Original Research Article

Neutrophil-lymphocyte ratio and platelet-lymphocyte ratios correlate with staging in patients with colorectal carcinoma

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ABSTRACT

Background: Systemic inflammation status is revealed to be associated with prognosis of solid tumours. Inflammatory markers including C-reactive protein, Neutrophil-lymphocyte ratio and platelet-lymphocyte ratio have been claimed to provide insight into resectability of carcinoma and in predicting prognosis. The objective of this study was to study neutrophil lymphocyte ratio and platelet lymphocyte ratio profiles in patients with colo-rectal cancers.
Methods: This study was done as a hospital based descriptive on 80 patients diagnosed with colonic and rectal cancers. The study was carried out from May 2017 to May 2018 at General Surgery and Radiotherapy departments at Government Medical College, Trivandrum. Neutrophil lymphocyte ratio and platelet lymphocyte ratio was calculated and correlated with the pre-operative staging, post-operative staging and the histopathological grade.
Results: Both neutrophil lymphocyte ratio and platelet lymphocyte ratio were found to be higher in patients with colo-rectal cancers as compared to values in normal healthy population. Neutrophil lymphocyte ratio was well correlated with tumour status, nodal status and overall stage in pathological staging. Platelet lymphocyte ratio was well correlated with tumour status and overall stage in CT staging and with tumour status, nodal status and overall stage in pathological staging.
Conclusions: Neutrophil lymphocyte ratio and platelet lymphocyte ratio are correlated with colo-rectal carcinomas and may provide valuable information in staging the patients. They are cost-effective, easily measurable but affected by race, sex, age, co-morbidities and many other potential factors. Routine estimation of these ratios can serve as adjunct to staging as well as help to prognosticate the patients.

Keywords: Colonic cancer, Neutrophil-lymphocyte ratio, Platelet-lymphocyte ratio, Rectal cancer

INTRODUCTION

Colonic and rectal cancers are among the most common cancers of the digestive tract. They also form a leading cause of cancer related deaths in the world. Although there have been rapid developments in diagnostic and treatment modalities, 5-year survival rates are not very much promising for these cancers as a result of local tumour recurrence or distant metastases. Classically the TNM staging system by AJCC has been commonly considered to be the best method to estimate the outcome in patients with coo-rectal cancers. The TNM system focuses on tumour size, lymph nodes and distal metastasis. Though this system remains the 'gold standard' for guiding therapy, there are limitations in predicting the prognosis precisely and guiding the clinical practice appropriately Therefore, it is vital to seek other effective prognostic factors for these patients in order to choose appropriate modalities of systematic treatment.

Studies have demonstrated that biomarkers may provide insight into resectability of carcinoma, sometimes even

better than conventional pathological staging classification. Carcino embryonic antigen (CEA) has been studied for long as a classical marker in predicting the prognosis and to assess response to treatment. Inflammatory markers including C-reactive protein (CRP) have been reported to be effective as prognostic markers in several cancers. High CRP has been found to have relationship with poor prognosis and is a promising predictor of recurrence in patients with rectal cancer treated by chemo-radio-therapy.[1] The neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR), platelet-lymphocyte ratio (PLR), and mean platelet volume (MPV) are claimed to be used as factors to determine the prognosis of patients in various clinical situations. Neutrophilia as an inflammatory response inhibits the immune system by suppressing the cytolytic activity of immune cells such as lymphocytes, activated T cells, and natural killer cells. Neutrophils could promote tumor invasion and metastasis by contributing to angiogenesis and releasing circulating growth factors.[2] Lymphocytes, on the other hand, were reported to play a key role in cytotoxic cell death and could inhibit proliferation and metastasis of tumor cells.[3]

With the correlation between inflammatory status and disease or cancer prognosis, there is a growing interest in research aimed at better understanding the disease status or predicting the prognosis of patients with simple blood tests. The NLR, which can be measured in simple blood tests, is easily obtained, and determined in a cost-effective manner. As a marker of systemic inflammation, NLR has been shown to be effective in predicting the prognosis of cancer treatments, coronary interventions, coronary artery bypass grafting, and even Alzheimer disease.[4] Likewise, the LMR, PLR, and MPV have been reported to measure the degree of systemic inflammation and indicate prognosis in critically ill patients during postoperative and intensive care. Indeed, NLR was reported as an unfavorable prognostic factor in many cancers, including breast cancer, colorectal cancer and lung cancer.[5-10]

One potential mechanism underlying the prognostic impact of NLR may be an association of high NLR with inflammation. Inflammatory cytokines and chemokines can be produced by both the tumour and associated host cells such as leukocytes and contribute to malignant progression. An elevated NLR has been associated with an increase in the peri-tumoural infiltration of macrophages and an increase in interleukin 17.[11] Serum concentrations of IL-6 have been shown to be increased in 13 different cancer types and have been associated with tumour stage and adverse prognosis.[12]

Recent researches have shown platelets to be secreting several angiogenic and tumour growth factors, such as vascular endothelial growth factor and platelet-derived growth factor, which might influence tumour progression, and also release micro-particles that help tumour cells escape from the elimination of natural killer. On the contrary, lymphocytes are basic components of the adaptive and innate immune system and the cellular basis of immuno-surveillance and immuno-editing, and CD8+ and CD4+ T-lymphocyte interaction among each other could be proven to induce tumour cell apoptosis in antitumor reaction of the immune system.[13]

To reiterate, the current staging system still leaves room for improvement to better stratify patients and to predict to their survival. Hence, it is advisable to search other criteria and newer prognostic indicators to further classify patients and optimize the therapeutic approach, which can both improve survival rates in high risk patients and avoid overtreatment in low risk patients. With this idea in mind, we attempted to study the profile of the two ratios namely NLR and PLR in patients with colo-rectal cancers. Being a tertiary level teaching institution, we do encounter and treat a large volume of colo-rectal cancer patients at our centre.

METHODS

This study was designed as a hospital based descriptive study. The study setting was in the departments of General Surgery and Radiotherapy at Government Medical College Hospital, Trivandrum. The study was conducted for a period of 1 year from May 2017 to May 2018. The primary objective of the study was to study the neutrophil lymphocyte ratio and platelet lymphocyte ratio profile in patients with colo-rectal carcinomas admitted in our institution. The secondary objectives were to correlate neutrophil-lymphocyte ratio and platelet lymphocyte ratio with the preoperative CT staging, post-operative TNM staging and histopathological grade in patients with colo-rectal carcinomas.

The study population included diagnosed cases of colonic and rectal carcinoma admitted in General Surgery and Radiotherapy wards in the institution. All cases meeting these criteria were included in the study. Patients who had any other concurrent diagnosed inflammatory conditions were excluded to avoid interference with the values of the calculate parameters. Consecutive cases meeting eligibility criteria were included in the study till the study period was over.

Institutional review committee and ethics committee clearance were obtained before commencing the study. Patients fulfilling inclusion criteria are enrolled and informed consent obtained for including in the study. The patients were assessed by the treating physician and routine management carried out as per institutional protocols. Semi-structured proforma was used to enter data, along with secondary data from patient records and laboratory reports and histopathology reports. Data was entered in to excel sheets and stored electronically. All quantitative variables were expressed as means along with standard deviations and all qualitative variables were expressed as proportions. Data were analyzed using EpiInfo statistical software released by the CDC.

Appropriate statistical tests done included Mann-Whitney U Test and Kruskal Wallis Test. Results were considered statistically significant wherever the p value was less than 0.05.

RESULTS

Mean NLR was 4.16 in patients less than 60 years and was 3.97 in those above 60 years. The mean NLR was 4.88 in males and 2.83 in females respectively which was found to be significant. The mean NLR was 4.04 in patients who did not receive neo-adjuvant therapy and IQ range was 1.9-4.4. Whereas it was 2.86 in those who received neo-adjuvant therapy. Comparing NLR to histological grade, mean NLR was found to be highest in poorly differentiated, but decreased from well differentiated to moderately differentiated and was lowest in undifferentiated. Mean NLR in well differentiated was 3.77±3.28, in moderately differentiated was 3.51±3.07, in poorly differentiated was 5.87±5.81, and in undifferentiated was 2.65±2.33. But this was statistically insignificant with a p value of 0.082.

Compared to CT staging of CRC, mean NLR was found to increase along with T stage progression (Table 1). The mean NLR in T2 was 2.16±0.64, in T3 was 4.27±3.21 and in T4 was 4.65±5.1. This was statistically not significant with a p value of 0.087. Mean NLR was found to increase from N0 to N1 but was lower in N2 or more category than N1. The mean NLR in N0 was 2.86±1.68, in N1 was 5.43±5.32 and in N2 or more was 4.18±4.14.

This was statistically not significant with a p value of 0.077. Mean NLR was found to increase from M0 to M1. The mean NLR in M0 was 3.85±3.97, in M1 or more was 4.92±3.94. This was statistically not significant with a p value of 0.139. Mean NLR was found to increase along with TNM stage progression. The mean NLR in stage 1 was 2±0.65, in stage 2 was 3.26±1.87 and in stage 3 was 4.77 ± 5.15 and stage 4 was 4.92 ± 3.94. This was statistically not significant with a p value of 0.082.

Compared to pathological staging of CRC, mean NLR was found to increase along with T stage progression from T2 to T3 to T4, but mean NLR in T1 was found to be higher than in T2 (Table 2). The mean NLR in T1 was 3.1±0, T2 was 1.95±0.72, in T3 was 4.34±3.15 and in T4 was 5.05±5.37. This was statistically significant with a p value of 0.013. Mean NLR was found to increase from N0 to N1 but was lower in N2 or more category than N1. The mean NLR in N0 was 2.42±1.25, in N1 was 4.77±4.77 and in N2 or more was 5.25±4.02. This was statistically significant with a p value=0.005. Mean NLR was found to increase from M0 to M1. The mean NLR in M0 was 3.87±4, in M1 or more was 4.73±3.85. This was statistically not significant with a p value of 0.209. Mean NLR was found to increase as stage of the disease progressed from stage 1 to stage 2 to stage 3 but mean NLR in stage 4 was found to be lower than in stage 3. The mean NLR in stage 1 was 1.98±0.62, in stage 2 was 2.74±1.5 and in stage 3 was 4.93±4.91 and stage 4 was 4.73±3.85. This was statistically significant with a p value of 0.019.

Mean PLR was 206.70 in cases less than 60 years and was 200.76 in those above 60 years. Mean PLR was 237.86 in males and 152.96 in females respectively. The mean PLR was 203.19 in those without history of neo-adjuvant therapy and 173.13 in those who received neo-adjuvant therapy. Comparing PLR to histological grade, mean PLR was found to be highest in well differentiated, then poorly differentiated, then in moderately differentiated and was lowest in undifferentiated. Mean PLR in well differentiated was 228.92±224.03, in moderately differentiated was 192.29±212.15, in poorly differentiated was 222.85±127.81, and in undifferentiated was 150.09±99.48. But this was statistically insignificant with a p value of 0.209.

Table 1: Comparison of NLR with CT staging.

CT staging		Mean±SD	Median (IQ Range)	Test statistics		P value
T status	T2	2.16±0.64	2.34 (1.53 - 2.74)	χ^2\$	4.88	0.087
	T3	4.27±3.21	3.11 (2.29 - 6)			
	T4	4.65±5.1	3.05 (1.83 - 4.63)			
N status	N0	2.86±1.68	2.32 (1.38 - 4.38)	χ^2\$	5.14	0.077
	N1	5.43±5.32	2.95 (2.46 - 7.93)			
	N2 / more	4.18±4.14	2.76 (1.9 - 3.98)			
M status	M0	3.85±3.97	2.59 (1.84 - 4.44)	Z#	1.48	0.139
	M1 / more	4.92±3.94	3.17 (2.6 - 7.85)			
Staging	Stage I	2±0.65	2.1 (1.29 - 2.55)	χ^2\$	6.71	0.082
	Stage II	3.26±1.87	3.45 (1.66 - 5.19)			
	Stage III	4.77±5.15	2.72 (2.17 - 5.33)			
	Stage IV	4.92±3.94	3.17 (2.6 - 7.85)			

\# Mann-Whitney U Test, \$ Kruskal Wallis Test

Compared to CT staging of CRC, mean PLR increased along with T stage progression from T2 to T3, but mean PLR in T4 was lower than in T3 (Table 3). The mean PLR in T2 was 113.21±37.27, in T3 was 238.14±236.33

and in T4 was 209.55±165.39. This was statistically significant with a p value of 0.016. Mean PLR was found to increase from N0 to N1 but mean PLR in N2 or more was lower than in N1. The mean PLR in N0 was 144.24±64.78, in N1 was 260.31±213.51 and in N2 or more was 221.93±246.13. This was statistically not significant with a p value of 0.072. Mean PLR was found to increase from M0 to M1. The mean PLR in M0 was 195.94±183.05, in M1 or more was 235.51±210.58. This

was statistically not significant with a p value of 0.372. Mean PLR was found to increase as stage of the disease progressed from stage 1 to stage 2 to stage 3 but mean PLR in stage 4 was found to be lower than in stage 3. The mean PLR in stage 1 was 103.75±40.46, in stage 2 was 163.42±66.02 and in stage 3 was 244.19±238.67 and stage 4 was 235.51±210.58. This was statistically not significant with a p value of 0.017.

Table 2: Comparison of NLR with pathological staging.

Pathological staging		Mean±SD	Median (IQ Range)	Test statistics	P value
T status	T1	3.1±0	3.1 (3.1 - 3.1)	$\chi^2\$$	10.73*	0.013
	T2	1.95±0.72	2.1 (1.22 - 2.66)		
	T3	4.34±3.15	3.11 (2.29 - 6)		
	T4	5.05±5.37	3.22 (1.97 - 5.19)		
N status	N0	2.42±1.25	2.15 (1.59 - 2.75)	$\chi^2\$$	10.47**	0.005
	N1	4.77±4.77	2.8 (2.11 - 6)		
	N2 / more	5.25±4.02	3.51 (2.87 - 7.45)		
M status	M0	3.87±4	2.6 (1.82 - 4.44)	Z#	1.26	0.209
	M1 / more	4.73±3.85	3.09 (2.43 - 7.83)		
Staging	Stage I	1.98±0.62	2.1 (1.29 - 2.53)	$\chi^2\$$	10*	0.019
	Stage II	2.74±1.5	2.25 (1.64 - 3.9)		
	Stage III	4.93±4.91	3.1 (2.26 - 6)		
	Stage IV	4.73±3.85	3.09 (2.43 - 7.83)		

Mann-Whitney U Test, $ Kruskal Wallis Test, **: - Significant at 0.01 level, *: - Significant at 0.05 level

Table 3: Comparison of PLR with CT staging.

CT staging		Mean ± SD	Median (IQ Range)	Test statistics	P value
T status	T2	113.21 ± 37.27	118 (78.4 - 139.5)	$\chi^2\$$	8.22*	0.016
	T3	238.14 ± 236.33	140 (116.5 - 240.75)		
	T4	209.55 ± 165.39	155.5 (104.5 - 233.75)		
N status	N0	144.24 ± 64.78	118.5 (81.03 - 206.75)	$\chi^2\$$	5.26	0.072
	N1	260.31 ± 213.51	141.5 (119.54 - 383.23)		
	N2 / more	221.93 ± 246.13	152 (123.16 - 214.5)		
M status	M0	195.94 ± 183.05	138 (104.75 - 212)	Z#	0.89	0.372
	M1 / more	235.51 ± 210.58	152 (108.25 - 306)		
Staging	Stage I	103.75 ± 40.46	81.1 (72.9 - 122.95)	$\chi^2\$$	10.26*	0.017
	Stage II	163.42 ± 66.02	197 (103 - 233)		
	Stage III	244.19 ± 238.67	142 (119.54 - 258.25)		
	Stage IV	235.51 ± 210.58	152 (108.25 - 306)		

Mann-Whitney U Test, $ Kruskal Wallis Test, *: - Significant at 0.05 level

Table 4: Comparison of PLR with pathological staging.

Pathological staging		Mean ± SD	Median (IQ Range)	Test statistics	P value
T status	T1	358±0	358 (358 - 358)	$\chi^2\$$	16.16**	0.001
	T2	106.55±36.28	95.05 (77.25 - 134.47)		
	T3	240.82±234.57	140 (116.5 - 240.75)		
	T4	216.17±171.56	177.5 (114.86 - 233.75)		
N status	N0	129.25±51.41	118.5 (88 - 140)	$\chi^2\$$	10.44**	0.005
	N1	219.98±176.01	153 (109.5 - 240.5)		
	N2 / more	318.5±334.67	184 (143.25 - 389)		
M status	M0	197.36±184.36	139 (104.5 - 214)	Z#	0.68	0.497
	M1 / more	226.91±204.86	149 (106.74 - 272)		
Staging	Stage I	107.08±39.57	99.55 (74.35 - 129.42)	$\chi^2\$$	11.51**	0.009

Continued.

Pathological staging	Mean ± SD	Median (IQ Range)	Test statistics	P value
Stage II	145.09±54.25	126 (103.75 - 212)		
Stage III	246.89±227.09	197 (118 - 245.5)		
Stage IV	226.91±204.86	149 (106.74 - 272)		

Mann-Whitney U Test, $ Kruskal Wallis Test, **: - Significant at 0.01 level

Compared to pathological staging of CRC, mean PLR increased along with T stage progression from T2 to T3, but mean PLR in T4 was lower than in T3 and highest was in T1 (Table 4). The mean PLR in T1 was 3.1±0, T2 was 106.55±36.28, in T3 was 240.82±234.57 and in T4 was 216.17±171.56. This was statistically significant with a p value of 0.001. Mean PLR was found to increase from N0 to N1 to N2 or more. The mean PLR in N0 was 129.25±51.41, in N1 was 219.98±176.01 and in N2 or more was 318.5±334.67. This was statistically significant with a p value of 0.005. Mean PLR was found to increase from M0 to M1or more. The mean PLR in M0 was 197.36±184.36, in M1 or more was 226.91±204.86. This was statistically not significant with a p value of 0.497. Mean PLR was found to increase as stage of the disease progressed from stage 1 to stage 2 to stage 3 but mean PLR in stage 4 was found to be lower than in stage 3. The mean PLR in stage 1 was 107.08±39.57, in stage 2 was 145.09±54.25 and in stage 3 was 246.89±227.09 and stage 4 was 226.91±204.86. This was statistically significant with a p value of 0.009.

DISCUSSION

The mean NLR was 4.04 in patients without neo-adjuvant therapy. In another study carried out on healthy adults in China, the mean baseline NLR was 1.5±0.05.[14] In Chennai, Shiny et al, reported a NLR of 1.5±0.41 among healthy non-diabetic individuals.[15] These variations in the values of NLR may be an indication that race and environment have effect on the NLR. With the Chennai study being most comparable to our centre in terms of race and locality, our study has found that CRC patients have a much higher NLR of 4.04. This is in accordance with previous studies which have shown that an elevated NLR is found in CRC patients 2. At the same time, the mean NLR was 2.86 in post neo-adjuvant therapy category which shows that other modalities of treatment can alter or control the disease process and probably reduce the NLR. Previous studies also demonstrate the same.[16,17]

The mean PLR was 203.19 in patients without neo-adjuvant therapy and 173.13 in neo-adjuvant therapy received category. Study providing preliminary reference data on PLR, from different age and sex groups in Nigeria found the mean PLR to be 132.40.[18] The mean PLR from another previous study was 137±62.[19] Other results also suggest that different cutoff values should be applied to the various patient populations.[18] Our study shows that CRC patients have a much higher PLR of 203 compared to normal healthy population.[19] This is in accordance with previous studies which have shown that an elevated PLR is found in CRC patients 8. At the same time, the mean PLR was 173.[13] in neo-adjuvant therapy received category which shows that other modalities of treatment may alter or control the disease process and probably reduce the PLR. Previous studies also demonstrate the same.[8,17]

Mean NLR was 4.16 in less than 60 years and was lower, at 3.97 in more than 60 years. Available study shows that older individuals between the ages of 51 to 85 years had significantly higher mean NLR (p=0.019) than younger candidates aged 18 to 50 years.[20] This may be as a result of increase in inflammatory environment associated with chronic conditions like diabetes, and cardiovascular diseases which are common with increasing age. An older age was related to an increase in PLR and, to a lesser extent, to an increase in NLR.[21] In a previous study, an inverse relationship was observed between NLR and age.[19] Our study did not correlate with the former studies but the latter study was not statistically significant with a p value of 0.852. Mean PLR was 206.7±231.73 in less than 60 years and was lower at 200.76±152.58 in more than 60 years. Available study shows young individuals aged 18 to 50 years had significantly lower PLR (p<0.05) than older individuals aged 51 to 85 years.[18] An older age was related to an increase in PLR.[18] Our study did correlate with the former studies but was not statistically significant with a p value of 0.475.

The mean NLR was 4.88±4.77 in males and 2.83±1.8 in females respectively. There were sex differences in mean levels, with higher NLR in men compared with women.[21] A study has also shown that mean NLR values for men and women were 1.63 (0.76) and 1.66 (0.82).[14] Our study has shown higher values for males and was statistically significant with a p value of 0.048. The mean PLR was 237.86±227.29 in males and 152.96±88.01 in females respectively. The mean PLR values for men and women were 117.11 (40.27) and 125.05 (42.81), respectively in a study.[21] There were sex differences in mean levels, with lower PLR in men compared with women. Our study did not correlate with this and was statistically not significant with a p value of 0.103.

Mean NLR was found to be highest in poorly differentiated, but decreased from well-differentiated to moderately differentiated and was lowest in undifferentiated. Mean PLR was found to be highest in well differentiated, then poorly differentiated, then in moderately differentiated and was lowest in undifferentiated. It has been found there is association between elevated pre-treatment NLR and PLR and clinic-pathological parameters in CRC like tumour

differentiation.[8] Our results were inconclusive and also not statistically significant.

It has been found there is some association between elevated pre-treatment NLR and PLR and clinical outcomes and clinic-pathological parameters in CRC like tumour differentiation, tumour depth, size and stage of the disease.[8] Our study demonstrates that NLR is directly related to the T, N and M status as well as stage of the disease with respect to both CT staging and pathological staging. Of these T, N statuses and stage in pathological staging were found to be statistically significant. Our study demonstrates that PLR is directly related to the T, N, M statuses and stage of the disease with respect to both CT staging and pathological staging. Of these, association of PLR with T status and stage in CT staging and T, N and stage in pathological staging were found to be statistically significant.

This work has several limitations. First, the sample size which was collected from single centre was relatively small. Hence the validity, both internal as well as external could be taken with a pinch of salt. In addition, information on co-morbidities other than active inflammatory conditions were not taken into respect, which may have influenced the analysis findings. Another limitation is the fact that we did not measure and analyze other systemic inflammatory serum markers, such as CRP and pro-calcitonin.

CONCLUSION

Neutrophil lymphocyte ratio and platelet lymphocyte ratio are well correlated with colo-rectal carcinomas, especially with regard to the TNM staging. Since both of these parameters are cost-effective, and easily measurable, they can be suggested to be included in routine assessment of the patients. However, it is to be kept in mind that these values can be affected by various factors including race, sex, age, co-morbidities and many others. Estimation of these ratios can serve as useful adjunct to clinical staging and imaging in patients with colo-rectal cancers as well as help to predict prognosis.

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