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Original Research Article

Derived neutrophil by lymphocytes ratio is a misnomer, implication of derived leucocytes ratio in diagnosing gastric cancers

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ABSTRACT

Background: Gastric malignant neoplasms are well-known common malignant disease seen in routine clinical practice. In India incidence are comparatively low but accounts for significant mortality and morbidity. Gastric malignancy incidence adds significant numbers every year to cancer related deaths worldwide. And prognosis is not satisfactory in spite of medical innovations and technological advancements. Early diagnosis helps for successful surgical removal of gastric cancer and to achieve a curative resections. Present study objectives are to solve the paradox of misnomer derived neutrophil by lymphocyte ratio and to evaluate statistical differences of blood leucocyte parameters in patients with gastric malignancies as compared to control cases and its application as screening markers in diagnosing gastric cancers.
Methods: Hundred cases of gastric malignancy and hundred controls-age, gender matched to cases without malignancy or infection were included. Both groups evaluated with routine complete blood count and upper GI endoscopy reports, Data regarding WBC counts, neutrophil counts, lymphocyte counts, monocytes, eosinophils and basophils were noted and Derived Leucocytes Ratio (DLR) were calculated and compared to look for statistical differences.
Results: Hematological leucocyte parameters revealed statistical differences in gastric cancer patients in comparison to controls. Neutrophils were increased and lymphocytes decreased with elevated DLR levels.
Conclusions: Leucocyte parameters like neutrophils and lymphocytes shows varying trends in gastric cancer and elevated derived leucocytes ratio can be utilized as a screening marker in Gastric cancers.

Keywords: Derived leucocytes ratio, Derived neutrophil/lymphocyte ratio, Gastric cancer, Leucocyte parameters, Misnomer, Screening markers

INTRODUCTION

Gastric cancer is a well-known common malignancy seen in routine clinical practice. Gastric cancer shows a wide geographical variation, with high incidence in China and Japan. In India incidence are comparatively low, but accounts for significant mortality and morbidity. Gastric malignancy incidence adds significant numbers every year to cancer related deaths worldwide. Gastric cancer is a malignant disease with third leading cause of global cancer death, with a high mortality rate despite the decreasing incidence in the recent decade globally.[1] Whereas in china it is second most common cancer and the third leading cause of death.[2] Despite significant progress in the diagnosis and treatment of gastric cancer, prognosis still remains poor, could be due to delayed presentation, local relapses or metastasis after surgery due to inadequate resection or inability to achieve R0 resection. Newer innovations have brought significant changes in the detection and treatment of gastric cancer, but overall 5-year survival rates are not satisfactory. Due to multifactorial reasons prognosis still remains poor.

Early diagnosis helps in the successful surgical removal of gastric cancer and prevents local advancement of tumor and other technical difficulties in surgical removal. Omentum and peritoneal spread, distal metastases occurs in the late stages and reduces the efficacy of treatment.[3,4] Inflammation plays an important genesis role in the initiation and development of tumor growth.[5] Chronic inflammation, repeated, prolonged unresolved infection and persistent inflammation may lead to malignancies like gastric carcinoma.[6] Tumor cells stimulates and activates neutrophils and monocytes and releases specific chemokine's, cytokines and prostaglandins.[7,8] Tumor cells also activates other hematological parameters like platelets and alters RBC indices. Lymphocytes has antitumor effect and tries to restrict tumor cells by cytotoxic T-cell mediated apoptosis.[9]

In the literature several studies have been described and documented the statistical significant role of derived neutrophil/lymphocyte ratio (dNLR) in various malignancies. To enumerate a few-Wood G et al, and Grenader T et al described the prognostic role of derived neutrophil by lymphocytes in colorectal malignancy, similar other studies like Ascierto FP, et al in malignant melanoma, Ren K et al and Li Y et al and Krenn-Pilko S et al and Dirican A et al in breast cancer (denominator--WBC-lymphocytes), Du JH et al in metastatic gallbladder carcinoma, Sylman JL et al and Proctor MJ in various malignant conditions, Suzuki R et al in pancreatic carcinoma, Zhou D et al in hepatocellular carcinoma, Szkandera J et al in soft tissue scarcomas and Absenger G et al in colon carcinoma.[11-22] Deng et al in gastric carcinoma.[2]

$$\text{Derivation of dNLR} = \frac{\text{Absolute neutrophil count}}{\text{Total white cell count} - \text{Absolute neutrophil count}}$$

In denominator WBC is subtracted with neutrophils counts, so denominator is formed by other variants of leucocytes such as lymphocytes, monocytes, eosinophils and basophils. So, it is a ratio of neutrophil counts/other variants of leucocytes. Neutrophils and lymphocytes together form the majority of circulating leucocytes in blood. Though normally monocytes and other variants of leucocytes accounts for small percentage of leucocytes in blood. In malignancy as described above, there is a rise in neutrophils and monocytes, whereas lymphocytes decreases, forming a comfortable tumor microenvironment for cancer cells to develop and progress with the influence of chemokines and other biomolecules.[9,23]

In a study by Fan Feng et al, on gastric malignancy described increased monocytes and decreased lymphocytes, with monocytes and lymphocytes are independent predictors of prognosis.[24] In malignancy monocytes can increase and together with lymphocytes and other variants of leucocytes their number increases. Based on these findings, we describe that the terminology derived neutrophil/lymphocyte is a misnomer. Since denominator of the ratio is not just formed by lymphocytes, it includes all other leucocyte variants except neutrophils. So, we feel that proper terminology to be used to describe this ratio is derived leucocytes ratio. So, in this present study, we tried to evaluate the role of hematological biomarker derived leucocyte ratio in gastric cancer as screening marker.

METHODS

It's a retrospective single center study conducted at a tertiary care hospital. About two hundred medical records were included in the study presented from January 2015 to August 2018. Institutional ethical committee approval was taken, with no proposed funding source and no conflict of interests.

Inclusion criteria

Around 100 cases of gastric malignancy are selected as CASES. For each case - age, gender, TNM stage of the disease, complete blood count values and upper gastrointestinal endoscopy findings and histopathology reports were noted.

Exclusion criteria

Patients with altered liver/renal function test or with the active form of infection, presence of autoimmune disease and medical comorbidities were excluded. Equal number control were selected. The upper GI endoscopy register was scanned for age and gender matched to cases. And selected as control if their upper GI endoscopy was normal, and did not suffer from hypertension, diabetes mellitus, hepatic or renal failure, hyperlipidemia, and autoimmune disease and were not on antiplatelet drugs but had undergone evaluation for complete blood counts.

Data regarding WBC counts, neutrophil count, lymphocyte count, monocytes, eosinophils and basophils were noted and derived leucocyte ratios were calculated. Data was processed using SPSS software, to compare and analyze between cases and control groups and looked for statistical significance (p value <0.05). Data was further evaluated with Receiver operating curve analysis to obtain optimal cut off values.

RESULTS

Total 200 medical records of patients belonging to cases (100) and control (100) groups were statistically analyzed and evaluated with the following results. The Majority of our study group patients belong to late middle age and elderly individuals, with a mean age of 60 years. About 65% of the patients belong to 50-70-years age group. Figure 1 shows graphical representation of age distribution of patients involved in our study group.

About 65% of them were males and 35 % were females. Figure 2 is a bar chart of gender distribution of study

population involved in our study. About 4% in stage I disease and 14% in stage II disease, due to the small number of stage I disease, we clubbed both stage I and II as early gastric cancer-18% of patients, about 37% had stage-III disease and remaining 45% had stage-IV disease. Stage wise distribution of cases of gastric cancer involved in our study are graphically described in pie-chart graph in Figure 3.

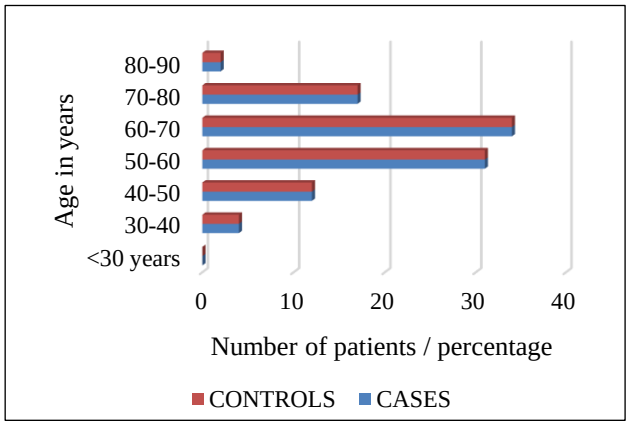

Figure 1: Age distribution.

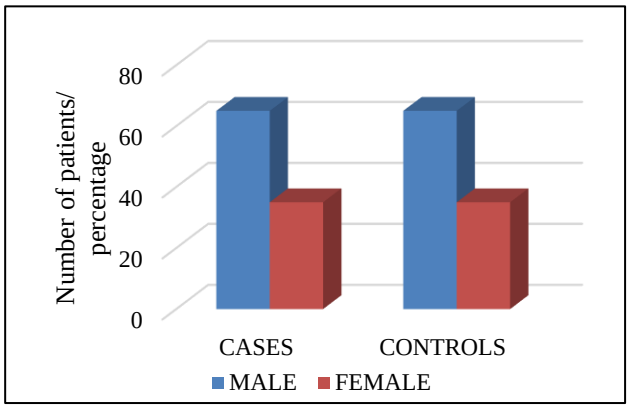

Figure 2: Gender distribution.

Statistical analysis of cases (group 1) (gastric cancer) and control (group 0) groups are shown in Table 1 that contains mean and standard deviation with statistical significance p value of blood parameters-absolute neutrophil count, absolute lymphocyte counts, absolute monocyte count, basophil and eosinophil count and derived leucocyte ratio.

Statistical difference with p value <0.05 was noted with absolute neutrophil count, absolute lymphocyte count and derived leucocyte ratio. There was no statistical significance with other leucocyte variables like monocytes, basophils and eosinophils and even total WBC in our study groups.

Stage wise data analysis with Dunett's t-test proved that the derived leucocyte ratio worsens as stage advances results tabulated in Table 2 that contains stage wise mean and standard deviation data. As stage advances (stage I to stage IV) mean value in different groups (group 2 to group 4) also increased.

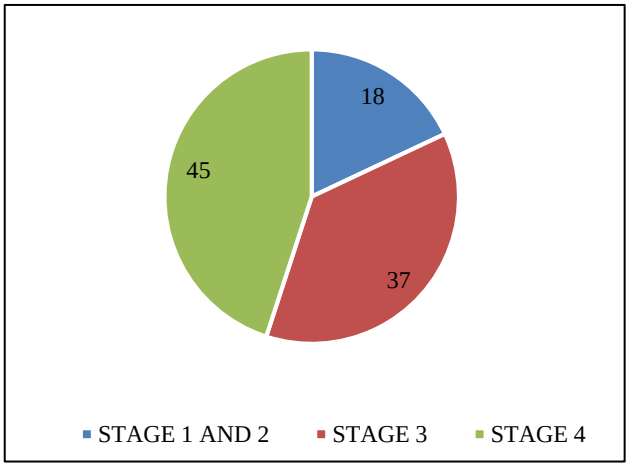

Figure 3: Stage wise gastric cancer distribution.

Table 1: Group 0: control, group 1: cases with gastric cancer.

	Group 0		Group 1		
Blood parameters	**Mean**	**SD**	**Mean**	**SD**	**Significance (P value <0.05)**
ANC	4646.57	1514.41	5717.26	3059.9	0.002
ALC	2372.6	786.25	1730.42	783.3	<0.001
AMC	698.4	182.19	645.67	298.96	0.134
Eosinophil	279.1	2.67	246.8	3.76	0.464
Basophil	47.79	0.28	38.1	0.38	0.141
DLR	1.49	0.68	2.44	1.74	<0.001

ANC-absolute neutrophil count, ALC-absolute lymphocyte count, AMC-absolute monocyte count. DLR- Derived Leucocyte Ratio

To obtain optimal cutoff values for above hematological parameters, Receiver operating curve analysis was done. Results shown in Figure 4, which shows ROC curves of DLR, absolute neutrophil (ANC) and lymphocyte counts. DLR and ANC values increases, whereas lymphocyte values (AUC-70% with 95% CI-0.63-0.77) decreases so curves are seen on either sides of reference line accordingly. In Table 3, optimal cut off values,

sensitivity, specificity with area under curve values and 95% confidence interval (CI) of derived leucocyte ratio and neutrophils counts are summarized.

Table 2: Group 0: control, group 2: early gastric cancer stage I and II, group 3: stage III, group 4: stage IV.

Group		Neutrophils	Lymphocytes	DLR
0	Mean	4646.57	2372.61	1.49
	N	100	100	100
	SD	1514.41	786.25	0.684
2	Mean	5187.03	2095.68	1.917
	N	18	18	18
	SD	2329.92	858.98	1.182
3	Mean	4846.29	1636.45	2.1
	N	37	37	37
	SD	2562.16	574.035	1.29
4	Mean	6645.48	1661.57	2.94
	N	45	45	45
	SD	3458.95	871.26	2.11

N-number of patients. DLR- derived leucocytes ratio

Table 3: ROC curve analysis report with optimal cut off values of absolute neutrophil counts and derived leucocyte ratio.

Variables	Cut off values	Sensitivity %	Specificity %	Area under curve (AUC)	Confidence interval
ANC	4510	57	52	0.55	0.50-0.65
DLR	1.5	68	55	0.67	0.6-0.74

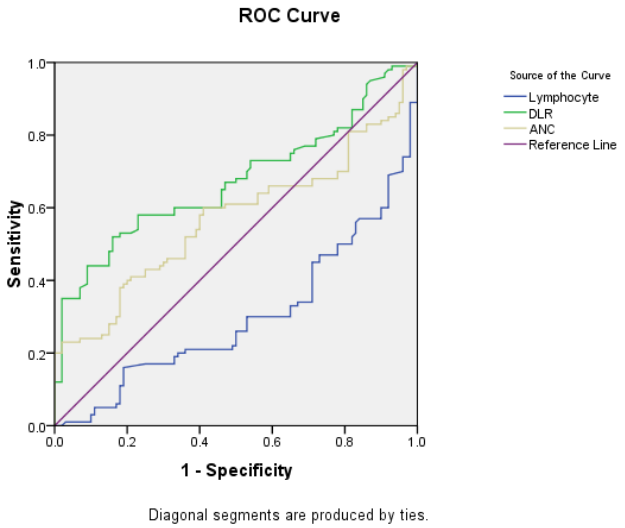

Figure 4: ROC curves of DLR, absolute neutrophil (ANC) and lymphocyte counts.

DISCUSSION

On statistical evaluation of 200 medical records details in our retrospective study found hematological leucocyte parameters-neutrophils and lymphocytes were statistically different in Gastric carcinoma patients and control group patients.

Most of the patients in gastric malignancy group belong to late middle age and early elderly individuals with a mean age of 60 years. Neutrophil and lymphocyte counts were both statistically significant, neutrophil counts showed an increasing trend and lymphocyte count decreased trend in patients with gastric malignancy as compared to control group. With a mean of 5.7k/ul and 4.6k/ul for neutrophils in gastric malignancy patients and control group patients. For lymphocytes obtained a mean of 1.7k/ul and 2.3k/ul for cases and control group respectively. Derived leucocyte ratio (DLR) analysis between groups showed a mean of DLR-1.49 for controls and 2.44 for gastric cancer group with a P value<0.001.

In a study by Feng F et al, on gastric cancer found high neutrophil count and monocyte count and low lymphocytes in patients with gastric cancer.[24] Hsueh et al, study on laryngeal squamous cell carcinoma found statistically significant neutrophil count difference between the groups with absolute neutrophils count cut off >4.3k/ul.[25] Kim et al, on ovarian clear cell carcinoma study revealed elevated neutrophils and monocytes with cut off values as >4.37k/ul and >0.39k/ul for neutrophils and monocytes respectively.[26] Preoperative evaluation of leucocyte parameters by Wang et al on gastric

malignancy found increased neutrophils >7.5k/ul.[27] In our study, we found similar results with increased absolute neutrophil counts and decreased absolute lymphocyte counts both were statistically significant with a P value <0.05. But we did not find any statistically significant differences in monocyte counts. On ROC curve analysis for optimal cutoff values for neutrophils and DLR obtained a cutoff value of >4.51k/ul and >1.5 respectively.

Deng Q et al, on gastric cancer study obtained an optimal cutoff of >1.85 for DLR.[2] Proctor et al, study on multiple cancers found a cut off of DLR >2.[18] In comparison with different stages, noticed that DLR worsens as stage advances. Mean DLR in early gastric cancer stage I and II was 1.92, stage III-2.1, stage IV-2.94. This shows that as stages advances DLR value increases and are associated with poor prognosis.

CONCLUSION

Based on these results we conclude that nomenclature derived neutrophil by lymphocyte ratio is a misnomer and proper terminology to be used is derived leucocytes ratio, as it is a ratio involving all variants of leucocytes in circulating blood. Leucocyte parameters are altered in patient with gastric malignancy and shows varying trends in their numbers in circulating blood. Implication of derived leucocytes ratio in atypical and nonspecific presentations of gastric cancers improves detection rate. Utilization of these simple, easily accessible and convenient blood related biomarkers as screening markers in diagnosing gastric cancers improves the diagnostic ability for better management of patients and for better survival. Higher values were noticed in advanced stages indicates associated poor prognosis in advanced gastric cancer.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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