

Retrospective Analysis of Prognostic Value of Neutrophils to lymphocyte Ratio and Platelet Count in Patients with Colorectal Carcinoma

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Abstract: Background: Colorectal cancer (CRC) is the third most common cancer in men and second in women with 1.8 million new cases (1,026,000 men and 823, 3 women) and almost 881.000 deaths. Rates are substantially higher in males than in females Worldwide in 2018. **Aim of the work:** In this retrospective study we aimed to evaluate the prognostic impact of baseline NLR and platelet count on the clinicopathological factors and outcome in patients of all stages Colorectal cancer treated from 1st of January 2014 to the end of December 2016 in Department of Clinical Oncology and Nuclear Medicine, Ain Shams University hospitals, Cairo, Egypt. **Patients and methods:** Out of 409 patient's medical records in the GI oncology unit, Ain Shams Clinical Oncology Department were reviewed from the period between 1st of January 2014 to 30 December 2016. Total neutrophils, lymphocytic, and platelets' counts were available for only 169 patients. Study ended in 1st of August 2018 with median period of follow up of 27.5 month, ranging between 1/1/2014 to 1/8/2018. All patients (169) were pathologically proven colorectal adenocarcinoma, with age ranging from 18-75 years old (median age: 55.5 yrs). **Results:** Out of 169 patients enrolled in this study, 124 patients were respectable and underwent curative surgeries, 44 patients tumour was right located and 80 patient's tumour located in the left sided colon. 45 patients were metastatic from the start. Postoperative Platelets ≥ 310 in our study was statistically significant regarding OS, PFS and DFS (P values $<.001$, $<.001$ and 0.007) respectively. Pre-treatment platelet revealed more frequent thrombocytosis in metastatic group than locally advanced group, yet statistically was not significant (P Value=.066). Postoperative NLR ≥ 2 was significant regarding OS, PFS and DFS among 169 enrolled patients (P values $<.001$, $.002$ and $<.001$) respectively. In the multivariate analysis, elevated postoperative NLR was proven as both independent prognostic and predictor factor for DFS, PFS and OAS. (sig. =.03, .03, ≤ 0.001 respectively). And platelet count is both independent prognostic factor and predictor for both PFS, OS with significance =.04, =.03 respectively). **Conclusion:** Abnormal NLR ratio (≥ 2) acting as a prognostic and predictor of decrease in DFS, PFS and OS in all patients groups. It also showed that abnormal platelet count (≥ 310) is prognostic and predictor of significant decrease in PFS and OS. Multidisciplinary management is needed to aware surgeons about importance of adequate lymph node dissection, our study showed a statistically significant decrease in OAS in patients underwent inadequate LNs dissection. [Mohamed Elbassiouny, Dina Ragab, Ghada Refaat, Suhad A. Ali. **Retrospective Analysis of Prognostic Value of Neutrophils to lymphocyte Ratio and Platelet Count in Patients with Colorectal Carcinoma.** *Cancer Biology* 2019;9(3):39-51]. ISSN: 2150-1041 (print); ISSN: 2150-105X (online). <http://www.cancerbio.net>. 6. doi:[10.7537/marscbj090319.06](https://doi.org/10.7537/marscbj090319.06).

Key words: Neutrophils, lymphocyte, platelet Count, Colorectal Carcinoma

1. Introduction

Colorectal Cancer (CRC) is the third most common cancer worldwide and the fourth after breast, lung and prostate cancers in males, the 3rd in females according to latest Surveillance, Epidemiology, and End Results (SEER) data in United States ⁽¹⁾.

In 2017, about 95,520 new cases diagnosed with colon cancer in the United States and about 39,910 cases with rectal cancer (23,720 males and 16,190 females), and an estimated 27,150 men and 23,110 women died from CRC in 2017⁽²⁾.

In Egypt, according to the Egypt National Cancer registry, the incidence rates/100,000 population of individual cancer sites are: in Upper Egypt in 2008 were 6.2 and 9.6, respectively; in Middle Egypt incidences were 6.7 and 9.7,

respectively; while in Lower Egypt values were 8.0 and 10.7, respectively for both males and females ⁽³⁾.

Aside from age and race, many of the known risk factors for CRC including heredity and family history (30% of colorectal cancer is associated with family history and 5% with inherited syndromes such as Familial Adenomatous Polyposis (FAP), Attenuated FAP, and human non-polyposis colorectal cancer), chronic inflammatory bowel disease, overweight, diabetes, obesity, physical inactivity, smoking, alcohol use, low calcium, fiber and folate diet all are considered personal and behavioral risk factors for colorectal cancer ⁽⁴⁾.

Surgery is the main treatment modality in treating potentially curable cases aiming at complete removal of tumor with negative margins and involved

lymph nodes (LNs). Adjuvant chemotherapy is standard for patients with stage III disease. Its use in stage II disease is controversial, with ongoing studies seeking to confirm which markers might identify patients who would benefit ⁽⁵⁾.

According to College of American pathologists (CAP) guidelines, factors that were determined to merit inclusion in Category I prognostic factors include: local extend of tumor according to American Joint Committee on Cancer (AJCC), regional Lymph nodes metastasis, residual tumor following surgery with curative intent and tumor grade (considered a stage independent prognostic variable) ⁽⁶⁾.

However, it's increasingly recognized that variations in outcome in cancer patients are not solely determined by the characteristics of the tumor, but also by the host response factors and systemic inflammatory response. ⁽⁷⁾

The tumor microenvironment, particularly the inflammatory response) especially neutrophil to lymphocyte ratio and platelet count), proven to play an important role in in cancer development and progression ⁽⁸⁾.

Interleukin -6 is known to be multifunctional cytokine that acts on variety of cells, stimulates hepatocytes to induce acute phase proteins including CRP and decrease in serum albumin level ⁽⁹⁾.

It elicits that elevated platelets are also related to mechanism underlying host systemic inflammatory response (SIR). So, SIR can be assessed by examining the changes in the cellular components such as neutrophils, lymphocytes, monocytes, and platelets ⁽¹⁰⁾.

Over the last 10 years, many international studies investigated those laboratory markers of SIR as prognostic factors in different cancer populations with the best evidence for their use in surgical patients with CRC ⁽¹⁰⁻¹³⁾.

In 2014, a systematic review and meta-analysis took place in China, it was carried out based on the data from 16 studies to evaluate the association between NLR and overall survival (OS) and progression-free survival (PFS) in patients with CRC. Results supported that elevated pretreatment NLR predicted poorer OS (HR: 1.813, 95%CI: 1.499–2.193) and PFS (HR: 2.102, 95% CI: 1.554–2.843) in patients with CRC ⁽¹⁴⁾.

Aim of the Work

To evaluate the prognostic impact of baseline NLR and platelet count on the clinicopathologic factors and outcome in patients of all stages Colorectal cancer treated from January 2014 to December 2016 in Department of Clinical Oncology and Nuclear Medicine, Ain Shams University hospitals, Cairo, Egypt.

2. Subjects and Methods

1. Patients

This retrospective study was approved by the ethical committee of Ain Shams University in 8th April 2017. The need to obtain informed consent was waived. A retrospective review of the medical records of CRC patients who were registered in the GI oncology unit, Clinical Oncology department, Ain Shams University hospitals was done for a total of 409 consecutive patients in the period between 1st of January 2014 to 30 December 2016 period. Total neutrophils, lymphocyte, and platelets' counts were available in the records of only 169 patients who were registered in the chemotherapy unit, Clinical Oncology department, Ain Shams University hospitals, through which all the data analysis was done.

They were divided into two groups:

First group: Early and locally advanced (initially non- metastatic)

Second group: metastatic cases (metastatic at the time of diagnosis).

Patients were followed till 1/8/2018.

2. Inclusion and exclusion criteria

Inclusion Criteria were: patients aged 18 years old or more; patients who have pathologically proved colorectal adenocarcinoma; and who have started treatment in our department with documented baseline NLR and platelet count.

3. Data collection

The files of all patients were reviewed for the following: Date of diagnosis. Personal, medical and family history of the patient. Neoadjuvant treatment data. Adjuvant treatment data. Date of progression in metastatic patients if happened, sites of metastases and type of 1st line of chemotherapy received. Date of recurrence in curative patients, sites of recurrence and chemotherapy received. All initial laboratory data before starting treatment, including carcinoembryonic antigen levels, albumin, granulocyte, leukocyte, lymphocyte, monocyte, neutrophil, and platelet counts. Pathological reports details.

4- Data interpretation:

Results were obtained according to some definitions, progression free survival (PFS) was defined as the time elapsed between disease diagnosis (pathology) and tumor progression or death from any cause, with censoring of patients who were lost follow-up. Overall survival (OS) was defined as the time from the date of diagnosis of cancer (pathology), till the date of death due to any cause, last date of follow up, or lost follow up. Disease-Free Survival (DFS) was defined as the time from diagnosis until recurrence of tumor or death from any cause.

TNM disease stage was classified according to the American Joint Committee of Cancer, 7th edition (15).

The system used to grade tumor pathological response to neoadjuvant chemoradiation as recommended by the AJCC cancer staging manual, 8th Edition and the CAP guidelines is that as modified from *Weiser et al* (16).

The response categorized based on modified RECIST Criteria 1.1 (17).

- Evaluation of the performance status of the patients according to the Eastern Cooperative Oncology Group scoring (ECOG) (18).

- Toxicity assessment during treatment was recorded using Common Toxicity Criteria – NCI version 4.03 (CTC - v4.03) (19).

5- Statistical analysis methods:

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean± standard deviation (SD).

Qualitative data were expressed as frequency and percentage.

The following tests were done:

- Independent-samples t-test of significance was used when comparing between two means.

- Chi-square (x²) test of significance was used in order to compare proportions between two qualitative parameters.

- Receiver operating characteristic (ROC curve) analysis was used to find out the overall predictively of parameter in and to find out the best cut-off value with detection of sensitivity and specificity at this cut-off value.

- **Kaplan-Meier** Survival Analysis: is a descriptive procedure for examining the distribution of time-to-event variables.

- **Log rank** test to compare time-to-event variables by levels of a factor variable.

- The confidence interval was set to 95% and the margin of error accepted was set to 5%.

Table (1): Diagnostic Performance of Laboratory Data in Discrimination of outcome.

Laboratory	cut-off	sen.	Spe.	PPV	NPV	Accuracy
CEA	≥5	49%	85%	70%	54%	56%
Alb	≥4	45%	60%	88%	58%	61%
NLR	≥2	68.2%	75.4%	78.4%	64.5%	75.5%
Platelet count	≥310	56.5%	90%	90%	62%	58.9%

Sen.: sensitivity, Spe.: Specificity PPV: positive predictive value, NPV: negative predictive value.

3. Results

Among patients enrolled in this study, 119 (70.4%) patients have underwent successful diagnostic colonoscopy, while 35 (20.7%) patients were unable to do complete colonoscopy up to the cecum.

169 patients enrolled in this study, 90 patients where located in the left colon, sigmoid and rectum, while 79 patients where located in the right and transverse colon.

Table (2): Demographic data distribution of the patient's groups.

Demographic data (n=169)	All patients	Non metastatic (n=124)	Metastatic (n=45)	x ²	p-value
Sex					
Female	103 (60.9%)	81 (65.3%)	22 (48.9%)	3.746	0.053
Male	66 (39.1%)	43 (34.7%)	23 (51.1%)		
Age (years)					
<40 years	51 (30.2%)	40 (32.3%)	11 (24.4%)	0.957	0.328
>40 years	118 (69.8%)	84 (67.7%)	34 (75.6%)		
Address					
Rural	22 (13%)	18 (20.9%)	4 (16.0%)	0.296	0.586
Urban	89 (52.7%)	68 (79.1%)	21 (84.0%)		
Not recorded	58 (34.3%)	38 (30.6%)	20 (44.4%)		

Table (3): Type of surgery in not metastatic group from the start.

Surgery	Early and locally advanced (n=124)
Type of surgery	
APR	25 (20.16%)
LAR	27 (21.8%)
Rt hemicolectomy	34 (27.4%)
Lt Hemicolectomy	28 (22.6%)
Total colectomy	10 (8.1%)

All patients in non-metastatic group received Adjuvant chemotherapy, 105 patients (84.7%) received FOLFOX/XELOX as a standard protocol for adjuvant treatment in resectable colorectal cancer patients.

Twenty percent of patients received Xeloda/ 5FU instead of platinum based Chemotherapy as an alternative protocol for adjuvant treatment.

Table (4): Adjuvant treatment per stage.

Stage	Treatment
Stage I (8 patients)	All- Observation after Surgery
Stage II (42 patients)	11 pt. (Single agent 5FU/Xeloda), 21 pt. (oxaliplatin based regimens)
Stage III (64 patient)	All- FOLFOX/XELOX
Stage IV (45 patient)	All- FOLFOX/XELOX

Table (7): Post-surgical details in non-metastatic group.

Post-surgical details	non-metastatic (n=124)
Adjuvant Type	
FOLFOX/Xelox	105 (84.7%)
Xeloda/ 5fu	12 (9.7%)
Not recorded	7 (5.6%)
Recurrence	
No	93 (75.0%)
Yes	31 (25.0%)

Table (5): Site of recurrence distribution of the initially non-metastatic group.

Site of recurrence	(n=31 recurrence)
Local (including pelvic LNs)	22 (43.9%)
Lung	5(16.1%)
Liver	8(25.8%)
1st line	
Received	26 (83.9%)
Not received	5 (16.1%)
Folfiri	21 (67.7%)
Folfox	5 (16.1%)

Table (6): Comparison between initially non-metastatic and metastatic according to laboratory data.

Laboratory Data	All patients (n=169)	Initially Non-metastatic (n=124)	Initially metastatic (n=45)	t-test	p-value
CEA	0.02-2375 [84.63±302.49]	34.41±167.57	213.33±486.20	8.594	0.004*
Alb	1.6-28 [3.85±2.56]	4.17±2.27	3.17±1.74	0.858	0.359
NLR	0.4-9.8 [2.51±1.65]	2.38±1.46	2.90±2.06	3.308	0.071
Platelet count	89-776 [305.6±144.49]	293.25±131.15	339.44±173.28	3.424	0.066

*p-value < 0.05 S

CEA as tumor marker was statistically significant between initially non-metastatic and metastatic groups.

All metastatic patients received first line chemotherapy. Oxaliplatin based regimen (FOLFOX

or CAPOX) had been received in 42 (93.4%) of metastatic patients with total progression on first line occurred in twenty six patients (57.8%).

Table (7): Distribution of data for the metastatic group (metastatic from the start).

1st line of metastatic	Metastatic (n=45)
Sites of metastasis	
Liver	25(55.6%)
Lung	17(37.8%)
Mesenteric LNs	6(13.3%)
Peritoneal	4(8.9%)
Ovary	1 (2.2%)
Bladder	1(2.2%)
1st line of metastatic	
FOLFOX / Capox	42 (93.4%)
single agent 5FU/ capecitabine	2 (4.4%)
single agent Irinotecan	1 (2.2%)
Progressed disease	26(57.8%)

Table (8): Comparison between initially non- metastatic and initially metastatic according to fate.

Fate	All patients (n=169)	Initially non- metastatic (n=124)	Initially metastatic (n=45)
On FU	68 (40.2%)	59 (47.6%)	9 (20.0%)
Died	50 (29.6%)	21 (16.9%)	29 (64.4%)
Lost FU	51 (30.2%)	44 (35.5%)	7 (15.6%)
Total	169 (100.0%)	124 (100.0%)	45 (100.0%)

At the end of this study, fifty patients (29.6%) died, about forty percent (68 cases) enrolled were on F.U at the end of this study.

Table (9): Overall survival in all patients (n=169).

Median			
Estimate	Std. Error	95% C.I.	
		Lower	Upper
50.64	9.79	31.43	69.85

Table (10): Disease free survival in the initially non-metastatic group (n=124)

Median			
Estimate	Std. Error	95% C.I.	
		Lower	Upper
19.800	2.046	15.79	23.81

Table (11): Progression free survival in the initially metastatic group (n=45).

Median			
Estimate	Std. Error	95% C.I.	
		Lower	Upper
15.00	4.62	6.54	24.66

Inadequate LNs dissection (<12 LN) was statistically significant (P Value=.003) with DFS in locally advanced resected patient group. PVI and grade were statistically significant (P Value=.033), (P Value=.048) with PFS.

Table (12): Overall survival based on death between all data characteristics in all patients is shown.

Parameters		Median (m)		95% C.I.		Log Rank (Mantel-Cox)	
		Estimate	SE	Lower	Upper	χ^2	Sig.
Pathology report							
Inadequate	No	27.00	2.54	22.02	31.98	9.245	0.002*
	Done	17.55	2.41	14.32	20.78		
M	No	31.44	2.38	26.78	36.10	10.230	<0.001**

Parameters		Median (m)		95% C.I.		Log Rank (Mantel-Cox)	
		Estimate	SE	Lower	Upper	χ^2	Sig.
Pathology report							
	Done	19.92	1.25	17.48	22.36		
Stage	NA	27.00	6.62	14.02	39.98	2.373	0.499
	I	46.80	28.03	0.00	101.73		
	II	33.12	9.32	14.84	51.40		
	III	30.48	3.99	22.66	38.30		
Grade	NA	11.88	1.08	9.77	13.99	6.036	0.110
	I	12.24	1.02	9.28	13.29		
	II	32.40	3.27	26.00	38.80		
	III	15.12	2.86	9.51	20.73		
PNI	No	32.40	2.59	27.33	37.47	1.521	0.217
	Done	21.60	3.57	14.61	28.59		
PVI	No	32.40	3.18	26.16	38.64	5.328	0.021*
	Done	15.60	3.76	8.24	22.96		
Mucinous activity	No	27.96	3.03	22.02	33.90	1.324	0.250
	Done	33.12	6.48	20.41	45.83		
Peritoneal disease	No	31.44	3.00	25.56	37.32	0.546	0.460
	Done	25.20	3.56	18.22	32.18		
Underlying disease	No	32.40	3.78	24.98	39.82	0.000	0.998
	Done	28.32	2.77	22.88	33.76		
	Yes	28.32	2.03	24.35	32.29		

P-value > 0.05 NS; **p-value* < 0.05 S; ***p-value* < 0.001 HS

This table shows statistically significant between inadequate LN dissections and metastatic disease with Overall Survival (OS).

Table (13): Disease free survival in relation to laboratory data in 1st group (n=124).

Laboratory data		Median (m)		95% C.I.		Log Rank (Mantel-Cox)	
		Estimate	SE	Lower	Upper	χ^2	Sig.
CEA	Normal	22.80	1.92	19.03	26.57	0.024	0.877
	Abnormal	21.96	5.00	12.17	31.75		
ALB	Normal	19.20	4.22	10.93	27.47	1.376	0.241
	Abnormal	20.28	7.07	6.43	34.13		
NLR	Normal	33.00	2.28	28.52	37.48	13.652	<0.001**
	Abnormal	12.00	1.64	8.78	15.22		
Platelet count	Normal	25.92	1.68	22.63	29.21	7.192	0.007*
	Abnormal	7.80	0.94	5.95	9.65		

P-value > 0.05 NS; **p-value* < 0.05 S; ***p-value* < 0.001 HS

This table shows statistically significance between NLR and platelet count parameters in disease free survival.

Table (14): Progression free survival based on death between laboratory data characteristics in metastatic group (n=45).

Laboratory data		Median (m)		95% C.I.		Log Rank (Mantel-Cox)	
		Estimate	SE	Lower	Upper	χ^2	Sig.
CEA	Normal	37.56	1.48	28.17	46.95	7.766	0.005*
	Abnormal	9.24	1.34	6.61	11.87		
ALB	Normal	10.08	2.64	4.90	15.26	0.620	0.431
	Abnormal	25.80	4.83	19.35	32.25		
NLR	Normal	25.80	4.39	17.19	34.41	9.413	0.002*
	Abnormal	8.88	1.78	5.38	12.38		
Platelet count	Normal	25.80	3.49	18.96	32.64	19.017	<0.001**
	Abnormal	8.16	1.32	5.58	10.74		

P-value > 0.05 NS; **p-value* < 0.05 S; ***p-value* < 0.001 HS

This table shows statistically significance between CEA, NLR and platelet count parameters in progression free survival.

N.B: Albumin as a laboratory data was not sufficiently recorded in medical files, so can't comment on its result.

Table (15): Overall survival relation to laboratory data characteristics in all patients.

Laboratory data		Median (m)		95% C.I.		Log Rank (Mantel-Cox)	
		Estimate	SE	Lower	Upper	χ^2	Sig.
CEA	Normal	33.24	4.99	22.39	44.09	11.752	<0.001**
	Abnormal	24.00	3.60	15.60	34.80		
ALB	Normal	50.64	7.60	32.92	73.43	3.221	0.073
	Abnormal	46.00	8.40	26.40	61.20		
NLR	Normal	41.00	6.15	26.65	59.45	46.186	<0.001**
	Abnormal	23.28	3.49	19.26	27.30		
Platelet count	Normal	50.64	7.60	32.92	73.43	68.768	<0.001**
	Abnormal	15.12	2.27	11.24	19.00		

*P-value >0.05 NS; *p-value <0.05 S; **p-value <0.001 HS*

This table shows statistically significant CEA, NLR and platelet count parameters in overall survival.

Table (16): Relation between NLR according all pathological parameters of all patients.

Parameters		NLR				Chi-square	
		Normal (n=73)		Abnormal (n=96)			
		No.	%	No.	%	χ^2	p-value
Grade	NA	0	0.0%	3	3.1%	5.284	0.152
	I	1	1.4%	1	1.0%		
	II	55	75.3%	55	57.3%		
	III	2	2.7%	7	7.3%		
PNI	No	47	64.4%	48	50.0%	3.553	0.059
	Done	6	8.2%	16	16.7%		
PVI	No	51	69.9%	57	59.4%	2.095	0.148
	Done	2	2.7%	7	7.3%		
Mucinous activity	No	39	53.4%	45	46.9%	0.134	0.715
	Done	19	26.0%	19	19.8%		
Peritoneal disease	No	38	52.1%	40	41.7%	0.541	0.462
	Done	14	19.2%	20	20.8%		
Underlying disease	No	32	43.8%	40	41.7%	0.67	0.413
	Done	17	23.3%	15	15.6%		
Adjuvant Type	1.00	46	63.0%	47	49.0%	2.639	0.62
	2.00	6	8.2%	6	6.3%		
	3.00	4	5.5%	8	8.3%		
	4.00	1	1.4%	1	1.0%		
	5.00	1	1.4%	4	4.2%		
Recurrence	No	43	58.9%	50	52.1%	0.043	0.835
	Yes	15	20.5%	16	16.7%		

*P-value >0.05 NS; *p-value <0.05 S*

This table shows non-statistically significant relationship between NLR and all patient's parameters.

Table (17): Relation between platelet count according all parameters of the of the patients

Parameters		Platelet count				Chi-square test	
		Normal (n=104)		Abnormal (n=65)		x2	p-value
		No.	%	No.	%		
HCV	No	100	96.2%	63	96.9%	0.069	0.793
	Yes	4	3.8%	2	3.1%		
Renal disease	No	103	99.0%	64	98.5%	0.114	0.736
	Yes	1	1.0%	1	1.5%		
Neoadj.	No	27	26.0%	10	15.4%	1.989	0.158
	Done	20	19.2%	15	23.1%		
Type of surgery	APR	16	15.4%	9	13.8%	2.596	0.627
	LAR	15	14.4%	12	18.5%		
	Rt hemicolectomy	24	23.1%	10	15.4%		
	Lt Hemicolectomy	19	18.3%	9	13.8%		
	Total colectomy	8	7.7%	2	3.1%		
Side	Right colon	30	28.8%	10	15.4%	2.075	0.15
	Left colon	52	50.0%	32	49.2%		
Inadequate	No	52	50.0%	28	43.1%	1.16	0.107
	Done	29	27.9%	12	18.5%		
M	No	82	78.8%	42	64.6%	4.146	0.042*
	Lung	22	21.2%	23	35.4%		
Stage	NA	6	5.8%	4	6.2%	0.863	0.834
	I	5	4.8%	3	4.6%		
	II	30	28.8%	12	18.5%		
	III	41	39.4%	23	35.4%		
Grade	NA	0	0.0%	3	4.6%	3.715	0.053
	I	1	1.0%	1	1.5%		
	II	77	74.0%	33	50.8%		
	III	4	3.8%	5	7.7%		
PNI	No	64	61.5%	31	47.7%	0.112	0.738
	Done	14	13.5%	8	12.3%		
PVI	No	74	71.2%	34	52.3%	2.167	0.141
	Done	4	3.8%	5	7.7%		
Mucinous activity	No	54	51.9%	30	46.2%	1.049	0.306
	Done	28	26.9%	10	15.4%		
Peritoneal disease	No	54	51.9%	24	36.9%	1.144	0.285
	Done	20	19.2%	14	21.5%		
Underlying disease	No	45	43.3%	27	41.5%	2.458	0.117
	Done	25	24.0%	7	10.8%		
Adjuvant Type	1.00	63	60.6%	30	46.2%	2.612	0.625
	2.00	9	8.7%	3	4.6%		
	3.00	7	6.7%	5	7.7%		
	4.00	1	1.0%	1	1.5%		
	5.00	2	1.9%	3	4.6%		
Recurrence	No	57	54.8%	36	55.4%	3.889	0.069
	Yes	25	24.0%	6	9.2%		

This table shows non-statistically significant relationship between platelet and all patient's parameters unless extend of the disease at diagnosis (P-value >.042).

Table (18): Logistic Multi-regression analysis of factors affecting NLR diagnosis.

NLR	B	Sig.	Exp. (B)	Lower	Upper
Disease free survival	-0.932	0.032*	1.073	0.504	2.006
Progression free survival	-0.297	0.038*	1.526	0.717	2.854
Overall survival	-2.235	<0.001**	2.408	1.132	4.503
Sidedness	-0.337	0.364	0.663	0.312	1.240

Binary Logistic Multi-Regression analysis was done for NLR and of DFS, PFS and OS variables that showed statistically significant. It showed that abnormal NLR have predictors and significance decrease of DFS, PFS and OS.

Table (19): Logistic Multi-regression analysis of factors affecting platelet count diagnosis.

Platelet count	B	Sig.	Exp. (B)	Lower	Upper
Disease free survival	-0.811	0.091	0.955	0.449	1.785
Progression free survival	-0.306	0.043*	1.358	0.638	2.540
Overall survival	-1.944	0.031*	2.023	0.951	3.782
M	-1.020	0.047*	1.917	0.901	3.584

Binary Logistic Multi-Regression analysis was done for platelet count and of PFS, OS and M variables that showed statistically significant. It showed that abnormal platelet count have predictors and significance decrease of PFS and OS.

4. Discussion

Colorectal cancer remains a prominent cause of cancer morbidity and mortality, despite progress in its management. It is therefore clinically important to discover and validate prognostic markers for the disease that are practical, reliable, and inexpensive. This would help clinicians modulate their plan of management⁽²⁰⁾.

Immune and other cells originating from the peripheral blood and recruited to the tumor environment can shape the tumor behavior both directly and indirectly through production of cytokines. More recently, immune cells have come to the forefront of cancer research with the successful introduction of immune blockade inhibitors, drugs that potentiate anti-cancer immune function by blocking inhibitory receptors expressed in lymphocytes (e.g., CTLA4, PD-1)⁽²¹⁾.

Perturbations in the number of immune cells in peripheral blood may be the result of cytokines produced in the tumor which may in turn affect tumor progression. Lymphocytosis has been associated with positive prognosis in various cancers, therefore, increased numbers of circulating lymphocytes may be a marker of increased cytokine signals from the tumor that would mobilize and attract marrow or tissue lymphocytes to the tumor microenvironment where they could attack tumor cells under the right conditions⁽²²⁾.

Neutrophils, on the other hand, have a more controversial role in cancer. Certain subsets of these pro-inflammatory cells may have a pro-tumorigenic effect by induction of immune suppression⁽²³⁾. Due to this effect, neutrophilia has generally been found to be a negative prognostic factor in several malignancies⁽²⁴⁾.

Thrombocytosis has been associated with adverse cancer outcomes in several cancer sites. Mechanistically, platelets may promote carcinogenesis in several ways, such as a mechanical

protection of tumor cells in transit in the circulation, as well as by enriching the tumor micro-environment for several bioactive pro-tumorigenic molecules transported and released from their granules⁽²⁵⁾.

The current study was designed to give a close picture to the role of platelet count and neutrophil lymphocyte ratio in relation to progression free survival (PFS), disease free survival (DFS) and overall survival (OS) in colorectal cancer patients. It aimed also at evaluation of the relation between NLR and platelet count with various clinicopathological factors that are known to affect the clinical outcome, as well as exploring if these values could be an independent prognostic factor.

In our study females were more affected than males, 66 (39.1%) were males and 103 (60.9%) were females.

Urban residents constituted 52.7% of cases, while rural residents constituted 13% of cases; this finding is similar to that reported from developed countries. As rural dwellers have a lower incidence of colorectal than urbanities⁽²⁶⁾.

Fifty three patients in our study were heavy smokers (31.4%), 29 (17.2%) patients were hypertensive, 24 (14.2%) were diabetic on treatment. Family history was positive in 18.9% of all patients with increased risk but with no statistical significance, may explained by the deficient recording of data, maybe a larger number of patients needed to be investigated.

TNM Classification of Malignant Tumors (TNM) disease stage was classified according to the American Joint Committee of Cancer, 8th edition. In our study, 124 patients presented with early and locally advanced tumors (stage I, II, III) and 45 patients presented with metastatic disease (stage IV).

At the end of this study, 50 patients (29.6%) died, 21 patients were locally advanced and 29 (64.4%) metastatic patients, which is statistically significant difference according to fate (P Value<.001).

Out of 169 patients enrolled in this study, 124 patients were resectable and underwent curative surgeries (right hemicolectomy, left hemicolectomy, APR and LAR).

Out of 124 patients, in 44 patients tumour was right-side located and 80 patient's tumour located in the left sided colon.

In many studies, primary tumor location is a prognostic factor in CRC. In a meta-analysis of 66 studies including 1,427,846 patients with all stages of disease, left-sided primary tumor location (tumor location at or beyond the splenic flexure) was associated with a significantly reduced risk of death and this was independent of stage, race, and use of adjuvant chemotherapy ⁽²⁷⁾.

Inadequate lymph node dissection (less than 12 lymph nodes) was noted in 41 (33.1%) patients in resected patients and it was statistically significant for both DFS and OS.

Overall survival was 27 month for adequately resected patients and 17.5 month among inadequately resected patients with P Value =.002.

Disease free survival was 19 month vs. 14 month in 1st group and 2nd group, respectively with P Value =.003).

This met the western literature that recommended that the larger number of nodes may reflect the quality of the surgery and a more complete resection of the mesenteric pedicle, guidelines from expert groups recommend at least 12 nodes be examined histologically to accurately determine nodal status ⁽²⁸⁾.

Histologic grades in our study ranges between grade I-III, found to be statistically significant with disease free survival (P Value=.048).

Disease free survival was 28, 13 and 7.2 months for patients with grade I, II and III tumors, respectively.

Grade reflects the degree of tumor differentiation, poorly differentiated histology is one of the clinicopathological features used to define "high-risk" stage II disease by ASCO, NCCN, and ESMO ⁽²⁹⁾.

In our study LVI found to be an adverse prognostic factor statistically significant (P Value=.033) which met the western literature that admit tumor invasion into veins or small nonmuscularized vessels is an important prognostic determinant represent independent adverse prognostic factors ⁽³⁰⁾.

Perineural invasion (PNI), mucinous activity and peritoneal disease are generally associated with an increased risk. PNI in the current study was reported only in 58% of patients, mucinous activity reported in 62% and peritoneal disease was reported in 54% only of cases with P Value equals (.21,.25 and.46, respectively) in relation to overall Survival for all patients. This discrepancy may be explained by the deficient recording of the pathological data of patients

that has rendered proper assessment of these variables as prognostic variables.

In metastatic group (45 patients) 25 patients (55.6%) were metastatic to liver; 17 patients (37.8%) were metastatic to lung. Among those patients: 7 patients were metastatic to both lung and liver at time of diagnosis.

During follow up of patients who finished adjuvant treatment, recurrence occurred in 31 patients (25%) of all patient group. The most frequent sites of recurrence was locally by 29% (mostly in rectal cancer) and to liver by 25.8% (mostly colonic origin) of the total sites. These results have met the international studies. In 2007 a meta-analysis done in Japan enrolled 5,230 patients who underwent curative resection for colorectal cancer, recurrence occurred in 906 patient (17%). The liver was the most frequent recurrent site (41.1%), the second site was the lung by (27.5%) ⁽³¹⁾.

Back to pre-treatment laboratory data values, Receiver operating characteristics (ROC) curve was used to define the best cut off value of those laboratory data.

In this study CEA cut-off was ≥ 5 , Platelet was ≥ 310 and NLR was ≥ 2 .

Although the applicable thresholds of NLR, albumin, CEA and platelet count were observed by the ROC curves, the optimal thresholds of these parameters in our study were consistent with other studies and wasn't consistence to the range of some previous studies.

An example for studies resulted in near same cut-off values was a study conducted in 2017 when Chenet al. enrolled 1383 cases with colorectal cancer, PLR cut-off was 210 and NLR cut-off was 2.70 ⁽³²⁾. In 2017, Absenger et al. conducted a study on 370 colon patients where optimum cut-off NLR was 2.2 ⁽³³⁾.

On the other hand, here are some previous reports that weren't consistence with our values.

Such an example in a study conducted in 2017 in China, optimum cutoff of NLR was 10.5 ⁽³⁴⁾. Also a study conducted in 2018 by Mercier and his colleagues, 152 metastatic colon cancer patients were included. The optimum cut-off of Plt was ≥ 350 and NLR was ≥ 5.6 ⁽³⁵⁾.

In our study CEA cut-off was ≥ 5 , with sensitivity of 49% specificity of 85% positive predictive value of 70%, negative predictive value of 54% with diagnostic accuracy of 56%.

CEA value correlates with poorer prognosis in our study as there is statistical significant difference between CEA values in early stages colorectal cancer and stage IV, with P Value=.004, Also was statistically significant with overall survival of all patients (P Value \leq .001) which met many western studies discussing the same issue ^(32 & 33,36).

In our study Platelet count cutoff was ≥ 310 , with sensitivity of 56.5% specificity of 90% positive predictive value of 90%, negative predictive value of 62% with diagnostic accuracy of 58.9% (according to ROC curve).

Among 169 enrolled patients in the current study, OS, PFS and DFS were shorter in patients with elevated platelet counts than in patients with normal counts with significance statistically, OAS was 50.6 and 15.1 month for normalized and elevated platelet groups, respectively.

Disease free survival was 25.9m for normalized platelet count limb and 7.8 month for the other limb. PFS was 26 vs. 8 months among both limbs.

P values $<.001$, $<.001$ and 0.007 respectively.

Values of pre-treatment platelet revealed more frequent thrombocytosis in metastatic group than locally advanced group, yet statistically was not significant (P Value=.066).

These results met the end point of several studies ^(36,37).

However, one study revealed a different conclusion. It included 630 patients and used a cut-off platelet count value of more than 450; the authors did not find a significant association between elevated platelet counts and survival ⁽³⁸⁾.

In our study the **NLR** cut-off was ≥ 2 , with sensitivity of 68.2% specificity of 75.4% positive predictive value of 78.4%, negative predictive value of 64.5% with diagnostic accuracy of 75.5% according to ROC Curve.

Among 169 enrolled patients, OS, PFS and DFS were shorter in patients with elevated NLR ratio than in patients with normalized ratio with significance statistically.

Disease free survival among the initially non metastatic group was 33 month in normalized NLR limb and 12 month in $\text{NLR} \geq 2$ limb with P value $<.001$. Progression free survival among the initially metastatic group was 25.8 month among normalized NLR limb and 8.8 month among $\text{NLR} \geq 2$ limb with P Value.002.

Overall survival for all patients was 41 month for normalized ratio and 23 month for $\text{NLR} \geq 2$ limb with P value of $<.001$, which met end point of many international studies ^(10,35).

Neutrophil lymphocytes ratio remained significant in the multivariate analysis including OS, DFS and PFS for total number of patients.

In univariate analysis, the elevated postoperative NLR was associated with worse OS, DFS and PFS.

Platelet remained significant in the multivariate analysis and confirmed as independent prognostic factor to Worse OS, DFS and PFs in colorectal cancer patients.

These data are consistence with those showed in some previous studies, as shown in a study conducted by Wanbin et al. ⁽³⁴⁾ where the main finding was that NLR confirmed as independent prognostic factor regardless Age, sex and stage in coloncancer patients. Also in previous study conducted by Absenger et al., showed the same results regarding multivariate analysis of those studied factors ⁽³³⁾.

Those data may provide new ideas and evidence for clinical applications aimed at evaluating prognosis in patients with colorectal cancer. A less expensive and simpler method of bio-prediction may therefore be developed in the near future.

Regarding platelet count that can be influenced by several diseases and drugs (including blood coagulation disorders, blood diseases, splenic disease, and aspirin), those factors should be excluded in the future studies to more rigorously demonstrate the prognostic value of platelet counts.

Our study is of retrospective design, small sample size (especially in metastatic group) and single-center experience with exclusion of approximately two third of the initial number of patients for various reasons including absence of many essential data in medical reports, which could not be representative of all CRC patients in general and might weaken the meaning of our finding, so we can't generalize our results.

But at least it helps to recognize more adverse prognostic and predictive factors for newly diagnosed CRC patients and offering appropriate treatment strategies, optimum surveillance schedule and monitoring. It may open the door for further investigation with larger scale and long term follow-up in the near future.

Conclusion

1. The association between cancer and inflammation was first recognized on the basis of observations that tumors frequently arise at sites of chronic inflammation so many triggers of chronic inflammation increase the risk of developing cancer.

2. This study is demonstrating a strong association between elevated neutrophil count and poor outcome in patients with cancer in both overall survival and disease free survival.

3. This study demonstrates a great link between thrombocytosis and OAS, PFS and DFS in both locally advanced and metastatic sittings.

4. Median of OAS in locally advanced group is 31.4 month while in metastatic group it's 19.9 month, median of DFS in locally advanced group is 19.8 month and PFS in metastatic group is 15 month, with statistically difference.

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7/7/2019