Preoperative Delta Neutrophil Index, Platelet Lymphocyte Ratio and Immature Granulocyte Count for Differentiating Metastatic Colon Cancer from Non-Metastatic Colon Cancer: A Retrospective Study

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AIM: Immature granulocytes show bone marrow activation before neutrophil response and there are studies in the literature showing that the number of immature granulocytes is an auxiliary marker in the diagnosis and treatment of different diseases. The Delta Neutrophil Index (DNI), Immature Granulocyte Count (IGC) have previously been studied as markers in thyroid and breast cancers. The aim of this study was to determine whether immature granulocyte IGC and DNI values measured in preoperative blood parameters have a diagnostic benefit for the detection of advanced colon cancer.

METHODS: A study was conducted on patients who had undergone selective operation for colon cancer in our clinic from February 2015 to February 2020. The patients were divided into two groups: early stage (stage I–III) and advanced stage (stage IV) colon cancer. The IGC and DNI values as well as other hematological parameters, demographic parameters (sex, age) in these two groups were compared.

RESULTS: A total of 43 patients with mean age 67.47 (35–96) years were included in the study. Eighteen of the patients were male and 25 were female. When the early stage and advanced stage colon cancer groups were compared, no statistically significant difference was found between age, sex, white blood cell count, lymphocyte-to-monocyte ratio, eosinophil count, basophil count, mean platelet volume and: systemic immune-inflammation index score. It was observed that platelet-to-lymphocyte ratio, IGC and DNI or Immature Granulocyte Percentage (IGP) values were statistically significantly higher in the metastatic colon cancer group compared to the non-metastatic group. When the specificity and sensitivity of laboratory markers in metastatic colon cancer were examined, it was observed that the specificity and sensitivity of DNI or IGP and IGC were statistically higher than other values.

CONCLUSIONS: DNI, IGC and PLR values, which are the parameters measured in the preoperative period are easily measurable laboratory parameters and do not involve additional costs in differentiating metastatic from non-metastatic colon cancer in the preoperative period.

Keywords: Immature Granulocyte Count; Delta Neutrophil Index; metastatic colon cancer; biomarker

Introduction

Colorectal cancer is the most common cancer in the gastrointestinal system. It is the 3rd most common cancer in men (after lung cancer and prostate cancer) and in women (after lung cancer and breast cancer) [1]. Approximately 1.2 million new cases are diagnosed every year worldwide [2].

The annual expected number of deaths is 600,000 [2]. Of the 2020 deaths in the USA, 53,200 are from colorectal cancer (CRC) [3]. At the time of diagnosis, 40% of CRC patients have liver metastases [3]. While synchronous tumors are seen in approximately 20% of the cases, metachronous tumors develop in the colon in 20% of the remaining [3]. According to a study conducted after the diagnosis of patients diagnosed with metastatic CRC, the survival time is 1 year survival in 70%–75% of patients, 3 years survival in 30%–35%, and 5 years survival in less than 20% of patients [2].

Tumor-associated inflammation may cause uncontrolled malignant transformation as a result of bone marrow activation. While neutrophils play a role in tumoral development, lymphocytes do not play a role in tumoral development [4].

Delta Neutrophil Index (DNI), and Immature Granulocyte Count (IGC) are parameters that show the activity of the bone marrow. When immature granulocytes are called, promyelocytes, myelocytes and metamyelocyte cells are included band neutrophils and myeloblasts are absent [4, 5].

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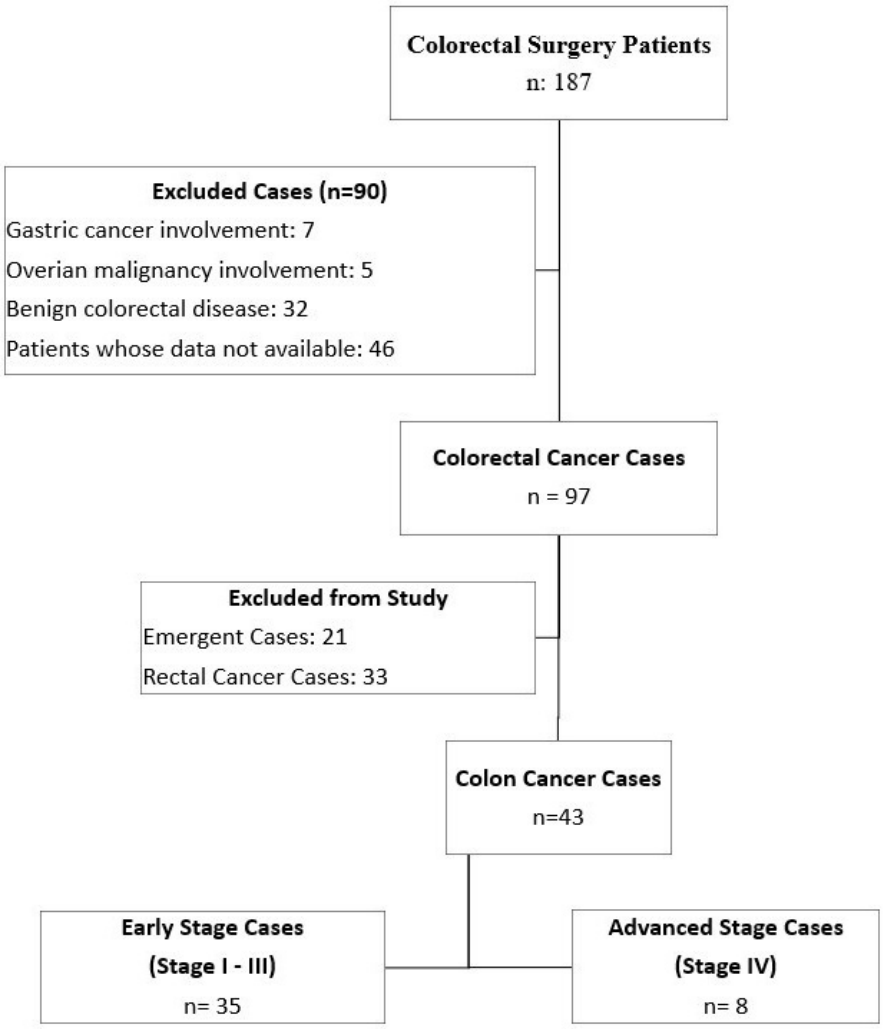

Fig. 1. Flowchart of the study.

The number of immature granulocytes increases in inflammatory conditions and infections. An increased number of immature granulocytes, precursors of neutrophils, in the peripheral blood, are a sign of bone marrow activation, and there are studies in the literature showing that the number of immature granulocytes is an auxiliary marker in the diagnosis and treatment of different diseases. The DNI and IGC have previously been studied as markers in thyroid and breast cancer [4, 5].

The aim of this study was to determine whether IGC and DNI values measured in preoperative blood parameters have a diagnostic benefit for the detection of advanced colon cancer.

Materials and Methods

A study was conducted on, patients who underwent a selective operation for colon cancer in our clinic from February 2015 to February 2020. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The study was approved by the Ethics Committee of the Medical Faculty of Kahramanmaraş Sütçü Imam University (Date: 04/03/2020; Session Number: 2020/05; Decision No: 09). Informed consent was obtained from the patient.

The inclusion criteria were as follows: Patients over 18 years of age, with right colon (cecum, ascending colon, hepatic flexure and transverse colon) or left colon (splenic flexure, descending colon, and sigmoid colon) tumors (Fig. 1). The exclusion criteria were as follows: Emergency cases, colon surgery performed for benign reasons, colon surgery due to other cancer involvements, rectal cancer patients, and patients with missing data (Fig. 1).

Patients Information

Patients older than 18 years old who were diagnosed with colon cancer were evaluated. Both sexes were included in the study. Selective surgical cases were included to the study. Emergent cases, rectum cancer cases and patients with missing data were excluded from the study.

Table 1. Demographic parameters and blood parameters according to the stage of the colon cancer.

	Stage				*p* value	*Z* score
	Early Stage (Stage I–III) n = 35 (81.4%)		Advanced Stage (Stage IV) n = 8 (18.6%)			
Sex						
Male	15 (34.9%)		3 (7%)		0.781[a]	
Female	20 (46.5%)		5 (11.6%)			
Total	35 (81.4%)		8 (18.6%)			
	Median (25%–75% Values)	Mean ± SD (Min–Max Values)	Median (25%–75% Values)	Mean ± SD (Min–Max Values)		
Age (years)	68 (62–82)	68.6 ± 12.84 (35–90)	63 (47–75.25)	62.5 ± 19.09 (37–96)	0.332[b]	–0.32
Postoperative Hospitalisation time (days)	8 (7–13)	10.17 ± 4.59 (3–21)	12 (7–18)	13.25 ± 7.11 (7–27)	0.288[b]	0.24
WBC ($\times10^3$/mm^3)	8.59 (6.87–10.5)	9.04 ± 3.30 (3.26–19.25)	10.39 (7.13–12.75)	10.16 ± 3.00 (6.27–14.33)	0.288[b]	1.46
Neutrophil Count ($\times10^3$/mm^3)	5.58 (4.21–6.91)	6.20 ± 3.06 (1.53–15.03)	6.53 (4.68–9.61)	7.07 ± 2.48 (3.99–10.68)	0.235[b]	0.08
Lymphocyte Count ($\times10^3$/mm^3)	1.69 (1.24–2.28)	1.87 ± 0.72 (0.55–3.58)	1.82 (1.55–2.40)	2.11 ± 1.01 (1.14–4.41)	0.702[b]	–0.13
Monocyte Count ($\times10^3$/mm^3)	0.66 (0.49–0.87)	0.72 ± 0.298 (0.35–1.64)	0.695 (0.45–0.88)	0.71 ± 0.28 (0.39–1.24)	1[b]	–0.06
Platelet Count ($\times10^3$/mm^3)	330 (263–465)	376 ± 169 (140–938)	359 (309–490)	397 ± 118 (245–605)	0.381[b]	–0.11
Eosinophil Count (/mm^3)	100 (50–290)	198.57 ± 21.55 (0–910)	95 (62.5–290)	165 ± 24.06 (30–470)	0.988[b]	–0.45
Basophil Count (/mm^3)	40 (20–50)	40.86 ± 21.06 (10–120)	35 (12.5–65)	38.75 ± 26.42 (10–80)	0.725[b]	–0.02
MPV (fL)	9.8 (9.1–10.3)	9.7 ± 1.08 (6.4–11.9)	9.3 (7.75–9.78)	8.98 ± 1.31 (6.9–11)	0.199[b]	–0.23
NLR	2.66 (2.19–4.54)	3.84 ± 3.45 (1.18–20.02)	4.67 (2.51–5.31)	4.57 ± 2.3 (2.19–9.31)	0.124[b]	0.25
PLR	175.76 (130.06–236.33)	212.2 ± 134.59 (68.03–740)	269.88 (249.07–416.49)	304.61 ± 114.54 (135.36–488.99)	0.02[b]	0.37
LMR	2.32 (1.83–3.46)	2.93 ± 1.58 (0.8–7.48)	2.97 (2.55–3.53)	2.97 ± 0.58 (2.04–3.71)	0.302[b]	0.02
IGC (/mm^3)	30 (20–50)	35.43 ± 22.41 (10–80)	115 (85–137.5)	112.5 ± 29.15 (70–150)	<0.001[b]	2.09
DNI (%)	0.30 (0.2–0.5)	0.38 ± 0.2 (0.1–0.9)	1.15 (0.9–1.28)	1.16 ± 0.35 (0.8–1.9)	<0.001[b]	1.75
SII score	95.15 (36.05–162.70)	164.12 ± 178.68 (31.37–814.74)	154.70 (84.36–209.90)	149.58 ± 73.54 (44.9–252.4)	0.433[b]	0.01

[a] according to the Fischer's Exact Test.

[b] according to the Mann-Whitney U-test.

SD, standard deviation; WBC, white blood cell count; NLR, Neutrophil-to-lymphocyte ratio; PLR, Platelet-to-lymphocyte ratio; LMR, Lymphocyte-to-monocyte ratio; IGC, Immature Granulocyte Count; DNI, Delta Neutrophil Index; MPV, Mean Platelet Volume; SII, Systemic Immune-Inflammation Index.

Study Design

The patients were divided into two groups early stage (stage I–III) and advanced stage (stage IV) colon cancer [6]. Age, sex, localization of the tumor, length of hospital stay, complete blood count (CBC) parameters, Delta Neutrophil Index (DNI) (or also known as Immature Granulocyte Percentage (IGP)), Immature Granulocyte Count (IGC) and manually calculated parameters (Neutrophil-to-lymphocyte ratio (NLR) (NLR was calculated as neutrophil count/lymphocyte count), Platelet-to-lymphocyte ratio (PLR) (PLR was calculated as platelet count/lymphocyte count), Systemic Immune-Inflammation Index (SII) score (SII was calculated as (platelet count × neutrophil count)/lymphocyte count), Lymphocyte-to-monocyte ratio (LMR) (LMR was calculated as Lymphocyte count/monocyte count)) were evaluated between the two groups.

Table 2. ROC analysis of preoperative blood parameters of advanced stage colon carcinomas.

Parameters	AUC	Asymptotic 95% Confidence Interval		*p* value	Sensitivity (%)	Spesivity (%)	Cut off value
		Lower Bound	Upper Bound				
WBC ($\times 10^3/mm^3$)	0.625	0.405	0.805	0.275	62.5	67.7	≥9.26
NLR	0.679	0.487	0.870	0.119	75	51.4	≥2.69
PLR	0.764	0.591	0.938	0.021*	87.5	77.1	≥240.81
LMR	0.621	0.454	0.789	0.289	87.5	54.3	≥2.54
IGC ($/mm^3$)	0.977	0.936	1.000	<0.001*	87.5	88.6	≥75
DNI (%)	0.989	0.966	1.000	<0.001*	100	91.4	≥0.75
SII Score	0.593	0.394	0.792	0.417	62.5	60.7	≥3.01

*$p < 0.05$.

AUC, Area under the curve; ROC, receiver operating characteristic.

Statistical Analysis

IBM Statistical Package for Social Sciences (SPSS Inc., Armonk, NY, USA) ver 20.0 was used for statistical analysis. For determining the normality of independent samples Shapiro Wilk test and variance homogeneity test were used. According to the distribution of normality, Mann-Whitney U test was used to evaluate numerical data. Fischer's Exact Test was used for the categorical data. For determining the efficacy of NLR, Mean Platelet Volume (MPV), DNI and IGC, a receiver operating characteristic (ROC) curve analysis was used. Numerical data were given as mean ± standard deviation (SD) (minimum-maximum values) and median (25% and 75% values); categorical values were given as count (n) and percentage (%). A $p < 0.05$ value was statistically significant.

Results

Forty-three patients with median age 67.47 (35–96) years were included in the study. Eighteen of the patients were male with median age 68 (62–72) years and 25 were female with median age 63 (47–75.25) years. According to the American Joint Committee on Cancer (AJCC) staging manual 8th edition [7], 35 of the patients were in stage I–III (early stage) and 8 patients were in stage IV (advanced stage).

When the early stage and advanced stage groups were compared, no statistically significant difference was found between age, sex, WBC, LMR, Eosinophil count, basophil count, MPV and SII score between the two groups. It was observed that PLR, IGC and DNI or IGP values were statistically significantly higher in the metastatic colon cancer group compared to the non-metastatic group. ($p = 0.02$, $p < 0.001$, and $p < 0.001$ respectively) (Table 1).

When the specificity and sensitivity of laboratory markers in metastatic colon cancer were examined, it was observed that the specificity and sensitivity of DNI or IGP and IGC were statistically higher than other values (Table 2). ROC curve analysis of the specificity and sensitivity of laboratory markers in metastatic colon cancer is shown in Fig. 2.

Discussion

Metastatic colorectal cancer is an important cause of disease-related death [8, 9, 10, 11]. In patients with a limited number of metastases from colorectal cancer, complete excision of the metastasis provides 10-year survival in up to 38% of patients [12]. Thus, early detection of metastatic colorectal cancer is crucial for surgical candidates [12]. Therefore, cheap and easily obtainable parameters are needed to detect metastatic disease in colon cancer in the preoperative period. In our study, we found that PLR, DNI or IGP and IGC were statistically significant parameters in the preoperative detection of metastatic disease in colon cancer, and the specificity and sensitivity of IGC, DNI and IGP were high in detecting metastatic disease.

Previously, NLR has been reported as a good marker for the identification of advanced hilar cholangiocarcinoma [13]. Many laboratory parameters have been studied in the literature to determine the stage and prognosis of colon cancer. Of these NLR and DNI have been studied before in detecting locally advanced or metastatic disease in colorectal cancer and it has been shown that they can be significant predictive markers [4, 5, 14, 15, 16]. Additionally, the SII score has been studied before in colorectal cancer and it has been shown that it can be significant predictive marker [17, 18, 19]. PLR was shown as an inexpensive predictor of liver and lymph node metastasis of colorectal cancer conducted by Turgut *et al*. [20]. Additionally, a study conducted by Abdallah *et al*. [21] showed that perioperative NLR and PLR can be good prognostic factors in colorectal cancers. In our study, the preoperative NLR value was not found to be statistically significant between early stage and advanced stage colon cancer. No statistically significant difference was found between the two groups in our study in the SII score. The studies have been shown that systemic inflammatory biomarkers NLR, MPV and PLR in colorectal cancer can be useful diagnostic methods for different stages separately or together [22, 23, 24]. In our study, when these parameters were examined, it was seen that PLR was statistically significant, but this significance was not observed for NLR and MPV.

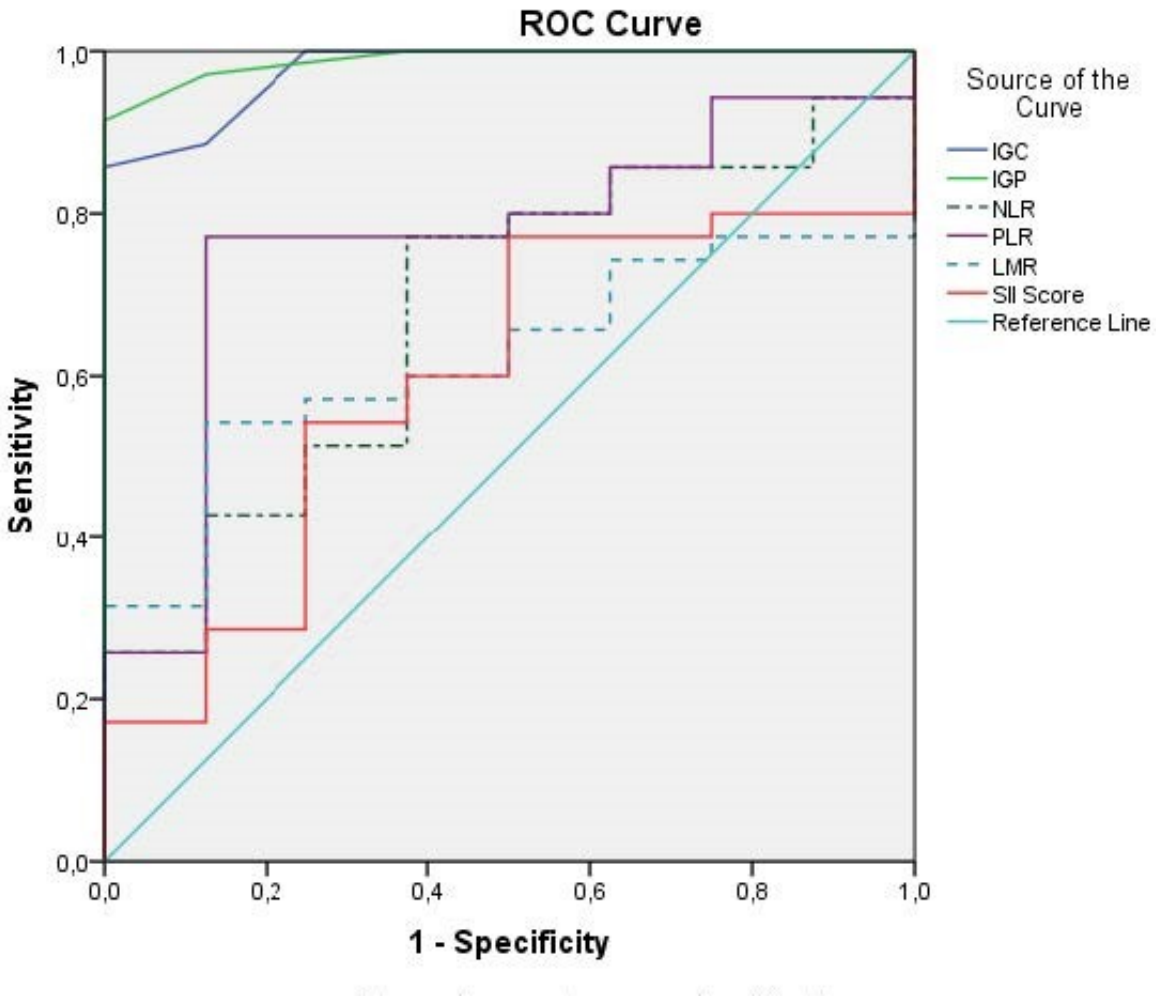

Fig. 2. ROC curve of advanced stage colon cancer cases.

In another study on inflammatory biomarkers, it was determined that WBC and hematocrit values showed the degree of mural invasion and accordingly the prognosis [25]. In our study, no correlation was found between preoperative WBC and diagnosis of advanced stage colon cancer.

Previous studies have shown that DNI and IGC can be used as predictive markers in the detection of thyroid malignancies and breast cancer with axillary metastases [4, 5, 14]. We found that IGC and DNI have high sensitivity and specificity in detecting advanced stage colon tumors.

Our study has some limitations. It is a retrospective study and low number of cases according to being a single center experience.

Conclusions

Tumor induced inflammation can be helpful for understanding stage of the colorectal and different types of cancers. DNI, IGC and PLR values can be helpful for estimating advanced stage preoperatively. These laboratory parameters can be measured easily in the preoperative period and do not involve additional costs in differentiating early stage and advanced stage colon cancers. Multicenter higher volume studies are needed to further investigate preopative differentiation of the early stage and advanced stage colon cancers.

Availability of Data and Materials

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

Conception and Design: MBB, FMY, İTK, Aİ, AÖ. Methodology: MBB, FMY, İTK. Analysis and Interpretation: AAB, SÖ, Aİ, AÖ, MBB, FMY. Writing - original draft preparation: MBB, FMY, AAB, SÖ. Writing - review and editing: MBB, FMY, İTK, AAB, Aİ, AÖ, SÖ. Resources: MBB, FMY, İTK. Supervision: İTK, FMY, MBB. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The Ethics Committee of the Medical Faculty of Kahramanmaraş Sütçü Imam University (Date: 04/03/2020; Session Number: 2020/05; Decision No: 09). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from the patient.

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Conflict of Interest

The authors declare no conflict of interest.

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