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New Phase in Gastric Carcinoma Diagnosis: Haematological Biomarkers As Screening Markers

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Abstract

Gastric carcinomas are a commonly encountered malignancy worldwide. In India though the incidence is low as compared to worldwide statistics, it accounts for significant morbidity and mortality. Prognosis remains poor even today due to delayed presentations and delay in diagnosing. In recent years, hematological parameters are being studied as prognostic indicators for various cancers. There are not many studies on these hematological biomarkers as screening parameters in Gastric cancers. So we conducted a retrospective single center study to evaluate if these blood biomarkers can be utilized as screening parameters for Gastric malignancies.

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

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

We observed Blood biomarkers are statistically different in Gastric malignancy patients in comparison to controls.

So we conclude that Hematological biomarkers can be utilized as a screening markers in Gastric malignancy.

Keywords: Gastric malignancy; hematological parameters; N-K Index; screening markers.

Introduction

Gastric malignancy is the sixth leading cause of malignancy and the eighth leading cause of death from cancer [1]. Significant geographical variation are seen in gastric cancers, Japan, China, Eastern Europe and few countries in Latin America are high risk areas. North American whites, India, Africa except few countries, Philippines and some Western European countries and Australia come under low risk population [2]. Incidence of gastric cancer in India is low compared to global incidence. Five year survival is less than 30% in developed countries and around 20% in developing countries [2].

In spite of many medical technological advances in diagnosing gastric carcinoma, prognosis remains poor due to delayed presentation, delay in diagnosis, and often due to diagnostic difficulties in patients with early gastric cancer, as symptoms resembles benign conditions affecting stomach. Atypical presentations for early gastric cancers and

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lack of a specific line of demarcation in presenting symptoms between gastric benign and malignant counterparts, produces difficulties in diagnosing and management of gastric malignancy.

The most common risk factors for the development of gastric cancer include Helicobacter pylori infection, consumption of alcohol, tobacco usage, smoking, consumption of hot beverages and high salt pickled vegetables [3-5]. Repeated and constant exposure to these irritants induce chronic inflammation which results in development of gastric cancer. Following chronic infection of gastric mucosa with H pylori, there is generation of inflammatory molecules. Anti-inflammatory molecules prevent the formation of gastric cancer. However, imbalance occurs due to over production of inflammatory molecules than anti-inflammatory molecules. Prolonged or repeated infections lead to exposure of normal mucosa to high concentrations of inflammatory molecules, which is a major reason for the causation of cancer [6]. Chronic inflammation, insult or irritation to tissue predisposes to tumor formation and tumor activates various leukocytes. It activates T cells, specific chemokines and prostaglandins which promotes neutrophils and monocytes proliferation and activation [7]. The pro-inflammatory state contributes to tumor growth, progression and metastasis [8].

As infection and inflammation is a risk factor for development of malignancy, we postulate that the biomarkers are raised long before the development of overt malignancy. Very few studies have been performed on using these biomarkers as a diagnostic tool. Despite substantial progress in management of gastric malignancies, the survival rate on diagnosis remains low as it is most often detected at a late stage. Early detection helps in better survival rate [9].

Cancer cells stimulate and promote inflammatory cytokines and growth factors (IL-1β, IL-3, IL-6, IL-11, IL-23, and TNF-α) [10]. An active hidden inflammatory process within the tumor leads to an increased proliferation of tumor cells, angiogenesis, and inhibition of apoptosis. VEGF accelerates angiogenesis in the tumor, and matrix metalloproteinases (MMPs) facilitate the infiltration and spread of tumor to adjacent tissues, which in turn promotes metastases [10]. IL-6 and IL-23 are actively involved in the pathogenesis and development of tumors. They facilitate tumor growth by inhibiting apoptosis of tumor cells and by angiogenesis induction within the tumor [11]. IL-23 induces IFN-γ secretion, which in turn promotes thrombocytopoiesis, and the production of neutrophils, and stimulates the production of acute phase proteins [10].

Lymphocytes has anti-tumor role. It induces T-cell mediated cytotoxic death and inhibits tumor cell proliferation and migration [12-13]. Platelets promotes cancer development and lymphocytes have cancer fighting roles in blood. Platelets helps in hemostasis and also promotes 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), [14] which enables tumor growth and metastatic spread. Platelets also protect tumor cells from killer T-cell-mediated cytolysis [15]. In a symbiotic manner, cancer cells promote a platelet count increase by release of thrombopoietic cytokines and their activation through platelet agonists [16-17]. So ratio of platelets by lymphocytes has been shown to have predictive value in assessing the presence and progression of cancer and the response to drug therapy [18]. Neutrophils interact with cancer cells, and produce cytokines and effector molecules like VEGF that stimulate tumor angiogenesis, growth, and metastasis [19]. Thrombopoietin and IL6 (both strong stimulators of thrombocytopoiesis) increase the production of platelets and in turn their circulating number in blood [20].

These hematological biomarkers are present in circulating blood and hence forms an easily accessible parameter for assessment of diagnosis and prognosis.

So in this study we have analyzed the role of hematological parameters as screening markers in diagnosing gastric malignancy. Hematological parameter like hemoglobin, neutrophils, lymphocytes, monocytes, mean platelet volume (MPV), Platelet count (PC), MPV/PC ratio, red blood cell distribution width (RDW), neutrophil to lymphocyte ratio (NLR), and platelet to lymphocyte ratio (PLR), PC/MPV ratio, lymphocyte/monocyte ratio(LMR), platelets/ lymphocyte ratio(PLR) and monocyte/lymphocyte ratio (MLR) are being studied and evaluated statistically. We have developed "Hematological MAHE- N-K index" as a screening biomarker.

Materials and Methods

The study was performed at a tertiary care hospital in India. It's a retrospective single center study. A total number of two hundred medical records were included in study presented from

January 2014 to September 2018. Institutional ethical committee approval was taken, with no proposed funding source and no conflict of interests.

Inclusion Criteria: 100 cases of Gastric malignancy were 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, presence of autoimmune disease and medical comorbidities were excluded.

Equal number *Control* were selected. The upper GI endoscopy register was scanned for age matched and gender matched patients. They were selected as Control if their Upper GI endoscopy was normal, and they fulfilled the following criteria. They did not suffer from hypertension, diabetes mellitus, hepatic or renal failure, hyperlipidemia, and autoimmune disease. They were not on antiplatelet drugs. They had undergone evaluation for complete blood counts. For both cases and controls, Hemoglobin, Differential count, Platelet count (PC), mean platelet volume (MPV), PC/MPV ratio, red blood cell distribution width (RDW), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), Monocyte/ lymphocyte ratio (MLR) were calculated.

Data was processed using SPSS software, to compare and analyze between cases and control groups and to look for statistical significance (p value <0.05). Data was further evaluated with Receiver operating curve (ROC) analysis to obtain optimal cut off values.

Results

Statistical analysis and evaluation of total 200 medical records of patients belonging to cases (100) and control groups (100) revealed results as follows. Majority of our study group patients belong to late middle age and elderly individuals, about 67% of patients belong to 50 – 70 years age group. With a mean age of 56 years. About 65% of them were Males and 35% were Females. About 18% of patients belong to early gastric cancer stage-I and II disease, 37% had stage-III disease and remaining 45% had stage-IV 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 (both with percentage and their absolute counts), Platelet

Table 1:

	Group 0		Group 1		
Blood Biomarkers	**Mean**	**Std. Deviation**	**Mean**	**Std. Deviation**	**significance (P value<0.05)**
Haemoglobin	13.2	1.63	10.1	2.59	<0.001
RDW	13.82	0.84	17.93	4.97	<0.001
Neutrophil (%)	56.88	12.63	65.02	14	<0.001
ANC	4646.57	1514.41	5717.26	3059.9	0.002
Lymphocyte (%)	29.31	8.54	22.34	9.9	<0.001
ALC	2372.6	786.25	1730.42	783.3	<0.001
Monocyte (%)	8.68	2.16	7.97	3.06	0.062
AMC	698.4	182.19	645.67	298.96	0.134
Eosinophil	3.35	2.67	3.02	3.76	0.464
Basophil	0.56	0.28	0.49	0.38	0.141
Platelet	260260	54828.2	339560	116022.49	<0.001
MPV	8.3	1.37	7.96	1.006	0.046
MPV-Platelet	0.000035	0.0000149	0.000027	0.0000137	<0.001
Neutrophil-Lymphocyte	2.26	1.32	4.18	3.67	0.011
Platelet-Lymphocyte	122.7	52.17	234.02	144.58	<0.001
Lymphocyte-Monocyte	3.62	1.49	4.52	12.1	0.463
Platelet-MPV	32.8	10.52	44.28	17.468	<0.001
Monocyte-Lymphocyte	0.32	0.14	0.434797	0.3	0.002
N-K Index	48.89	10.65	66.39	18.27	<0.001

Group 0: control, Group 1: cases with gastric malignancy.ANC-absolute neutrophil count, ALC-absolute lymphocyte count, AMC-absolute monocyte count. N-K index - Hematological MAHE-N-K index described its derivation in text.

count, MPV, MPV/PC, RDW, NLR, PLR, PC/MPV, MLR, and "Hematological MAHE N-K Index". There was no statistical significance with blood variables like LMR, monocyte, and other leucocyte variables like basophils, eosinophils and even total WBC (p value 0.412) in our study groups, though some studies have described statistical significance in their study with LMR and monocytes. Stage wise data analysis with Dunetts t - test proved that hematological parameters worsens as stage advances results tabulated in Table 2 and Table 3.

Table 2:

Group		HB	RDW	Platelet	Neutrophils	Lymphocyte
0	Mean	13.2	13.8	260260	56.88	29.31
	N	100	100	100	100	100
	Std. Deviation	1.63	0.84	54828.22	12.6	8.54
2	Mean	9.8	17.6	337500	61.66	26.45
	N	18	18	18	18	18
	Std. Deviation	2.81	4.23	112676.65	11.4	10.42
3	Mean	9.9	18.77	350216.22	63.65	24.3
	N	37	37	37	37	37
	Std. Deviation	2.79	5.43	102959.84	11.22	9.45
4	Mean	10.3	18.3	361844.44	67.51	19.08
	N	45	45	45	45	45
	Std. Deviation	2.36	4.87	128515.46	16.57	9.21

Group 0: Control, Group 2: Early Gastric Cancer Stage I and II, Group 3: Stage III, Group 4: Stage IV. N-Number of patients.

Table 3:

Group		NLR	PLR	Platelet/MPV x 103	MLR	N-K Index
0	Mean	2.02	122.7	32.8	0.32	48.89
	N	100	100	100	100	100
	Std. Deviation	1.32	52.17	10.52	0.145	10.65
2	Mean	2.5	216.21	44	0.401	66.78
	N	18	18	18	18	18
	Std. Deviation	2.75	181.79	18.46	0.24	19.99
3	Mean	2.9	232.26	45.32	0.402	68.74
	N	37	37	37	37	37
	Std. Deviation	3.75	112.15	14.91	0.337	16.19
4	Mean	3.9	242.58	45.55	0.475	69.94
	N	45	45	45	45	45
	Std. Deviation	3.79	154.16	19.26	0.288	19.54

Group 0: Control, Group 2: Early Gastric Cancer Stage I and II, Group 3: Stage III, Group 4: Stage IV. N-Number of patients.

Table 4: ROC Curve Analysis Report with Optimal cut off Values for Hematological Biomarkers

Variables	Cut off Values	Sensitivity %	Specificity %	Area under Curve (AUC)	Confidence Interval
N-K Index	54.3	82	75	83%	0.77-0.88
Platelets/ Lymphocyte (PLR)	120.7	82	70	83%	0.77-0.88
Neutrophils/ Lymphocytes (NLR)	2.17	70	56	70%	0.62-0.77
RDW	14.9	80	72	82%	0.75-0.88
Platelet/MPV	32.5 x103	73	60	74%	0.67-0.80
Monocyte/ Lymphocyte	0.32	62	50	62%	0.54-0.7
Platelets	279500	70	60	77%	0.71-0.83
MPV/PC	0.000031	70	59	73%	0.67-0.80

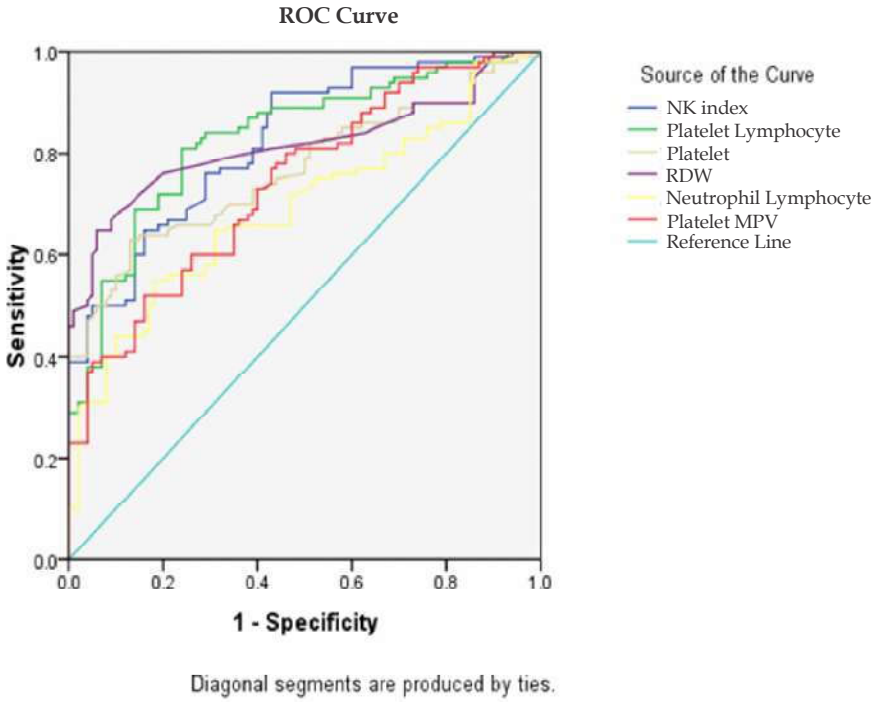

Fig. 1: ROC Curves Of N-K Index, Platelet/Lymphocyte ratio, Platelet counts, RDW, Neutrophil/ Lymphocyte ratio, Platelet/MPV ratio.

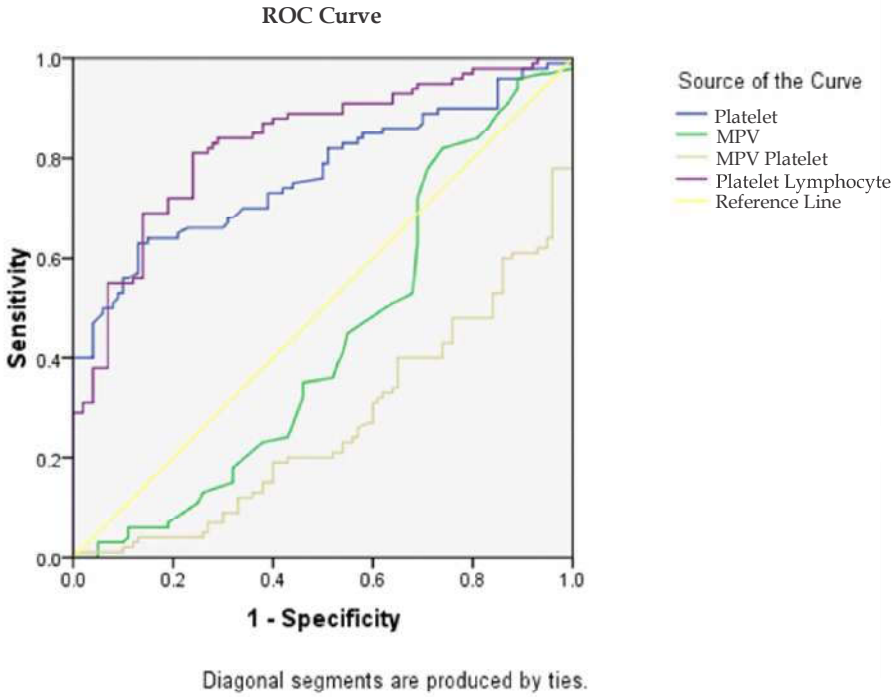

Fig. 2: ROC Curves of PLR, PC, MPV and MPV/platelet ratio. PLR and PC values increase so curves are on positive side of reference line, whereas MPV and MPV/PC values decrease so curves are on other side of reference line.

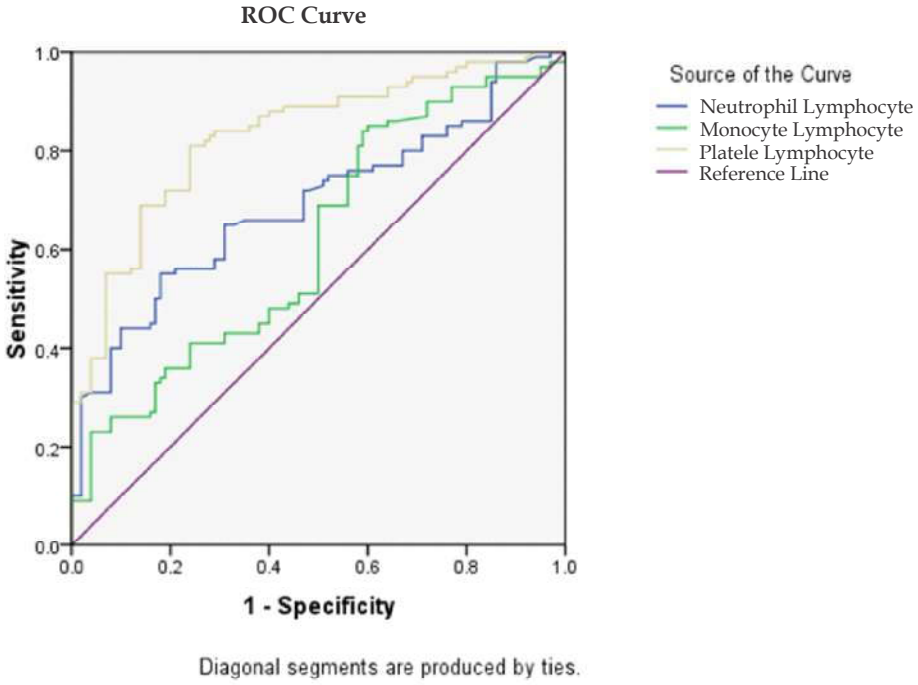

Fig. 3: ROC Curves of NLR, MLR and PLR.

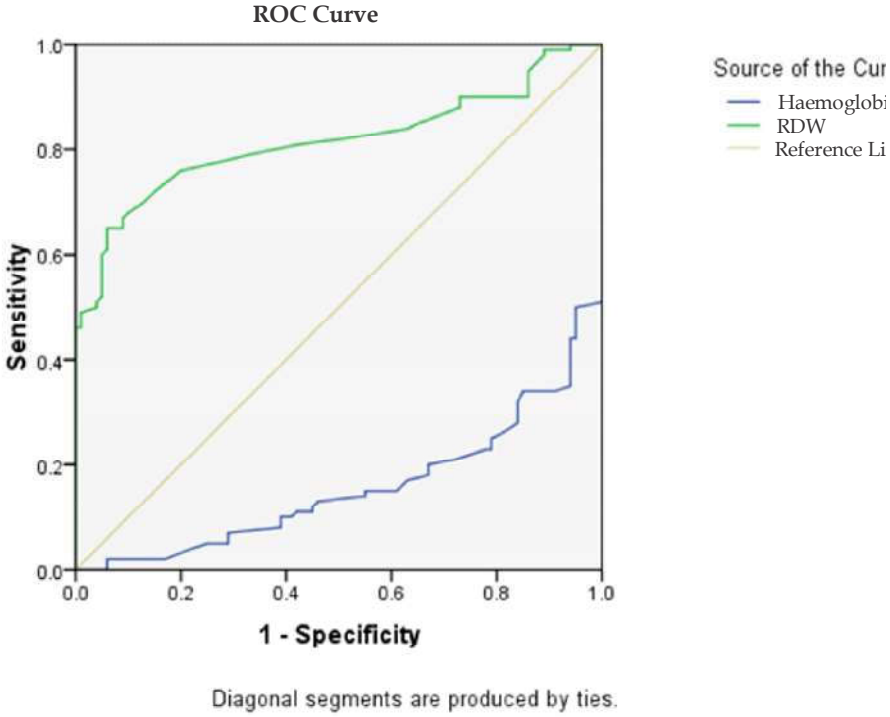

Fig. 4: ROC curves of Hemoglobin (Hb) and RDW. RDW values increase in Gastric Cancer whereas Hb values decrease so curves are seen on either sides of reference line.

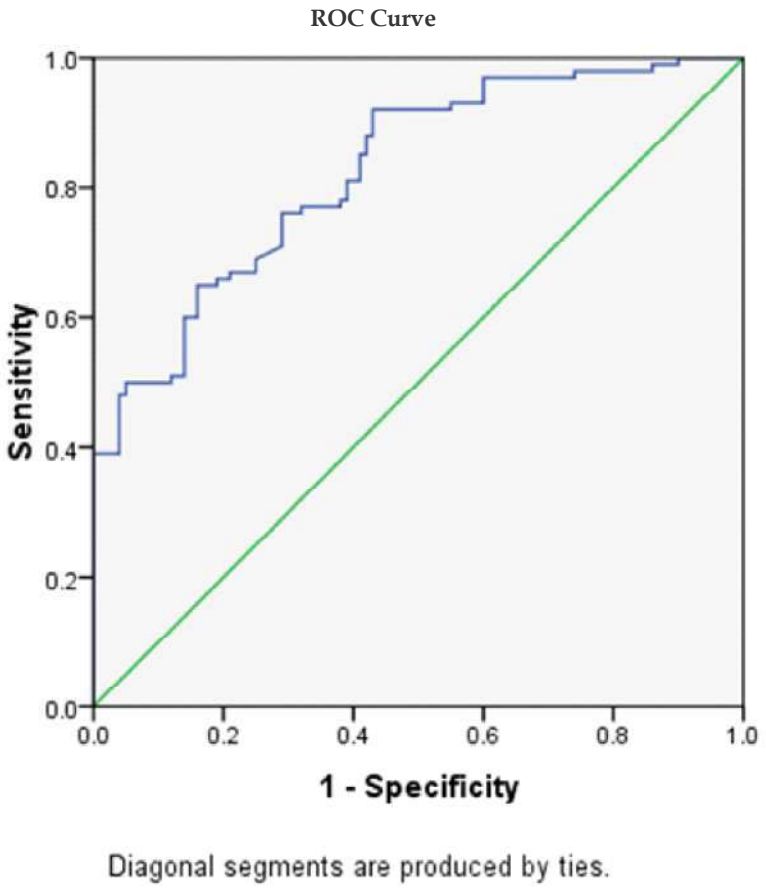

Fig. 5: Hematological MAHE- N-K Index ROC curve with AUC- 0.83%.

To obtain optimal cut off values for above hematological parameters, ROC analysis was done. Results shown in Figure 1, Figure 2, Figure 3, Figure 4, Figure 5. Optimal cut off values and sensitivity and specificity with area under curve (AUC) were summarized in Table 4.

Discussion

Most of the patients in gastric malignancy group belong to late middle age and early elderly individuals with mean age of 56 years. Mean hemoglobin value in group 1 was 10.1 g/dl and in group 0 which is 13.2 g/dl, so patients with Gastric malignancy in group 1 had low hemoglobin levels. Mean value of RDW in group 1 was 17.93 as compared to group 0 which is 13.82, normal range from our institute laboratory for RDW is 11.5 to 14. Hence RDW values were elevated in patients with gastric malignancy as compared to control group. Increased RDW is seen in several other malignancies like renal cell carcinoma, breast cancer, and colorectal malignancy and in gastric cancer. RDW might be influenced by inflammation and iron loss associated with chronic inflammatory status and increased levels of pro-inflammatory factors like interleukin-6, C-reactive protein, tumor necrosis factor alpha that are released in malignancy [21].

Neutrophil and lymphocyte counts were both statistically significant, neutrophil counts showed an increasing trend and lymphocyte count decreasing trend in patients with gastric malignancy as compared to control group. (Both absolute count and percentage values of neutrophils and lymphocytes). Platelet count was also statistically significant and showed an increasing trend. MPV showed decreased values in Group 1 than Group 0. Platelets plays an essential role in inflammation and cancer. Large platelets are more active than their smaller ones, in releasing variety of pro-inflammatory cytokines, and aggregation. The aggregation at the sites of inflammation

(tumor microenvironment) leads to the intensive infiltration of large platelets into vascular and tissue luminal wall, and the reduction of platelet size. Increased release of small size platelets from the bone marrow as excessive pro-inflammatory cytokines interfere with megakaryopoiesis. Therefore, lower MPV values could be suggestive of an enhanced production of platelets and consumption of large platelets in inflammatory states [22]. Park et al. described significant lower values of MPV in patients with gastric cancer are due to degranulation and release of the contents of granules after platelet activation [23]. In a study by Pietrzyk L, on gastric cancer found no statistical significance in MPV between two groups but the values between two groups showed comparable difference with decreased MPV in gastric cancer patients [21]. But in our study MPV was decreased in gastric cancer patients and was statistically significant including ratios MPV/PC and PC/ MPV were also statistically significant. Values of MPV/PC are too small almost equal to zero (mean in Group1-- 0.000027) though statistically significant so we reversed the ratio and analyzed i.e. PC/MPV which showed increasing values (mean in Group0-- 44.28 x 10^3)compared to control group. In malignancy platelets count increases and MPV decreases as explained above so PC/MPV ratio increased.

NLR and PLR were elevated in patients with Gastric malignancy. As neutrophils and platelets number increases and promotes tumor development and progression whereas lymphocyte number decreases in blood. Though LMR showed an increasing trend in our patients with gastric malignancy there was no statistical significance between group 0 and group 1 in our study. However a study by Deng Q et al. [24] on Gastric carcinoma LMR was statistically significant and was elevated. But on reversing the ratio and evaluation, found MLR statistically significant.

In a study by Feng F [25] found increased monocytes and decreased lymphocytes as independent risk factors for gastric malignancy. Monocytes differentiate into tumor associated macrophages (TAM) in tumor microenvironment. Tumor associated macrophages could promote tumor angiogenesis and tumor growth through secretion of TNF-alpha and VEGF. It also facilitate tumor invasion and migration by secreting various proteases and protease activators [25]. But in our study we didn't find monocytes statistically significant between the groups. But its ratio with lymphocytes, MLR was statistically significant with increasing mean value in cases group compared to control. LMR was not significant statistically but MLR was significant, this could probably due to the reason that monocytes shows slight increase and lymphocytes decrease in malignancy, so placing monocytes in numerator and lymphocytes as denominator is a better parameter than reversed way in gastric malignancy.

On comparison of different Stages, noticed that blood parameters worsens as stage advances. Mean RDW in early gastric cancer stage I and II was 17.6, Stage III-18.77, Stage IV– 18.3. Platelet counts, and neutrophils, platelet count/ MPV showed increasing values as disease Stage advanced. Whereas lymphocytes, MPV and MPV/PC (MPV/ PC--- Control-- 0.000035, early gastric cancer stage I and II-- 0.000029, stage III---0.000027, stage IV--- 0.000025) 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- 122.7 and NLR- 2.02. In early stage cancer (stage I and Stage II) it was 216.21 and 2.5, PLR and NLR respectively. In Stage III, PLR-232.26 and NLR- 2.9 and in Stage IV values were significantly elevated in comparison to control and stage II i.e., 242.58 and 3.9, PLR and NLR respectively.

Based on these results we postulated that hematological parameters are altered in patient with Gastric malignancy. These blood parameters or inflammatory blood indices are evaluated in several other malignancies too like upper gastrointestinal, colorectal cancers, breast cancer, hepatocellular cancer, pancreatic and gall bladder malignancy, and testicular tumors.

Our study results shows that hematological indices including red cell parameters, leucocyte parameters and platelet parameters are altered in gastric malignancy.

Ratios like PLR, NLR, MPV/PC, LMR, MLR, PC/ MPV, and derived NLR are studied and discussed in several other malignancies [18] too as prognostic and diagnostic markers.

Calculating and finding ratio value for each one of them is not possible in routine clinical practice. We calculated a new hematological index based on changes seen in hematological parameters in our study (and literature review) called "Hematological MAHE- N-K Index".

Tumor growth, progression and metastasis is directly proportional to rise in neutrophil and platelets counts which influences and promotes tumor development. Also supported by raised

RDW. However tumor growth, progression and metastasis is inversely related to lymphocytes count and MPV. We derived Hematological MAHE-N-K index with these parameters.

N-K Index = (leucocyte parameters) + (platelet parameters) + (red cell parameter)

=(Neutrophils count/ Lymphocyte count)+ (Platelet count/MPV)+(RDW)

Hematological MAHE- N-K Index =(NLR)+(PC/ MPV)+(RDW)

On comparison and statistical analysis of N-Kindex values between Group 1 (cases) and Group 0 (controls) found statistical significance with p value <0.001, and on ROC analysis, optimal cut off value- 54.3 with a sensitivity of 82% and area under curve of 81%. As the disease stage advances N-K index also increases in advanced disease. In control group N-K index mean was 48.89, where as in Group 2 early gastric cancer (Stage I and II) it is 66.78. In Group 3 (stage III) 68.74 and in Group 4 stage IV-- 69.94.

We therefore propose routine use of hematological N-K index as screening marker in gastric malignancy patients, and with prognostic significance in advanced stages. However with these encouraging, inspiring and promising results of N-K index, further studies are needed to confirm the significance in other solid organ tumors for universal application in several other malignancies.

On ROC curve analysis in our study we found optimal cut off values for PLR > 120.7,

N-K INDEX > 54.3, NLR > 2.17, PC/MPV > 32.5 $X10^3$, MLR > 0.32, RDW > 14.9. Though for platelets counts obtained a cut off of 277500 but clinically it is within normal platelet counts range. It cannot be applied as an independent marker, but can be considered as a supporting factor along with other variables. N-K index, PLR ratio and RDW in our study are strong predictors and can be considered for routine application in diagnosing Gastric Malignancy.

These hematological parameters have been studied in several other malignancies including Gastric carcinoma. In a study by Aizawa et al [26]. 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. [24] 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. [27] 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 Gastric malignancy group as compared to control with a mean value of 10.1 g/dl, neutrophil counts, platelets counts was marginally higher, Lymphocyte count was low, as compared to control group PLR > 120.7, N-K INDEX > 54.3, NLR > 2.17, PC/MPV > 32.5 $X10^{3,}$ MLR > 0.32, RDW > 14.9. But MPV/PC values were so small, almost equal to zero.

Conclusion

In our study we found statistical significance in most of the hematological parameters, which are altered in patients with Gastric malignancies. As hematological parameters plays significant role in onset, progression and metastasis of malignancies. Including them as screening markers in diagnosis of Gastric malignancy cases adds on to increased sensitivity of disease diagnosis. Using PLR > 120.7, N-K INDEX > 54.3, NLR > 2.17, PC/MPV > 32.5 $X10^{3,}$ MLR > 0.32, RDW > 14.9. And observing varying trends in blood parameters such as neutrophils, lymphocyte, platelets, MPV, MPV/PC in patients with atypical, nonspecific symptoms of gastric malignancy helps in better and convenient, early and easy diagnosis for 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/ chemo-radiotherapy) these patients with advanced Gastric malignancies. We described unique new hematological parameter *"Hematological Mahe-N-K index"* its routine use and application might help in coming years for better early diagnosis and management with improved survivals, and might bring a new phase in diagnosing malignancies including Gastric cancer.

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