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Haematological Parameters as Screening Markers in Upper Gastrointestinal Malignancies

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Abstract

Upper gastrointestinal cancers i.e. Esophageal and gastric cancers are common cancers worldwide and prognosis remains poor. In recent years, hematological parameters are being studied as prognostic indicators for various cancers. There are not many studies on these hematological parameters as screening markers in different cancers. So we conducted a retrospective single center study to evaluate if these blood parameters can be utilized as screening markers for upper GI malignancies.

Aims & objectives is to determine if blood parameters are significantly different in patients with upper gastrointestinal malignancies as compared to control cases.

Hundred (100) cases of upper GI malignancy and equal number of control – age, gender matched to cases without malignancy or infection was included. Both groups evaluated with routine complete blood count and upper GI endoscopy are included. Hematological parameters like hemoglobin, neutrophils and lymphocyte count, Platelet count (PC), mean platelet volume, MPV/PC ratio, red blood cell distribution width (RDW), neutrophil to lymphocyte ratio (NLR), and platelet to lymphocyte ratio (PLR) were calculated and compared to look for statistical difference.

Results proved that blood parameters are statistically different in cases (upper gastrointestinal malignancy) versus controls.

We conclude that hematological parameters can be utilized as a screening markers in upper GI malignancies.

Keywords: upper gastrointestinal malignancy, hematological parameters, neutrophil / lymphocyte ratio, platelets / lymphocyte ratio, screening markers.

Introduction

Cancers of the esophagus and stomach are associated with high mortality with poor prognosis, as most of these malignancies are diagnosed in late advanced stages. The majority of these neoplasms are detected at an advanced stage due to the insidious nature of the onset of symptoms and their similarity in early stages to benign causes of dysphagia and dyspepsia [1]. Esophageal cancer sixth leading cause of death from cancer worldwide. Gastric cancer is the sixth leading cause of malignancy and the eighth leading cause of death from cancer [2]. In India, Esophageal cancer is also the fourth most common cause of death [3]. Constant exposure to the irritants induce chronic inflammation, which results in the development of gastric cancer [4]. For example, in chronic infection of the gastric mucosa with H pylori, there is generation of inflammatory molecules. In most of the individuals, constant production of anti-inflammatory molecules prevent the formation of gastric cancer. However, inflammatory molecules are produced in larger quantities than anti-inflammatory effect of warding off the infection. Prolonged and repeated infections leads to exposure of normal mucosa to high concentrations of inflammatory molecules, which is a major reason for the causation of cancer [5]. The inflammatory response is initiated by raising white blood cells

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either locoregionally or systemically. The same has been seen in a pro-inflammatory bed of tumorigenesis. Chronic inflammation predisposes to tumor formation and tumor in-turn obtains the ability to activate various leukocytes. It activates T cells, specific chemokines and prostaglandins which reciprocate by inducing neutrophils and monocytes [6]. The pro-inflammatory state contributes to tumor growth, progression and metastasis [7]. These biomarkers are found in blood and hence forms an easily accessible parameter for assessment of diagnosis and prognosis.

Platelet/lymphocyte ratio (PLR) refers to the number of platelets to lymphocytes, platelets have cancer promoting and lymphocyte have cancer fighting roles in blood. Platelets are involved in hemostasis but also has role in cancer progression and metastasis. They can promote cancer cell extravasation *via* release of metalloproteases and tumor angiogenesis and growth at the metastatic site through release of angiogenic factors, platelet-derived growth factor (PDGF), and vascular endothelial growth factor (VEGF),[8] which enables tumor growth and metastatic spread. Platelets also protect tumor cells from killer T-cell-mediated cytolysis [9]. In a symbiotic manner, cancer cells promote a platelet count increase by release of thrombopoietic cytokines and their activation through platelet agonists [10-11].

Lymphocytes plays significant role in tumor defense by inducing cytotoxic death and inhibiting tumor cell proliferation and migration [12-13]. The PLR has been shown to have predictive value in assessing the presence and progression of cancer and the response to drug therapy [14].

Neutrophil/lymphocyte ratio (NLR) refers to number of neutrophils to lymphocytes. Neutrophils interact with cancer cells, and produce cytokines and effector molecules like VEGF that stimulate tumor angiogenesis, growth, and metastasis [15].

Materials and Methods

The study was performed at a tertiary care hospital in southwest of Karnataka, India. It's a retrospective single centre study. A total number of two hundred medical records were included in study presented from October 2015 to October 2018. Institutional ethical committee approval was taken, with no proposed funding source and no conflict of interests. *Inclusion Criteria*: 100 cases of Upper Gastrointestinal malignancy including esophageal, Gastro-Esophageal junction, and stomach carcinoma are selected as ***Cases.*** For each case - Age, gender, data regarding the location of malignancy, 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 active form of infection are excluded.

Equal number ***Control*** were selected. The upper GI endoscopy register was scanned for age and gender matched to Cases. And chosen as Control if their UGI endoscopy was normal, 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. Hemoglobin, Differential count, Platelet count (PC), mean platelet volume (MPV), MPV/PC ratio, red blood cell distribution width (RDW), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), Lymphocyte to monocyte ratio (LMR) 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

Majority of our study group patients belong to late middle age and elderly individuals, about 64% of patients belong to 50 – 70 years age group. About 68% of them were Males and 32% were Females, 24% had esophageal malignancy, 10% had GE junction malignancy and 66% had stomach malignancy. About 18% of patients belong to stage-2 disease, 36% had stage-3 disease and remaining 46% had stage-4 disease.

Statistical analysis of Cases (Group 1) and Control (Group 0) groups are shown in Table 1.

Statistical difference with p value <0.05 was noted with Hemoglobin, neutrophil, lymphocyte, Platelet count, MPV, MPV/PC, RDW, NLR, PLR.

There was no statistical significance with blood variables like monocyte, LMR in our study group though some studies have described statistical significance in their study. Stage wise data analysis with Dunetts t- test proved that hematological parameters worsens as stage advances results tabulated in Table 2, Table 3. To obtain optimal cut off values for above hematological parameters,

Receiver operating curve analysis was done. Results shown in Figure 1.

Optimal cut off values and sensitivity and specificity with AUC were summarized in Table 4.

Table 1: Group 1- cases with UGI malignancy, Group 0- controls. N- Number of patients.

Blood Parameters	Group	N	Mean	Std. Deviation	Sig. (p value)
Haemoglobin	1	100	10.3	2.69	
	0	100	13.5	1.67	<0.001
RDW	1	100	17.24	5.29	<0.001
	0	100	13.74	1.41	
Neutrophil	1	100	65.75	14.71	<0.001
	0	100	57.21	12.04	
Lymphocyte	1	100	20.91	9.79	<0.001
	0	100	29.73	8.91	
Monocyte	1	100	7.85	3.13	0.091
	0	100	8.57	2.79	
Eosinophil	1	100	2.73	2.84	0.269
	0	100	3.11	1.94	
Basophil	1	100	0.48	0.37	0.081
	0	100	0.61	0.62	
Platelet	1	100	333030	110051.5	<0.001
	0	100	257500	55059.1	
MPV	1	100	7.99	0.81	0.019
	0	100	8.36	1.29	
MPV/Platelet	1	100	2.8E-05	0.0000126	<0.001
	0	100	3.5E-05	0.000014	
Neutrophil/Lymphocyte	1	100	6.24	16.84	0.021
	0	100	2.31	1.55	
Platelet/Lymphocyte	1	100	310.82	105115.5	0.043
	0	100	96.04	4210.52	
Lymphocyte/Monocyte	1	100	4.39	12.12	0.608
	0	100	3.76	1.59	

Table 2: Stage Wise Comparision: Group 0- controls, Group 2- stage II, Group 3- stage III, Group 4- stage IV, N- number of patients.

Column 1	Column 2	Column 3	Column 4	Column 5	Column 6	Column 7
Group		Hemoglobin	Platelets	MPV	Lymphocyte %	RDW
0	Mean	13.3	257500	8.35	29.72	13.74
	N	100	100	100	100	100
	Std. Deviation	1.67	55059.105	1.2989798	8.9192571	1.4051852
2	Mean	10.5	309166.67	8.2	19.92	16.01
	N	18	18	18	18	18
	Std. Deviation	3.046	104140.88	0.8947377	11.3178571	2.6265363
3	Mean	9.9	332638.89	7.93	24.54	18.37
	N	36	36	36	36	36
	Std. Deviation	2.82	97428.993	0.7768628	9.4787126	6.2245877
4	Mean	10.5	342673.91	7.9	18.44	16.82
	N	46	46	46	46	46
	Std. Deviation	2.44	121827.21	0.8051795	8.695403	5.1869681
Total	Mean	11.8	295265	8.17	25.3175	15.48
	N	200	200	200	200	200
	Std. Deviation	2.68	94692.864	1.0947678	10.33725	4.236638

Table 3: Stage Wise Comparision: Group 0- controls, Group 2- stage II, Group 3- stage III, Group 4- stage IV, N- number of patients.

Group		Neutrophil-Lymphocyte	Platelet-Lymphocyte	MPV-Platelet
0	Mean	2.31	96.04	0.000035
	N	100	100	100
	Std. Deviation	1.5461525	4210.5249	0.000014
2	Mean	5.9	247.24	0.000031
	N	18	18	18
	Std. Deviation	5.4107934	23793.347	0.0000169
3	Mean	3.56	162.09	0.000027
	N	36	36	36
	Std. Deviation	3.7752453	9392.2193	0.0000113
4	Mean	8.46	452.09	0.000027
	N	46	46	46
	Std. Deviation	24.322121	153716.45	0.0000115
Total	Mean	4.27	203.43	0.000031
	N	200	200	200
	Std. Deviation	12.095474	74977.274	0.0000138

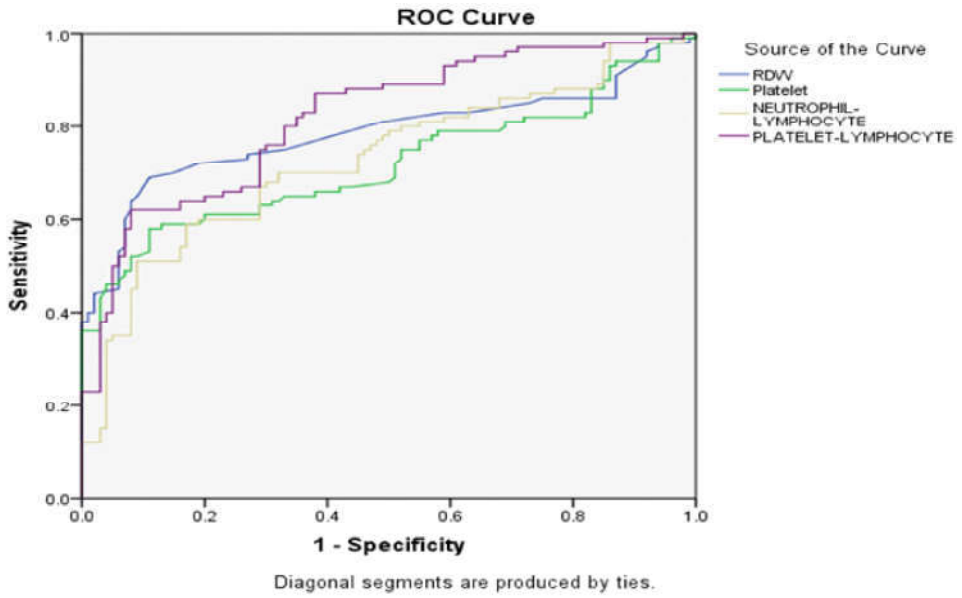

Fig. 1: ROC Analysis

Table 4: Optimal Cut off Values

Variables	Cut off Values	Sensitivity	Specificity	Area Under Curve (Auc)	Confidence Interval
RDW	14.5	0.70	0.89	78%	0.72-0.85
Neutrophils/ Lymphocytes	2.3	0.75	0.65	73%	0.73-0.87
Platelets/Lymphocyte	117.3	0.70	0.71	82%	0.73-0.77
MPV/Platelets	0	0.66	0.76	70%	0.63-0.77

Discussion

Mean hemoglobin value in group 1 was 10.3 g/dl as compared to group 0 which is 13.3 g/dl so patients with upper GI malignancy had low hemoglobin levels. Mean value of RDW in group 1 was 17.24 as compared to group 0 which is 13.74, normal range from our institute laboratory for RDW is 11.5 to 14. Hence, RDW values were elevated in patients with Upper GI malignancy above normal range but in control group it was well within normal range. Neutrophil and lymphocyte counts were

both statistically significant, neutrophil counts showed an increasing trend and lymphocyte count decreasing trend in patients with upper GI malignancy as compared to control group. Platelet count was also statistically significant and showed an increasing trend. MPV showed decreased values in Group 1 than Group 0. MPV/PC showed decreased values in Group 1, NLR and PLR were elevated in patients with upper GI malignancy. Though LMR showed an increasing trend in patients with upper GI malignancy there was no statistical significance between group 0 and group 1 in our study. However a study by Deng Q et al. [16] on Gastric carcinoma LMR was statistically significant and was elevated.

On comparison of different Stages, noticed that blood parameters worsens as stage advances. Mean Hemoglobinin stage II was 10.5 g/dl in stage III- 9.9 g/dl and in stage IV- 10.5 g/dl. Mean RDW in Stage II-16.01, Stage III– 18.37. Mean Platelet counts showed increasing values as disease Stage advanced. Whereas MPV and MPV/PC showed further more decreasing values as disease stage advanced in comparison to control group. Mean PLR and NLR were also increasing as disease stage advanced. In control group mean PLR- 96.04 and NLR-2.31. In Stage II it was 247.24 and 5.9, PLR and NLR respectively. In Stage IV values were significantly elevated in comparison to control and stage II i.e., 452.09 and 8.46, PLR and NLR respectively.

On ROC curve analysis in our study we found optimal cut off values for RDW- >14.5, NLR >2.3, PLR >117.3.

These hematological parameters have been studied in several other malignancies including Gastric carcinoma. In a study by Aizawa et al [17]. on Gastric malignancy, with preoperative evaluation on 264 patients, obtained optimal cut offs as NLR > 3.2, Hemoglobin < 13 g/dl, Platelet count > 250 K/μL, CRP > 1 mg/dL, albumin< 35 g/L.

Deng et al. [16] study on Gastric carcinoma with preoperative evaluation on 385 patients showed NLR > 2.36, dNLR> 1.85, PLR > 132, LMR > 4.95.

Pre-surgery study by Kim et al. [18] on Gastric malignancy with 1,986 as sample size presented optimal cut offs as NLR> 2, PLR > 126. In our study Hemoglobin was lower in the Upper GI malignancy group as compared to control with a mean value of 10.3 g/dl, neutrophil counts was marginally higher, Lymphocyte count was low, Platelet counts was high, as compared to control group. NLR >2.3, PLR >117.3, RDW >14.5, but MPV/PC values were so small, almost equal to zero, so we ignored it.

Conclusion

In our study we found statistical significance in most of the hematological parameters, which are altered in patients with upper GI malignancies. As hematological parameters plays significant role in onset, progression and metastasis of malignancies. Including them as screening markers in diagnosis upper gastrointestinal malignancy cases adds on to increased sensitivity of disease diagnosis. Using NLR >2.3 and PLR > 117 and observing varying trends in blood parameters such as neutrophils, lymphocyte, platelets, MPV, MPV/PC in patients with specific or nonspecific symptoms of upper GI malignancy helps in better, early and easydiagnosis and better survival. Since these hematological parameters worsens as disease Stage advances, so it also proposes prognostic significance, and helps treating physician for better decision making in managing (surgery/chemoradiotherapy) these patients with advanced upper GI malignancies.

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