ORIGINAL ARTICLE

The lymphocyte-to-monocyte ratio is a superior predictor of tumor stage and grade in comparison to established biomarkers of resectable colorectal cancer

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Abstract

Colorectal carcinoma is one of the most common cancer inflicting both male and female gender, more than 1.4 million cases diagnosed every year.

Inspite of lot of research work and recent advances cervival in advance stages remains poor.

To reduce mortality we will have to diagnose colorectal cancer at an early stag so that adjuvant chemo-radiotherapy and resection can be done.

Material and methods: It is a retrospective cohert study carried in the Department of Surgery, Liaquat National Hospital and Medical College, Karachi from January 2014 till December 2016.

Results: Total 139-consecutive patients of colo-rectal cancer included in this study. After meeting the inclusion and exclusion criteria 96-patients were included in this study. Our result showed that low lymphocyte-to-monocyte ratio is associated with advanced tumour stage-III and IV and in comparison high lymphocyte-to-monocyte ratio was associated with tumor stage I and II.

Conclusion: The lymphocyte-to-monocyte ratio is an independent and superior predictor of tumor stage and grade in comparison to the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) and can be used effectively in the management of colorectal malignancies.

Keywords: Colorectal cancer, carcino-embryonic antigen (CEA), alfa feto protein, lymphocyte-to-monocyte ratio, TNM stages of colo-rectal cancer

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Introduction:

World wide, colorectal cancer (CRC) remains third leading causes of cancer related deaths, and was the 3rd most common in males and 2nd most common in females, with more than 1.4 million cases diagnosed each year.[1] Despite recent advances, survival in advanced stages remains poor, which makes it critically important to identify it at early stage disease, and optimize treatment including use of adjuvant therapies. Still surgical resection remained the main-stay of non metastatic CRC treatment but unfortunately most of the people had advanced disease at the time of diagnosis.

It is well established that inflammation plays a critical role in the pathogenesis and progression of cancer.[2]

There is growing consensus that involved inflammation and ongoing systemic inflammatory response in the development of malignancy is associated with worse prognosis in numerous cancers.[3] The clinical and pathological TNM stages, the number of resected lymph nodes (nLNs), carcino-embryonic antigen (CEA), the lymphovascular invasion (LVI), the perineural invasion, in addition to some molecular markers (e.g. pinx1, ras, braf, mmr and so on) have been identified as prognostic markers.[4-8] But numerous weaknesses like lack of standardization, low consistency, poor reproducibility and high cost have limited their use in routine clinical application.[9-11]

Table 1:

Parameter	N	Percentage
Gender:		
Male	67	69.8
Female	29	30.2
Tumor site:		
Left colon	57	59.4
Right colon	21	21.9
Rectum	18	18.8
Tumor depth (T):		
T1	10	10.4
T2	40	41.7
T3	39	40.6
T4	7	7.3
Lymph node stage:		
N0	83	86.5
N1	12	12.5
N2	1	1.0
Tumor grade:		
Low	15	15.6
Moderate	69	71.9
High	12	12.5
Tumor stage:		
Stage 1	10	10.4
Stage 2	63	65.6
Stage 3	12	12.5
Stage 4	11	11.5

However there remains a proper prognostic marker to access colorectal cancer (CRC) patient in guiding appropriate treatment to improve therapeutic effectiveness. Thus prognostication using clinical, inflammatory, and molecular bio-marker that can be readily incorporated into routine practice to optimally predict prognosis and guide treatment has led to the study of markers of systemic inflammation in the hope of developing cost-effective prognostic bio-markers in CRC patients.

Specifically, the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) have both been studied and demonstrated to be independent prognostic markers of CRC in advanced disease patients receiving chemotherapy and in operable patients.[12-14] Of these, the NLR has been the more widely studied and has been adopted as a predictor of mortality and morbidity in other diseases.[15]

Although tumor associated macrophages which are derived from monocytes have found to be key player in tumor micro-environment, tumor progression and encouraging metastasis but has not been investigated widely despite evidence of being implicated in carcinogenesis.[16] Only recently has the lymphocyte-to-monocyte ratio (LMR) been proposed and investigated as a prognostic marker in patients with solid tumors. There is recent evidence that the pre-operative LMR is prognostic in patients with stage III and IV resectable CRC.[17] The clinical utility of the LMR across earlier stages of colon and rectal cancer, however, remains poorly defined.

In light of these recent findings, In addition, we aimed to compare the relative prognostic value of existing routinely available bio-markers in patients with CRC.

Material and methods:

This is a retrospective cohort study carried out at Liaquat National Hospital, Karachi, in department of General Surgery from January 2014 to December 2016.

Inclusion criteria: Patients who had undergone resection of their CRC between January 2014 to December 2016 were eligible for inclusion.

Exclusion criteria: Those treated endo-luminally only with histologies other than adeno-carcinoma those with partial synoptic reporting excluded patients with metastatic disease.

Results:

Total 139 consecutive patients with colo-rectal cancer treated from January 2014 to December 2016 were included in the study. After exclusion, the number of patients finalized to 96 with 67-males and 29-females. The mean age was 53.75 years. The basic characteristics of patients like age, tumor site, depth, grade and lymph node level are shown in table-1.

Cut point for LMR was defined as 2.3826. Patients were categorized in two groups i.e. High LMR (>2.38) and low LMR (≤ 2.38). The cut points for NLR and PLR are also labeled as 3.19 and 2.58 respectively.[26] 47 (48.95%) patients categorized as having low LMR and 49(51.04%) as high LMR. 89 (92.7%) were in the high NLR

Table 2: *Basic characteristics and relations with LMR groups*

Parameter	Total LMR N= 96	Low LMR N= 47	High LMR N=49	P- value
Age				
< 70 years	81(84.3)	39	42	0.712
>70 years	15()	8	7	
Gender				
Male	67(69.8)	31(66.0)	36(73.5)	0.423
Female	29(34.0)	16(26.5)	29(30.2)	
T stage				
T1	10(10.4)	2(4.3)	8(16.3)	0.008
T2	40(41.7)	15(31.9)	25(51.0)	
T3	39(40.6)	24(51.1)	15(30.6)	
T4	7(7.3)	6(12.8)	1(2.0)	
N stage				
N0	83(86.5)	36(76.6)	47(95.9)	0.008
N1	12(12.5)	10(21.3)	2(4.1)	
N2	1(1.0)	1(2.1)	0(0.0)	
Tumor stage				
Stage 1	10(10.4)	1(2.1)	9(18.4)	0.000
Stage 2	63(65.6)	27(57.4)	36(73.5)	
Stage 3	12(12.5)	9(19.1)	3(6.1)	
Stage 4	11(11.5)	10(21.3)	1(2.0)	
Tumor grade				
Low	15(15.6)	1(2.1)	14(28.6)	0.000
Moderate	69(71.9)	35(74.5)	34(69.4)	
High	12(12.5)	11(23.4)	1(2.0)	
Tumor Site				
Left colon	57(59.4)	27(57.4)	30(61.2)	0.333
Right colon	21(21.9)	13(27.7)	8(16.3)	
Rectum	18(18.8)	7(14.9)	11(22.4)	
NLR				
Low ≤3.19	7(7.3)	0(0.0)	7(14.3)	0.012
High >3.19	89(92.7)	47(100)	42(85.7)	
PLR				
Low ≤ 258	94(97.9)	45(95.7)	49(100)	0.237
High >258	2(2.1)	2(4.3)	0(0.0)	

group, whereas 7-patients (7.3%) were in the low group. For the PLR, high group has 2 (2.1%) patient while low group PLR has 94 (97.9%) patients. Table-2 illustrating the basic parameters of patient in relation to the low and high LMR groups. Male patients (69.8%) were pre dominating the females. Patients younger than 70-years of age were the major cohort of study population (84.3%). Most of the patient suffering from tumors of T stage ⅔ (41.7%/40.6%), and N stage 0(86.5%), with intermediate grade being the commonest type (71.9%). Left-sided colon tumors (59.4%) had the most frequent occurrence compared to 21.9% right-sided colon tumor and 18.8% rectal tumors.

The results showed no association of LMR with either age (P=0.712) or gender (P=0.423). However, significant association was found between T-stage (P=0.008), N-stage (P=0.008) and tumor grade (P=0.000) and LMR but not between LMR and site (p=0.333). Majority of patients with higher T-stage (51.1% in stage 3 and 12.8% in stage IV) were found to have a low LMR while in comparison high LMR was found to be associated with T-stage 1 and 2, that is 16.3% and 51.0% respectively. The data also concluded that the patient with low LMR were more often had the moderate or high-grade tumors (74.5/23.4%) in contrast to only 2.1% with low LMR patient having low grade tumor. overall tumor stage was noted to be significantly associated with LMR groups (p-value=0.000). Most of the patients in high LMR group were diagnosed with stage-1 and 2 tumor, 18.4% and 73.5% respectively. This is in contrast to only 6.1% and 2.0% patient of stage-III and stage-IV in the low LMR group. The association between tumor site and LMR was not defined as significant.

Both NLR and PLR were not found to have a significant association with tumor stage (p-value 0.497 and 0.784 respectively), However our study does found a significant association between LMR and NLR groups (P=0.012) but not with PLR (P=0.237). To a surprising extent, all the patients with high NLR had low LMR (100%).

Discussion:

A number of studies in past have found an association between the poor outcome and markers of the systemic inflammatory response in patients with either operable or unresectable colorectal cancer. However, what has been not decided is which marker of systemic inflammatory response is best to predict the outcome.[1] As the understanding develops regarding intricate relationship between the tumor micro environment and host's inflammatory response, it enables the physician to deal the malignancies with a better approach. In the past, C-reactive protein (CRP) elevated level were linked with the prognosis in primary colorectal malignancies.[2,3]

Though not completely understood, an association between tumor progression and raised levels of netrophills and monocytes has been found. The role of tumor micro environment in directing and controlling the white blood cells and there by inducing angiogenesis and invasion is well documented in literature.[4-7] Blood monocytes derived macrophages are proposed to be of critical importance in tumor- host relationship.[8] Neutrophills, a major component of leukocytes entity fight against a variety of tumor cells with their highly toxic granules. In addition they also have membrane receptors that help in identification and removal of micro-organism and tumor cells.[9] In ab number of malignancies including ovarian,[10] breast,[11] renal,[12] pancreatic cancers,[13] poor outcome has been linked to the decreased levels of lymphocyte number and function. Another pre-operative marker, neutrophil-lymphocyte ratio (NLR), has also been studied in predicting the outcome in colorectal[14] and ovarian cancer[15] population. Chua et al in their study compared the prognostic value of neutrophil-lymphocyte ratio (NLR) and derived neutrophil-lymphocyte ratio (dNLR). They concluded that the prognostic value of both the markers is similar so they can be used inter-changeably to predict survival in all cancer.[16] In another study by Chua et al, the results highlighted the crucial role of NLR in predicting the outcome in metastatic colorectal malignancies.[17] Similar results were stated in another study that concluded the NLR as an independent prognostic bio-marker for overall survival and cancer specific survival.[18]

Growing evidence suggests an important role of inflammation in tumor progression and metastasis has been studied in the recent past in relation to the inflammatory response. The stimulating as well as inhibiting effects of macrophages/ monocytes on the tumor cell progression has made their role controversial.[19] Dunn et al[20] stated the importance of lymphocytes as an integral component of immune system and backbone of immunosurveillance. Rabinowich et al[21] identified lymphocytes as the trigger for inducing an anti tumor reaction. In addition apoptosis of cancer cells was proven to be stimulated by synergistic interaction of CD4 and CD8 T-lymphocytes.[22,23] In other way round Hoffman[24] attributed the week immunologic reaction against tumor to the low level of lymphocytes in blood. Few studies in recent past have worked on the role of lymphocyte to monocytes ratio in predicting the prognosis in colorectal cancer patient[25] but with a variety of limitations.

Chan et al in their recent study concluded that the pre-operative LMR is a superior predictor of overall survival in colorectal cancer patients[26] in comparison to NLR and PLR. In our study we have evaluated the role of pre-operative LMR in predicting the stage and grade of tumor. The study also figured out the associations between LMR and age, gender, site of tumor, lymph node status, PLR and NLR. It was noted that the age and gender were independent factors and have no association with LMR. Similarly LMR has no liaison with the tumor site as it is also stated by Shibutani M et al[27]and Stotz et al[28] though this is in contradiction with the findings documented by Chan et al[26] that the left sided tumor had the low LMR level. We have witnessed the LMR association with the T-stage, N-stage of tumor, with high LMR mostly present in the patients presented with t-stage 1 or 2 and N0 lymph node status. In contrast, previous studies showed no association between LMR and lymph node status.[26,28] With our study we noticed a link between LMR and NLR similar to the findings by Shibutani M et al.[27] Furthermore, the study demonstrated a remarkable significance of pre-operative LMR with the tumor stage and grade. Patient with low LMR level were diagnosed with higher stage i.e. stage 3 and 4 cancer as also demonstrated by Chan et al.[26]

Our study pointed out the predictive value of LMR for the tumor grade. High grade tumor frequently associated with the low pre-operative LMR levels, similar results were reported by Chan et al contrary to the findings by Stotz et al.[28] These findings are directing towards the crucial role of LMR as an essential driver for tumor progression and invasion. We also compared the predictive prognostic value of LMR. NLR and PLR for tumor staging and the resulted clearly declared the LMR to be a superior predictor for

colorectal tumor stage prediction. The same results were reported by Chan et al.

Though our study has some limitation like it is a retrospective study and the follow up data is awaited to predict the overall survival, one thing is clearly evident that LMR is a better clinical marker to predict the stage and grade in patients with colorectal malignancies.

Conclusion:
The lymphocyte-to-monocyte ratio (LMR) is an independent and superior predictor of tumor stage and grade in comparison to the NLR and PLR and can be used effectively in the management of colorectal malignancies.

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Role and contribution of authors:
Dr Arslan Abro, collected the data, references and did initial write up.

Dr Faisal Siddiqui, helped in collecting the data, introduction and discussion and conclusion writing.

Dr Ahmer Ali, collected the references and helped in discussion writing.

Dr Afsheen Javaid Khokar, collected the references and helped in interpretation the data, went through the article did critical analysis and did final changes

Samiullah Khuhro collected the data and references.

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