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Study of neutrophil to lymphocyte ratio and lymphocyte to monocyte ratio in patients diagnosed with gastric carcinoma

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Abstract
Background: Carcinoma of the stomach stands as the fourth most common type of cancer worldwide but there have been no specific biomarkers has been identified for GC. Present studywas aimed to evaluate Neutrophil to Lymphocyte ratio and Lymphocyte to Monocyte Ratio in patients diagnosed with Gastric Carcinoma. Present study was aimed to evaluate Neutrophil to Lymphocyte ratio and Lymphocyte to Monocyte Ratio in patients diagnosed with Gastric Carcinoma.

Keywords: Neutrophil lymphocyte ratio, Lymphocyte monocyte ratio, gastric cancer, GI endoscopy

Introduction
Gastric cancer constitutes a global health problem, with more than one million new cases and 768,000 deaths in 2020, making it the fifth most frequently diagnosed cancer and the third leading cause of cancer-related deaths all over the world [1, 2]. Patients with gastric cancer always had a poor prognosis, since gastric cancer is generally diagnosed at an advanced or metastatic stage, with limited opportunity to receive radical operation. The median survival time for patients diagnosed with advanced or metastatic disease is <12 months [3, 4]. It should be an urgent need to prolong the survival time in such patients.
Nivolumab, a fully human IgG4 monoclonal antibody inhibitor of programmed death-1, has emerged as the first one to show superior survival time, with a median overall survival time exceeding 1 year in the first-line setting for patients with non-HER2-positive gastric, gastroesophageal junction, or esophageal adenocarcinoma [5]. However, 64% of patients who received nivolumab plus chemotherapy as first-line regimen still had disease progression in 1 year [5]. Subsequent monotherapy with pembrolizumab, another immune checkpoint inhibitor, has failed to improve survival time compared with paclitaxel for advanced gastric or gastroesophageal junction cancer with PD-L1 CPS of 1 or higher [6]. The current efficacy of further line treatment strategies could not satisfy clinical demand.
In most recent years, it is reported that the re-challenge of PD-1/PD-L1 inhibitors as further line treatment might still be effective in selective patients [7]. However, few studies were conducted to investigate the specific profiting population, with the mechanism of re-challenge remaining to be explored. A recent retrospective pooled analysis demonstrated that high pretreatment neutrophil to lymphocyte ratio (NLR) was significantly associated with poorer progression-free survival time (PFS, HR = 1.44, 95% CI 1.26–1.65; p<0.001) and overall survival time (OS, HR = 2.86, 95% CI 2.11–3.87; p<0.001) compared with those with low pretreatment NLR in patients with non-small cell lung cancer [8]. In addition, similar outcomes were also observed in metastatic melanoma and renal cell carcinoma [9].
Present study was aimed to evaluate Neutrophil to Lymphocyte ratio and Lymphocyte to Monocyte Ratio in patients diagnosed with Gastric Carcinoma.

Material and methods
Present study was hospital based, Unmatched Case Control Study was conducted in department of general surgery and surgical superspecialities at Justice K.S. Hegde medical academy, Deralakatte, Mangalore, India. Study duration was from January 2019-June 2020. Study was approved by institutional ethical committee.

Inclusion criteria

For cases

- Biopsy proven patients of Gastric Carcinoma (including Carcinoma Gastroesophageal junction) giving consent to take part in study.

For controls

- Patients with features of presentation similar to that of Gastric carcinoma and undergoing UGI endoscopy, and histopathological features other than Gastric Carcinoma & Carcinoma Gastroesophageal junction constitute Controls.

Exclusion Criteria (for both cases and control)

- Patients with fever
- Patients with chronic inflammatory diseases -tuberculosis, rheumatoid arthritis
- Pregnant patients

Study was explained to patients & a written informed consent was taken for participation. Patients were subjected to detailed history taking and clinical examination (Gender, Symptoms (vomiting, dysphagia, loss of appetite, loss of weight), history of smoking, alcoholism, family history of cancers, Pallor, Icterus, Cyanosis, Clubbing, Generalized Lymphadenopathy, bilateral pedal edema), UGI endoscopy, biopsy. From all the patients (cases and controls), 3ml of venous blood was drawn and DLC values were obtained to determine the levels of Neutrophil to Lymphocyte ratio (NLR) and Lymphocyte to Monocyte Ratio ((NLR). NLR, LMR ratio in GC was compared to Controls.

Data was collected and compiled using Microsoft Excel, analysed using SPSS 23.0 version. Difference of proportions between qualitative variables were tested using chi- square test or Fisher exact test as applicable. P value less than 0.5 was considered as statistically significant.

Results

Table 1: Age & gender distribution

Age	Control		Cases	
	Count	%	Count	%
10 – 19	2	2.0%	0	0.0%
20 – 29	12	12.0%	1	1.6%
30 – 39	16	16.0%	3	4.8%
40 – 49	24	24.0%	10	15.9%
50 – 59	25	25.0%	16	25.4%
60 – 69	14	14.0%	19	30.2%
70 – 79	6	6.0%	11	17.5%
80 – 89	1	1.0%	3	4.8%
Gender				
Male	44	44.0%	40	63.5%
Female	56	56.0%	23	36.5%

Table 2: Cross-tabulation of comparison of the median values of NLR and LMR between the groups

	Control			Cases			P-value
	N	Median	IQR	N	Median	IQR	
NLR	100	2.32	2.24	63	3.8	4.35	0.000*
LMR	13	19.83	28.33	62	6.37	8.54	0.001*

Table 3: Accuracy of the NLR and LMR in detecting cancer

Parameters	NLR	LMR
Cut-off value	2.61	7.83
Sensitivity	53.6	85.1
Specificity	77.2	24.1
PPV	71.4	64.5
NPV	61	50
Area under the curve	0.71	0.819

Discussion

In a study done by Wang SC, *et al*., [10] on pre-treatment neutrophil to lymphocyte ratio independently predicts disease free survival in resect able GE junction and gastric adenocarcinoma, 62% of cases were males (p-value 0.001), the median age of diagnosis was 66 years and significant association was noted (p-value 0.001). Similar findings were noted in present study.

In a study done by Jayalekshmi P A, *et al*., [11] on Gastric cancer risk in relation to tobacco use and alcohol drinking in Kerala, 65553 men of age 30-84years studied for a period from 1990 to 2009, 116 GC cases in the cohort were studied. This study analysed the risk factors like smoking, tobacco and alcohol habits of male cohort in South India. Risk of GC increased with the number and duration of bidi smoking (P = 0.017). Similar findings were noted in present study.

In a study done by N Nakaya, *et al*., [12] on Alcohol consumption and the risk of cancer in Japanese men, 40–64 years of aged males were included and the association between alcohol consumption and the risk of total cancer in Japanese male population. This study concluded that the risk of total cancer was higher in ex alcoholics and current alcoholics than in non-alcoholics. Study also concluded that there is a linear association between total cancer risk and amount of alcohol consumed. Similar findings were noted in present study.

In a study done by Moy KA, *et al*., [13] on alcohol and tobacco use in relation to gastric cancer, 18,244 subjects were studied. Cigarette smoking and alcohol use had shown significant association with gastric cancer (HR, 1.59; 95% CI, 1.27-1.99 and HR, 1.46; 95% CI, 1.05-2.04). Subjects with both alcohol and tobacco use had a two-fold increase in the risk of development of gastric cancer (p-value= <0.0001).

In our study the median NLR was higher in patients with gastric cancer (3.8) as compared to controls (2.32). Mann-Whitney testwas applied between the groups and was found to be statistically significant (p-0.000). Pre-treatment neutrophil to lymphocyte ratio independently predicts disease free survival in resectable GE junction and gastric adenocarcinoma, median NLR in cases was 2.8. Disease free survival to NLR showed statistical significance (p-value 0.001) [14].

A study done by Dan Hu *et al*., [15] on Elevated preoperative neutrophil-to-lymphocyte ratio can predict poor survival in early stage gastric cancer patients receiving radical gastrectomy: The Fujian prospective investigation of cancer (FIESTA) study showed that NLR of >2.61 (p<0.001) was significantly associated with an increased risk of gastric cancer mortality, while LMR <9 (p<0.001) was associated with a reduced risk.

In our study LMR was lower in patients with gastric cancer (6.37) as compared to controls (19.83) and it showed statistically significance (p-0.001). The cut off value for LMR was 7.83 with sensitivity of 85.1% and specificity of 24.1%. Study done by Jun-Peng Lin, *et al*. [16] on preoperative Lymphocyte to monocyte ratios as aimportant predictor of recurrence and

survival in gastric cancer after radical intent surgery LMR was significantly lower in patients with GC than in matched normal volunteers (p<0.001). The long-term outcomes were found to be poorer in the group with LMR <3.5 than in the group with high LMR (<3.5). Study also showed that LMR was an independent prognostic factor for overall survival (p<0.001) and Recurrence free survival (p<0.001). The recurrence rate was high in the low LMR group than as compared to high LMR group (p<0.05). The LMR also showed correlation with metastases to liver and lymph node (p<0.05).

A study done by Zhou D *et al*., [17] on a retrospective analysis of 103 patients on the prognostic value of pre-treatment combined RDW + Neutrophil lymphocyte ratio (NLR) showed high prognostic significance for overall survival in patients with gastric carcinoma. (HR: 3.252, 95% CI: 1.289–8.203, and p – 0.001) and high NLR (>2.755) had a more probability of poor OS and PFS than the low NLR group.

A study done by Aksoy EK *et al*., [18] on 'The importance of complete blood count parameters in the screening of gastric cancer', compared 73 gastric cancer patients, 79 patients with intestinal metaplasia and 70 healthy subjects. 2.11 was the cut-off value of NLR (sensitivity: 64.4%, specificity: 63.1%) and it showed statistical significance p<0.001. Significant association was also noted for mean platelet volume, platelet distribution width, platelet-to-lymphocyte ratio, monocyte-to-lymphocyte ratio in this study. They concluded that these had significant association with GC and intestinal metaplasia. In our study cut off value for NLR is 2.61, the sensitivity and specificity were found to be 53.6% and 77.2% respectively.

Area under the curves shows that LMR has more area under the curve (0.806) than NLR (0.71). With cut off value of 2.61 for NLR in cases, the sensitivity and specificity were found to be 53.6% and 77.2% respectively. The cut off value for LMR was 7.83in cases with sensitivity of 85.1% and specificity of 24.1%. Both the parameters were found to be significant. (p<0.05). Simple and routine blood counts from which NLR and LMR can be easily calculated which may be used as potential biomarkers can aid in detecting gastric cancer.

Conclusion

Neutrophil lymphocyte ratio and Lymphocyte monocyte ratio can be used in resource poor settings to aid in the early diagnosis of patients with suspicion of gastric cancer.

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