The prognostic significance of inflammation associated blood cell markers in metastatic colorectal cancer.

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ABSTRACT

Objectives: The aim is to perform prognostic evaluation with overall survival (OS) and progression-free survival (PFS) in hematological parameter-based groups in patients with metastatic colorectal cancer (mCRC).

Methods: In a single institution, 51 patients were retrospectively analyzed mCRC diagnosed between 2019 and 2022. Pretreatment hematological parameters of patients with mCRC receiving first-line chemotherapy in a single center were examined. The receiver operating characteristic curve was used to predict the tests. Median OS was calculated by the Kaplan-Meier method and compared with the log-rank test. Multivariate analyses were performed using a Cox regression model.

Results: The median OS of the patients included in the study was 27 months (3-88 months) by statistical calculation; the median PFS was 19 months (2-84 months). The median could not be reached. Among the risk factors affecting OS, it was found effective to have a bone metastasis site and a pancreatic metastasis site (p values 0.003 and 0.027, respectively). In the analysis of the risk factors affecting PFS, bone and pancreatic metastases were found to be significant (p values 0.001 and 0.004, respectively). Patients receiving chemotherapy and anti-VEGF therapy have a significantly reduced risk of death of 0.06 times compared to those who do not receive chemotherapy, which indicates that OS is significantly longer in people receiving chemotherapy in question (p=0.020). It was observed that blood cell marker levels were not statistically significant in PFS and OS. Of the 51 patients included in the study, 30 of them were still being followed up, while 21 of them died.

Conclusions: Chemotherapy plus anti-VEGF therapy is a treatment whose effectiveness has been determined in metastatic colorectal cancer. In the future, there is a need for more prospective and large patient group studies on this topic to measure the prognostic value of hematological parameters in metastatic colorectal cancer.

Keywords: metastatic colorectal cancer, parameters, overall survival

With many studies showing the relationship between cancer and inflammatory markers, it has been seen that inflammation plays a role in carcinogenesis [1-3]. Colorectal cancer (CRC) is the third most common cancer and results in more

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than 1 million new cases and 600,000 deaths per year [4]. Various biochemical markers associated with this malignancy, prognostic and diagnostic tools are being evaluated [5-7]. In addition to the classic 'inflammatory related markers such as acute phase proteins (CRP and globulins), these are the platelet / lymphocyte ratio (PLR) and the neutrophil / lymphocyte ratio (NLR) [5, 8]. Among them, red blood cell distribution width (RDW) shows how homogeneous or heterogeneous the blood is by measuring how different the sizes of red blood cells are and is used to types of anemia [9]. Recently, the importance of RDW has increased in many chronic inflammatory and cardiovascular diseases [10-12]. Recent reports have shown that it can be used as a prognostic marker in various cancers such as lung, esophagus-gastric and breast, liver [13-18]. The prognostic role of RDW in CRC has also been studied. However, its role in the context of this malignancy remains unclear, as published reports show inconsistent results. In CRC, as in other solid tumors, carcinogenesis is caused by inflammation [19, 20].

In recent years, many studies have investigated the viability of survival and predictive immune scores associated with systemic inflammatory response in CRC. For example, some of these include the lymphocyte/monocyte ratio, PLR, and the modified Glasgow Prognostic Score, which is determined using serum CRP and serum albumin [21, 22]. Promising results have been seen in NLR risk estimation. Those with low NLR showed worse survival outcomes than patients with CRC with high NLR. This condition has been confirmed at various stages of CRC, from early localized disease to advanced stages and surgical resection [23, 24]. NLR has also been studied in CRC patients who have undergone liver metastasectomy [25]. In the mCRC, the guidelines recommend dual or triple fluoropyrimidine-based chemotherapy (CTX) regimens in first-line treatment, as well as targeted therapy in addition.

In addition, the decision on the intensity of treatment, therapeutic goals are determined usually taking into account the clinical and radiological characteristics of the patient [26]. If the goal is to transform into a resectable disease for a final surgical treatment approach, a more intensive regimen is recommended. When the goal is disease control, a less intensive CTX regimen usually controls the progression of the disease and is the first option that also protects the quality of life.

The aim of this study is to perform progostic evaluation with Overall survival (OS), Progression free survival (PFS) in hematological parameter-based groups in patients with metastatic colorectal cancer (mCRC).

METHODS

This retrospective study was conducted after the approval of the ethics committee in patients. Metastatic colorectal cancer patients followed up at Medical Oncology Unit of Bursa City Hospital between 2019 and 2022 were evaluated. Exclusion criteria from the study were: Early stage CRC, secondary malignancy, kidney and liver failure, steroid use, active uncontrollable infection. Age, gender, tm localization of patients, whether there is metastasis at diagnosis, location of metastasis, ECOG performance status (ECOG PS), First-line CTX regimen, CEA, CA 19.9, LDH, CRP, albumin, neutrophil (NEU), platelet (PLT), mean platelet volume (MPV), RDW, lymphocyte (LEU), NLR, MPV/PLT ratio, RDW/PLT ratio, NEU x PLT)/LEU, NEU x 1000/PLT ratio were recorded as laboratory data. Blood values were studied during pre-chemotherapy and at the admission. OS, PFS informations were recorded.

Peripheral blood was taken before the first CTX cycle. OS, PFS of the patients were recorded. OS was determined as the period from the diagnosis of the patient to his death or the date of the study. PFS was determined as the period from the date of diagnosis to the progression.

Statistical Analysis

Descriptive statistics of the measurements were calculated as arithmetic mean, standard deviation (SD), median and quartiles. The compliance of the numerical measurement or diagnostic markers with the normal distribution was evaluated by the Shapiro-Wilk test and deviations from the normal distribution were observed. Deceased and living patients were compared with Pearson Chi-Square test or Fisher-Freeman-Halton exact test in terms of categorical characteristics distribution. The Mann-Whitney U test was used for comparison in terms of numerical characteristics. In addition, the success of 5 numerical diagnostic markers (NLR, MPV/PLT, RDW/PLT, (NEU x PLT) / LEU and NEU x 1000/PLT) in separating the deceased was also examined with the ROC curve. In addition, the factors affecting OS and PFS durations were first considered individually and evaluated using the univariate Cox regression model, and the uncorrected effects of the factors were calculated. Then,

all the variables were taken into the multivariate Cox regression model and the final model was established by leaving the variables with significant effects on OS and PFS in the model with the help of the stepwise variable elimination method. Mean and median values of OS and PFS were calculated and Kaplan-Meier survival curves were drawn. $p<0.05$ was taken as the statistical significance level and SPSS (ver. 23) the program was used.

RESULTS

The general characteristics of the patients and the distribution of categorical characteristics are shown in Table 1. The female sex ratio was observed as 29.4%. The most common tumor localization was observed in the rectum 27.5%, metastasis at diagnosis was observed in 64.7%, and the most common metastasis was observed in the liver 88.2%. Doublet CTX was given the most frequently as chemotherapy 51.0%. Laboratory data, descriptive values of OS, PFS and numerical characteristics are shown in Table 2.

Of the total 51 patients included in the study, 30 continued their lives, while 21 had died. The shortest duration for OS was 3 months, the longest duration was 88 months; the shortest duration for PFS was 2 months and the longest duration was 84 months.Other descriptive statistics for both OS and PFS are given in Table 5. The median OS was calculated as 27 months, while the mean OS was calculated as 42 months. The median could not be reached. Median PFS is 19 months, mean PFS is 35.3 months. Survival curves of PFS and OS (survival function) were given in Figure 1. The success of NLR, MPV/ PLT, RDW/ PLT, (NEU x PLT) / LEU and NEU x 1000/PLT diagnostic markers in differentiating deceased and living patients was evaluated using the ROC curve and the results given in Figure 2 were obtained. When Figure 2 was examined, it was determined that the 5 markers in question could not distinguish between the deceased and the living successfully at a meaningful level. The cut-off value could not be given because there was no significant relationship. The ROC curves are given in Figure 2. In the analysis of the factors affecting OS with the multivariate Cox regression model, the risk factors

Table 1. Patients characteristics

		n (%)	%
Gender	Female	15 (29,4)	29.4
ECOG PS	0	11	21.6
	1	27	52.9
	2	13	25.5
Status	Ex	21	41.2
Tumor location	Rectum	14	27.5
	Descending	11	21.6
	Ascending	13	25.5
	Sigmoid	8	15.7
	Transvers	5	9.8
Progression	Yes	37	72.5
Metastasis in the diagnosis	Yes	33	64.7
Chemotherapy	No	4	7.8
	Doublet plus anti-EGFR	7	13.7
	Doublet plus anti-VEGF	8	15.7
	Doublet CTX	26	51.0
	Fluoropyrimidine	6	11.8
Location of metastasis	Liver	45	88.2
	Lung	16	31.4
	Bone	9	17.6
	Surrenal	2	3.9
	Peritoneum	6	11.8
	Kidney	1	2.0
	Pancreas	1	2.0

ECOG performance status: ECOG PS

Table 2. Descriptive values of numerical properties

	n	median(min-max)
Age	51	64.00
CEA	51	26.90
CA 19.9	51	34.10
LDH	51	231.00
CRP	51	34.40
ALBUMİN	51	39.90
NEU/ LEU	51	2.480
MPV/ PLT	51	.029
RDW/ PLT	51	.033
(NEU x PLT) / LEU	51	804.46
NEU x 1000 / PLT	51	200.00
OS	51	17.00
PFS	51	8.00

OS: Overall Survey, PFS: progression free survival, NEU: neutrophil, PLT: platelet, MPV: mean platelet volume, RDW: red blood cell distribution width, LEU: lymphocyte

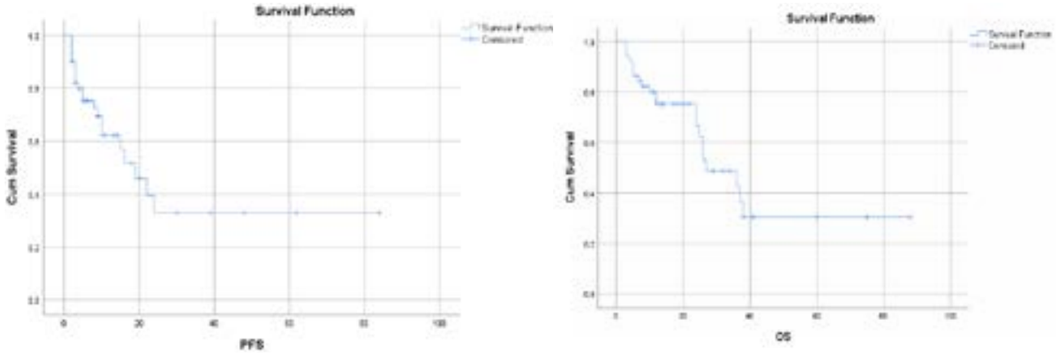

Figure 1. Survival curves of PFS and OS (survival function)

Table 3. Analysis of risk factors that have a significant impact on OS

Variable / Risk *vs* reference	HR 95.0% CI	P
Metastasis in the diagnosis		
Yes *vs* No	2.915 (0.841- 10.100)	.092
Site of metastasis		
Bone *vs* Other	6.862 (1.939 - 24.287)	.003
Pancreas *vs* Other	48.339 (1.550 -1507,25)	.027
Chemotherapy		
Doublet plus anti-EGFR *vs* no CTX	0.965 (0.169 -5.517)	.968
Doublet plus anti-VEGF *vs* no CTX	0.060 (0.006 -0.642)	.020
Doublet CTX *vs* no CTX	0.270 (0.049 -1.476)	.131
Fluoropyrimidine *vs* no CTX	0.405 (0.033 -5.036)	.483
CRP	1.008(1.003-1.013)	.003

HR: Hazard Ratio CTX: Chemotherapy, EGFR: epidermal growth factor receptor, VEGF: vascular endothelial growth factor

that have a significant effect on OS are included in Table 3. When the model results were examined, it was found that the risk of death was significantly higher by 2,915 times in those who had metastases at diagnosis, and therefore OS was significantly shorter. The risk in those with bone and pancreatic metastases has a significantly higher risk of death compared to those in other regions, so OS was found to be significantly shorter in these people. Patients who receive "Doublet plus anti-VEGF" as CTX have a significantly reduced risk of death by 0.06 times compared to those who do not receive CTX, and this indicates that the OS is significantly longer in people who receive CTX in question. Other than this, the risk of death in CTX groups did not differ significantly from those who did not receive CTX. As CRP increases by 1 unit from its own unit (>5 mg/L), the risk of death increases significantly by a factor of 1,008, and therefore the OS decreases. Examination of the factors affecting PFS with the multivariate Cox regression model Table 4 shows the risk factors that have a significant effect on PFS. The risk in those with bone and pancreatic metastases has a significantly higher risk of death compared to those in other regions, so PFS was significantly shorter in these people. As CRP increases by 1 unit from its own unit, the risk of death increases significantly by a factor of 1,005, and therefore PFS decreased. The effects of categorical factors on death are shown in Table 6. It has been observed that there is a significant effect on death with the presence of bone and peritoneal metastases. (p=0.014, 0.026)

DISCUSSION

The aim is to perform progostic evaluation with OS and PFS in groups based on hematological parameters in patients with mCRC. It is important to understand the cause-effect relationship between inflammation and cancer in terms of diagnosis and treatment of cancer. In our study, it was determined that the markers CEA, CA 19.9, LDH, CRP, Albumin, NLR, MPV/PLT, RDW/ PLT, (NEU x PLT) / LEU and NEUx1000/PLT could not distinguish between deceased and living patients successfully. Figure 2 shows that this situation is not statistically significant.

NLR and PLR are simple, easily accessible markers that indicate subclinical inflammation. Absolute neutrophil and lymphocyte counts can be affected by many factors. Many factors have proven to be useful

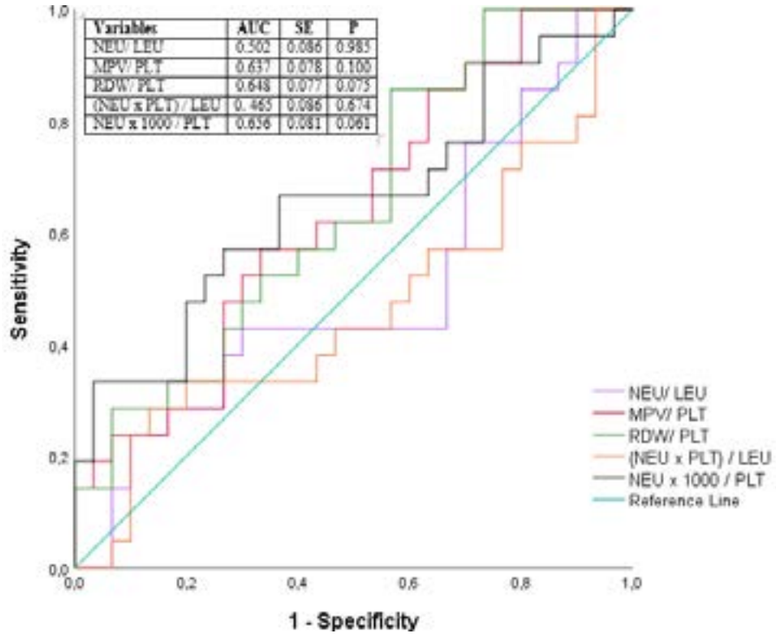

Figure 2. The power of NEU/ LEU, MPV/ PLT, RDW/ PLT, (NEU x PLT) / LEU ve NEU x 1000 / PLT to distinguish between died and alive (ROC curves)

Table 4. Analysis of risk factors that have a significant impact on PFS

Variable / Risk *vs* reference	HR 95,0% CI	P
Site of metastasis		
Bone *vs* Other	6.099 (2.125- 17.509)	.001
Pancreas *vs* Other	34.077 (3.177- 365.533)	.004
CRP	1.005 (1.001- 1.010)	.016

HR: Hazard Ratio CI: Confidence Interval, OS: Overall Survey, PFS progression free survival

Table 5. Descriptive values of OS and PFS

	Median	SE	95% Confidence Interval
OS	27.0	5.459	16.301-37.699
PFS	19.0	3.983	11.193-26.807

CI: Confidence Interval, SE: standart error, OS: Overall Survey, PFS progression free survival

Table 6. The effects of categorical factors on death

Site of metastasis	Metastasis	Ex n	Ex %	$P_{(status)}$*
Liver	No	2	33.3	.678
	Yes	19	42.2	
Lung	No	13	37.1	.387
	Yes	8	50.0	
Bone	No	14	33.3	**.014**
	Yes	7	77.8	
Surrenal	No	20	40.8	.796
	Yes	1	50.0	
Peritoneum	No	16	35.6	**.026**
	Yes	5	83.3	
Kidney	No	21	42.0	.398
	Yes	0	0.0	
Pancreas	No	20	40.0	.412
	Yes	1	100.0	

in determining the prognosis in mCRC. Patient-related (age, performance status, comorbidities), tumor-related (local growth, distant metastasis), biochemical (markers such as platelets, leukocytes, hemoglobin, CEA, LDH, alkaline phosphatase, albumin) and molecular factors (KRAS, NRAS and BRAF mutations) have all been associated with survival outcomes [27, 28].

As a result, various studies have suggested that the analysis of inflammatory factors, including the evaluation of inflammatory cells in the peripheral blood, may help in predicting survival in mCRC. Ratios between inflammatory cells such as NLR have been proposed, as other factors unrelated to cancer may also affect the systemic leukocyte count [29].

A high neutrophil count has been shown to be an independent prognostic marker for cancer recurrence and survival (including gastric cancer, metastatic melanoma, advanced non-small cell lung cancer, and metastatic renal cell carcinoma) [30, 31, 32]. Neutrophilia and lymphopenia are seen in systemic inflammation. NLR establishes the balance between antitumor functions and pre-tumor inflammatory pathways. An increase in NLR indicates that inflammatory cells affect tumor growth in the microenvironment. They also facilitate the escape of tumor cells from immunity by suppressing cell-mediated immunity [33]. High NLR is associated with tumor invasiveness, angiogenesis and metastasis [34].

The relationship between palliative CTX outcome and NLR was evaluated in 349 patients with mCRC and a significant effect of high NLR was found (p=0,002). In addition, significant improvement in PFS was observed in patients whose NLR returned to normal after one CTX cycle (p=0,012) [36].

Studies on PLT, PDW, MPV and other platelet-related indicators have appeared one after the other in recent years [37, 38]. In addition to the clotting process, platelets also regulate the inflammatory response and cancer pathogenesis. Activating platelets can promote tumor growth, angiogenesis, and invasion [39]. Studies conducted support that the PLT counts in the CRC are based on systemic inflammation, but it is not definitive as a risk factor for prognosis and survival [40, 41]. The PLR is an index that is believed by some authors to be related to the prognosis of CRC [42, 43]. The importance of prognostic risk for PDW varied between different cancers: High PDW in breast cancer was considered a poor prognostic marker [44]; low PDW was a negative predictive factor in gastric cancers and non-small cell lung cancers [45, 46]. The role of the PDW in the CRC has been examined in a small number of publications.

In our study, the risk in those with bone and pancreatic metastases has a significantly higher risk of death compared to those in other regions, so PFS and OS are significantly shorter in these people. Duraker et al. according to the data of their study, it was found that the most common place of metastasis in CRC patients was the liver, followed by the peritoneum [47].

In our study, patients receiving “Doublet plus anti-VEGF” as CTX have a significantly reduced risk of death at a level of 0.06 times compared to those who did not receive CTX, and this indicates that OS is significantly longer in people receiving CTX in question. Other than this, the risk of death in CTX groups did not differ significantly from those who did not receive CTX. Therefore, the importance of choosing CTX in primary care should be taken into account. According to the ASCO Guideline 2023, Doublet (folinic acid, fluorouracil [FU], and oxaliplatin [FOLFOX], or folinic acid, FU, and irinotecan [FOLFIRI]) backbone chemotherapy should be offered as first-line therapy to patients with initially unresectable microsatellite stable (MSS) or proficient mismatch repair (pMMR) mCRC. Capecitabine plus oxaliplatin therapy can be used instead of FOLFOX at the clinical discretion of the treating physician and by joint decision with the patient. All patients were given the anti-vascular endothelial growth factor (VEGF) antibody bevacizumab in addition to a double or triple chemotherapy regimen (48). Dual chemotherapy has previously been shown to be superior to FU and folinic acid (49); therefore, this analysis focused on the potential for additional benefits of triple chemotherapy compared to FOLFOX or FOLFIRI (50,51).

Our study had some limitations. The fact that it is retrospective, it is single-centered, the small number of samples may cause a relatively short follow-up period in some patients. Because of these, our study resulted differently from the literature. In addition, no molecular evaluation was performed in this study, such as determining the instability of the micro-satellite. The mutation status of the patients was not evaluated.

Prospective studies are needed to further understand the prognostic value of NLR. MPV/PLT, RDW/PLT, (NEU x PLT)/LEU and NEU x 1000/PLT. There is probably a process going on in the tumor microenvironment, and we don’t know the details of it.

CONCLUSION

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of Bursa City Hospital, Bursa, Türkiye. (Decision number: 2021-21/6, date: 17.11.2021).

Authors’ Contribution

Study Conception: AHT; Study Design: AU; Literature Review: AHT; Critical Review: AHT; Data Collection and/or Processing: AHT,; Analysis and/or Data Interpretation: AHT; Manuscript preparing: AHT.

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