with a mean age of 53.43±14.3 years.

The most common age group among the patients was 41–60 years showing 29 cases (48%) followed by the age group 61-80 years with 17 cases (28%). The age group 21–40 years had 11 cases (18%) while age group greater than 80 years had only 3 cases (5%). There were no patients in the age group 0–20 years.

Based on the site of colorectal carcinoma, we grouped all the cases into 5 categories, including right colon, left colon, recto-sigmoid, rectum, and the unlabelled cases (specific site not mentioned with the specimen received), as shown in the figure-2.

The most common histology was well differentiated adenocarcinoma showing 26 cases (43%) followed by both the moderately and poorly differentiated carcinomas with 17 cases (28%) each.

Coming on to gender distribution among the different tumour grades, we observed a greater percentage of males in all the three categories as shown in figure-3.

When we compared the tumour grade with age groups, specifically the age groups above and below 50 years, we found a significant difference between the two, as shown in Table-1.

This shows that patients with age less than 50 years showed a higher count of poorly differentiated carcinomas as compared to those with age greater than 50 years.

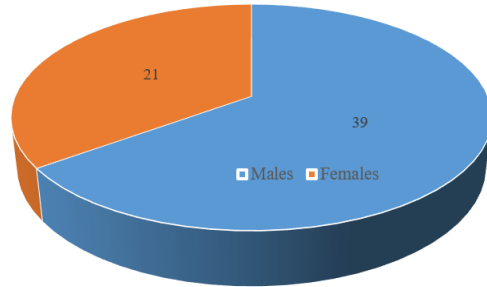
The haematological parameters included were total leukocyte count (TLC), neutrophil percentage, lymphocyte percentage, absolute neutrophil count (ANC), absolute lymphocyte count (ALC) and neutrophil to lymphocyte ratio (NLR). To compare these parameters between healthy and diseased subjects, we applied independent sample t test for each of the individual parameters, which showed that all the variables were significantly different between the healthy individuals and those with CRC as shown in Table-2.

Comparison of haematological parameters in males and females showed that most of the parameters were higher in females as compared to males, including TLC, lymphocyte percentage, ANC and ALC. On the other hand, the NLR was seen to be higher in males along with the neutrophil percentage as shown in Table-3. However, statistical association between gender and haematological parameters was not significant.

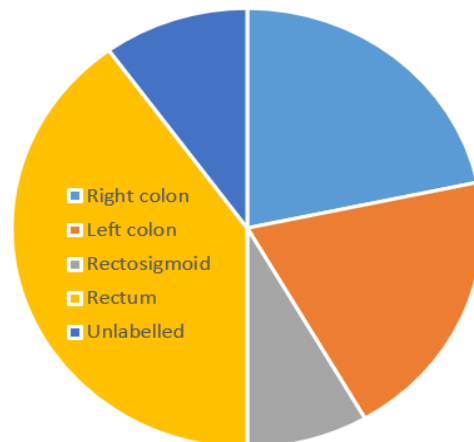
In order to correlate the grade of colorectal carcinoma and mean NLR, we applied one-way

ANOVA test, which showed that the mean NLR rises in direct proportion to the grade of colorectal carcinoma. However, no statistically significant association between the two variables was noted, as demonstrated in Table-4.

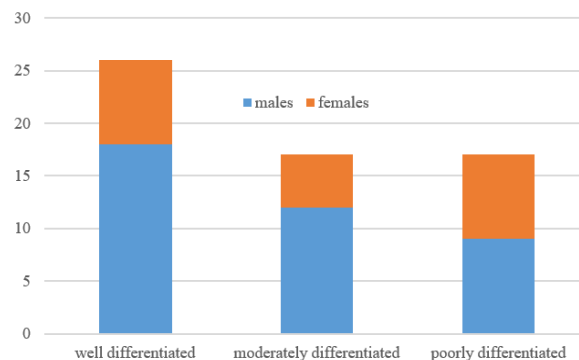
Coming to the age groups and NLRs, we found a significant association ( $p=0.028$ ) between the two groups, with the age above 50 years showing mean NLR of 4.1 and the age below 50 years showing a mean NLR of 6.8, as shown in Table-5.



**Figure-1: Male to female ratio**



**Figure-2: Sites of tumour**



**Figure-3. Tumor grades in males and females**

**Table-1: Association between tumour grade and age groups**

		Tumour grade			Total	p-value 0.038
		Well differentiated	Moderately differentiated	Poorly differentiated		
Age	Less than 50 years	9	4	11	24	
	greater than 50 years	17	13	6	36	
Total		26	17	17	60	

**Table 2: Comparison of haematological parameters between healthy patients and those with CRC**

Hematological parameters	Normal subjects (mean values)	CRC patients (mean values)	p-values
Total Leukocyte count (TLC)	7.9±2.2	9.0±3.2	0.03
Neutrophil %	60.8±9.6	71.3±9.0	<0.001
Lymphocyte %	29.2±8.8	18.9±7.2	<0.001
Absolute neutrophil count (ANC)	4.9±1.7	6.5±2.8	<0.001
Absolute lymphocyte count (ALC)	2.3±0.8	1.6±0.7	<0.001
Neutrophil to Lymphocyte Ratio (NLR)	2.4±1.2	5.2±4.7	<0.001

**Table-3: Haematological parameters of CRC patients based on gender**

GENDER		TLC	Neutrophil %	Lymphocyte %	ANC	ALC	NLR
MALE (n=39)	Mean	8.8	72.2	18.2	6.4	1.5	5.4
	Std. Deviation	3.5	9.3	6.7	3.1	0.7	5.1
FEMALE (n=21)	Mean	9.6	69.7	20.1	6.7	1.8	4.8
	Std. Deviation	2.5	8.4	8.1	2.3	0.8	3.8
Total (n=60)	Mean	9.0	71.3	18.9	6.5	1.6	5.2
	Std. Deviation	3.2	9.0	7.2	2.8	0.7	4.7
p-value		0.37	0.30	0.35	0.66	0.12	0.65

**Table-4: Association of tumour grade and mean NLR**

	No. of cases	Mean NLR	Std. Deviation	p-value
Well differentiated	26	4.5	3.4	0.4
Moderately differentiated	17	5.0	2.9	
Poorly differentiated	17	6.4	7.1	
Total	60	5.2	4.7	

**Table-5: Mean NLR based on age**

Age	N	Mean NLR	Std. Deviation	p-value
Less than 50 years	24	6.8	6.6	0.028
greater than 50 years	36	4.1	2.2	
Total	60	5.2	4.7	

**DISCUSSION**

Colorectal carcinoma is one of the major global public health concerns.<sup>10</sup>In this study, we aimed to find the utility of a simple parameter neutrophil to lymphocyte ratio, a quotient of the absolute counts of neutrophils and lymphocytes in blood, as a predictor of severity in colorectal cancer patients, and correlated it with the histological grade of cancer.

Cross-tabulation of the haematological parameters with the tumour grade, showed a positive correlation between the tumour grade and NLR. As we move from well differentiated to poorly differentiated pathology, the mean NLR gradually becomes higher. However, statistical significance was not observed (p-value=0.4), which may be attributed to small sample size. Previous studies have also showed that a high NLR in CRC is associated with a poor prognosis and severe disease.

Pine *et al*<sup>11</sup> demonstrated that in CRC, higher ratio predicts lower overall survival and disease-free survival; and is associated with a more aggressive tumour phenotype. Haram *et al*<sup>12</sup> from

Ireland observed worse prognostic signs in patients above a mean NLR cut off value of 5. These patients were reported to have higher tumour grade and stage along with poor differentiation and thus, lesser overall chances of survival. Similarly, Fuyan Han *et al*<sup>13</sup> from China kept a cut off value of 2.06 and reported the rising of NLR with worsening of the tumour grade and stage. Zhang *et al*<sup>14</sup> also observed that cases with NLR above the cut off value 5 were associated with decreased survival.

The NLR is a qualitative measure of inflammation in tissues and high NLR refers to a higher rate of inflammation with high neutrophils as compared to lymphocytes. The higher neutrophil count leads to an increase in chemokine production including IL-1, IL-6 and TNF all of which contribute to tumour progression. As we move from well differentiated to poorly differentiated cases, the neutrophilic infiltrate increases with the tumour grade leading to an increase in NLR. Özgehan *Get al*<sup>15</sup> found NLRs to be statistically higher in patients with T3 and T4 tumours than in those with T1 and T2

tumours (mean: 5.261 vs. 4.499,  $p=0.010$ ). They also showed statistically higher NLR values in the N1 and N2 groups than in the N0 group (mean: 6.597 vs. 4.501,  $p<0.001$ ). In addition, NLRs were statistically higher in M1 patients than in M0 patients (mean: 8.261 vs. 5.158,  $p=0.004$ ). They concluded that in the preoperative period, NLR was found to be a valuable predictive parameter for tumour staging in patients with colorectal cancer, thus informing the surgeon as to the type of tumour they will encounter upon opening the abdomen.

Moving on to the other variables, we observed a male to female ratio of 1.9 to 1 showing 65% males. Similarly, when comparing this finding with international studies, we observe a higher incidence of colorectal carcinoma in males as compared to females as demonstrated by Wanbinet *al* from China<sup>16</sup>, Khalil *et al* from Iraq<sup>17</sup> and Galceran *et al* from Spain<sup>18</sup> who reported 50%, 60.2% and 60% males respectively. There are various reasons behind this gender discrimination, one of which is that female sex hormones, including oestrogen and progesterone have been known to provide protective effect against the development of colorectal carcinoma.<sup>19</sup> Similarly, women taking hormone replacement therapy and oral contraceptive pills are found to have lesser chances of acquiring CRC.<sup>20</sup> A study done in Egypt in 2020 showed that the expression of oestrogen receptor (ER) is associated with smaller tumour size and that ER/PR (Progesterone Receptor) expression is associated with better survival and outcome.<sup>20</sup>

Mean age of patients in this study was 53.4±13 years while the most common age group was 41–60 years. This is slightly lower than the ages reported in other studies, by Sagario *et al* from Mexico<sup>21</sup>, Diaz de Arco *et al* from Spain<sup>22</sup>, Wanbinet *al* from China<sup>16</sup> and Remo *et al* from Italy<sup>23</sup>, which reported the mean ages of 59.1 years, 65 years, 62.6 years and 55 years respectively. Various factors play a role in the rising trend of CRC among the lower age groups in Eastern countries, including sedentary lifestyle and higher intake of spicy foods and red meat by the people of this region. On the other hand, Alipur from Canada<sup>24</sup> and Berger *et al* from USA<sup>25</sup> reported the ages of 68 years and 66 years which shows a higher trend of the disease in advanced age groups in the West.

Regarding tumour location, we observed that rectum was the most common site of colorectal carcinoma among our patients (24%) followed by the right hemicolon (21.7%). This compares favourably with Sharjeel *et al* from USA<sup>26</sup> and Anup Sunil *et al* from India<sup>27</sup> that also showed rectum to be the most common site of CRC. However, variations in site are commonly seen as Mima *et al* from USA<sup>28</sup> observed

right colon to be the most frequent site of tumour, appearing in 49% of their cases.

The tumours were graded into well, moderate and poorly differentiated categories out of which the highest number of cases in our study was in the well differentiated group (43%). This means that most of our patients at the time of presentation had a low tumour grade, which is a good sign of prognosis as compared to the tumours which presented at a higher grade and hence had lesser chances of survival. When comparing this value with other studies, we observed that Anan Fathiet *al* from Egypt similarly reported 52% cases of well differentiated carcinomas.<sup>28</sup> However, Jaudah from Saudia Arabia<sup>29</sup> and M Jaiswal from India<sup>30</sup> reported a higher number of poorly differentiated tumours in their studies. Cases which are diagnosed at a higher grade and stage have subsequently lesser chances of overall survival.

When we correlated the tumour grades with the patients' age, we found a statistically significant association between the two. More than half of the patients (65.4%) in the well differentiated category were above the age of 50 years whereas 65% of the patients in the poorly differentiated category were below the age of 50. This shows that most of the cases diagnosed at a young age are at of higher grade and would have worse prognosis and lesser chances of survival as compared to those diagnosed in older age. A similar observation was noted by Dennis *et al* from USA<sup>31</sup> who also reported that young onset CRC is usually poorly differentiated and presents at an advanced stage as compared to the elderly. Similarly, a few studies from Pakistan<sup>32,33</sup> have also reported that CRC that appears before the age of 50 years is usually observed to be of poor prognosis with unfavourable pathology.

When we compared the remaining haematological parameters of the healthy and CRC patients, we found a statistically significant association between all the parameters studied. All patients of CRC had higher TLC ( $p=0.03$ ) along with higher absolute neutrophil count and total neutrophil percentage as compared to their normal healthy counterparts ( $p<0.001$ ).

As the treatment of CRC is based on tumour grade and stage<sup>34</sup>, besides other factors, the NLR can be used pre operatively to assess whether the tumour is at an advanced stage so that it can be dealt with accordingly. According to Milica *et al*<sup>35</sup>, NLR can also be used as an independent screening marker for CRC since it shows very low levels in normal colonic epithelium. Furthermore, Nikolata *et al*<sup>36</sup> in their study showed that pre-treatment NLR values above 4.7 were related to worse prognosis and overall

survival in patients undergoing curative resection of colorectal tumours.

In conclusion, our study showed that the mean NLR values increased gradually with the increment in histological grade of patients, thus depicting direct relationship with poor prognosis. The strength of this study is that it highlights the importance of a simple, affordable and easily available haematological biomarker which can have significant clinical implications. Neutrophil to Lymphocyte Ratio value can predict the grade of tumour, and since higher grade tumours have a greater potential of recurrence and metastasis, the NLR can be utilized by surgeons to elucidate the nature of tumour, its prognosis and impact on patient survival before the detailed histopathological report is ready, which may take some time. However, the limitations of this study were its small sample size and lack of follow-up data regarding overall survival and disease free survival. Additional multi-center studies with larger sample size are required to reinforce and validate these findings.

#### AUTHORS' CONTRIBUTION

SA: Conceptualization of study design, data collection, data analysis, write-up, manuscript revision. SS: Literature search, data analysis, write-up. M: Literature search, data collection, data analysis, proof-reading. SKR: Data analysis, data interpretation, manuscript revision. AK: data interpretation. JT: data interpretation.

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