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Neutrophil-to-Lymphocyte Ratio, Platelet-to-Lymphocyte Ratio, and Red Blood Cell Distribution Width as New Biomarkers in Patients with Colorectal Cancer

ORIGINAL INVESTIGATION

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ABSTRACT

Objective: The incidence of colorectal cancer in developed countries has been found to increase with age. Early diagnosis and screening decrease the mortality rates in colorectal cancer. This study aimed to use inflammatory markers neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and red blood cell distribution width (RDW) as new biomarkers for early diagnosis and screening in patients with colorectal cancer.

Materials and Methods: A total of 59 patients with colorectal cancer and 59 age- and sex-matched healthy participants were included in the study. Localization, tumor node metastasis (TNM) stage, and preoperative hemoglobin levels, neutrophil counts, lymphocyte counts, platelet counts, and RDW values were obtained from medical records. Using the receiver operating characteristic (ROC) curve, the optimal cutoff levels of the biomarkers were determined.

Results: NLR, PLR, and RDW were significantly higher in patients with colorectal cancer than in healthy participants ($p<0.001$). According to ROC analysis, the cutoff value for NLR was 2.05 [area under the curve (AUC): 0.740, sensitivity: 78%, specificity: 66%]; the cutoff value for PLR was 130 (AUC: 0.702, sensitivity: 65%, specificity: 72%); and the cutoff value for RDW was 14 (AUC: 0.774, sensitivity: 68%, specificity: 73%).

Conclusions: NLR, PLR, and RDW were found to be significantly higher in patients with colorectal cancer than in healthy participants. Therefore, it is recommended that these additional biomarkers can be used for early diagnosis and screening of colorectal cancer.

Keywords: Biomarkers, colon cancer, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, red blood cell distribution width

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INTRODUCTION

Colorectal cancer is the second most prevalent cancer type in women and the third most prevalent type in men. The incidence of colorectal cancer is 9.7%, and it occurs more frequently in men than in women. Colorectal cancer ranks fourth as the cause of cancer-related deaths. The incidence of colorectal cancer in developed countries has been found to increase with age (1). In patients with colorectal cancer, the most important prognostic factor is the disease stage. In colorectal cancer cases, the 5-year survival rate is 90.1% for patients in the localized stage, 69.2% for patients with regional spread, and 11.7% for patients with distant spread. The mortality rate of colon cancer patients considerably decreases with early diagnosis and treatment (2).

Fecal occult blood tests, genetic stool tests, flexible sigmoidoscopy, colonoscopy, capsule endoscopy, virtual colonoscopy, and magnetic resonance colonography are used for early diagnosis and screening purposes in patients with colon cancer (3). Colorectal cancer screenings have proved to be cost efficient and economical (4). The tests used for early diagnosis and screening of colorectal cancer should be easily accessible and inexpensive and should not cause distress for patients. In inflammation, various mechanisms such as inflammatory cells, chemokines, cytokines, and proinflammatory mediators (cyclooxygenase and lipoxygenase) contribute to tumor cell formation, proliferation, and metastasis (5). Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and red blood cell distribution width (RDW) biomarkers reflect the systemic inflammatory condition in many cancer types, and they have been determined to be early diagnosis and prognostic factors (6-8).

This study aimed to investigate the use of the inflammatory markers NLR, PLR, and RDW in complete blood counts as biomarkers that can be easily accessible for early diagnosis and screening of colon cancer, are inexpensive and simple to use, and do not cause distress for patients.

MATERIALS AND METHODS

The records of patients who were diagnosed with colon cancer at Sivas Numune Hospital between January 2010 and January 2015 were analyzed. This study was approved by the ethics committee of Cumhuriyet University's Faculty of Medicine (2015-07/01). Medical records were used to determine the patients who underwent a colonoscopy screening for various reasons and who were diagnosed with colon adenocarcinoma on the basis of the biopsy. The demographic, clinical, pathological, and laboratory data of these patients were retrospectively examined. Patients with coexisting infections, hematologic diseases, renal diseases, vascular diseases, or other cancer types were excluded from the study. A total of 59 patients with colon cancer and 59 age- and sex-matched healthy participants were included in the study.

The localization of the tumor of patients with colon cancer was detected, and staging was performed according to tumor node metastasis (TNM). The colon cancer cases were categorized into two groups in terms of localization: right-sided localization (cecum, ascending colon, or transverse colon) and left-sided localization (descending colon, sigmoid colon, or rectum). The preoperative hemoglobin levels, lymphocyte counts, platelet counts, and RDW values of the patients were noted from the records. In cancer patients and healthy participants, anemia was defined using the World Health Organization criteria of hemoglobin levels of <13 g/dL for men and <12 g/dL for women (9). NLR and PLR were calculated by dividing the neutrophil and platelet counts by the lymphocyte count, all of which were obtained from the preoperative complete blood counts of the patients. Complete blood count was performed using a Beckman Coulter LH 780 hematology analyzer (Beckman Coulter Biotechnology, Pasadena, CA, USA) with ethylenediaminetetraacetic acid blood samples. Blood samples were analyzed 1 h after venous entry. This study was approved by Cumhuriyet University ethics committee, was in accordance with the Declaration of Helsinki, and was designed as a retrospective case-controlled study.

Statistical analysis

The Statistical Packages for the Social Sciences (SPSS) version 22.0 (IBM Corp.; Armonk, NY, USA) was used to conduct statistical analyses. Data obtained from our study were expressed as mean±SD and uploaded to the SPSS 22.0 program. For the evaluation of data, the independent sample t-test, one-way ANOVA-Tukey test, and chi-square test were used when parametric test counts were fulfilled. The receiver operating characteristic (ROC) curve analysis was performed to determine optimum cutoff values of NLR, PLR, and RDW. A p value of <0.05 was considered to be statistically significant.

RESULTS

A total of 59 patients with colorectal cancer and 59 healthy participants who served as the control group were included in this study. The mean age of the patients with colorectal cancer was 65.40±12.10 (32-86) years; 27 (45.8%) patients were females and 32 (54.2%) were males. The demographic characteristics, laboratory results, tumor localization, and TNM stages of the patient and control group are shown in Table 1. No statistically sig-

Table 1. Clinical and demographical characteristics of patients with colorectal cancer and the control group

Variables	CRC patients (N=59)	Control group (N=59)	* p
Age (mean±SD) years	65.4±12.1	65.7±10.7	0.860
Sex (male/female)	32/27	31/28	0.85
Tumor location			
Left-sided	40 (67.8)		
Right-sided	19 (32.2)		
TNM staging [n (%)]			
I	8 (13.6)		
II	23 (39)		
III	17 (28.8)		
IV	11 (18.6)		
Anemia [n (%)]			
Yes	40 (67.8)		
No	19 (32.2)		
Hb (mean±SD) (g/dl)	11.9±2.2	14.4±1.1	<0.001
Platelets (mean±SD) (109/l)	308.9±99.1	243±46.2	<0.001
NLR (mean±SD)	2.9±1.4	2.0±0.6	<0.001
PLR (mean±SD)	163.6±71.1	118.5±32.7	<0.001
RDW (mean±SD) (%)	16.1±3.4	13.6±0.6	<0.001

CRC: colorectal cancer; Hb, hemoglobin; NLR: neutrophil/lymphocyte ratio; PLR: platelet/lymphocyte ratio; RDW: red blood cell distribution width; TNM: tumor-nodes-metastases
Data are shown as the mean±SD
* p values of <0.05 are presented in boldface

Table 2. NLR, PLR and RDW values in patients with colorectal cancer compared to the control group according to TNM stages

	NLR	PLR	RDW	*p
TNM staging of CRC patients (N=59)				
I (n=8)	3.35±2.25	166.20±85.1	15.60±1.39	<0.001
II (n=23)	2.86±1.05	164.93±72.7	17.10±4.03	<0.001
III (n=17)	2.74±1.13	152.80±53.5	15.50±2.71	<0.001
IV (n=11)	3.36±1.90	176.01±87.6	15.20±3.77	<0.001
Control group (N=59)	2.01±0.60	118.50±32.7	13.60±0.60	<0.001

CRC: colorectal cancer; NLR: neutrophil/lymphocyte ratio; PLR: platelet/lymphocyte ratio; RDW: red blood cell distribution TNM: tumor-nodes-metastases
Data are shown as the mean± SD
* p values of <0.05 are presented in boldface

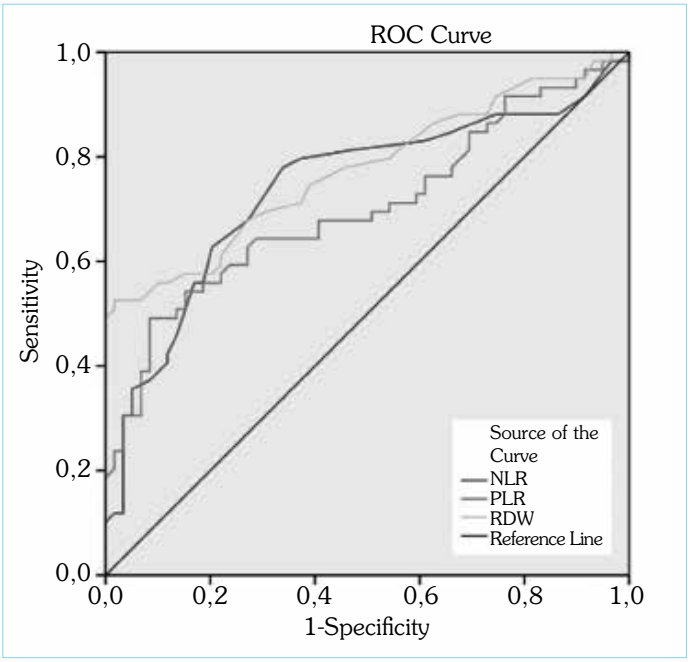

Figure 1. ROC curves for NLR, PLR, and RDW for preoperative patients with colon cancer and healthy participants

nificant difference was found between the groups in terms of age (p=0.860) and sex (p=0.854). In patients with colorectal cancer, 40 had anemia (67.8%) and 19 (32.3%) did not. The incidence of anemia was found to be significantly higher in patients with colorectal cancer than in healthy participants (p<0.001). When the preoperative platelet counts, NLR, PLR, and RDW values in patients with TNM stage-independent colorectal cancer were compared with healthy participants, these values were found to be significantly higher in patients with colorectal cancer (p<0.001) (Tables 1 and 2). In terms of colorectal cancer localization, 40 patients were left sided (67.8%) and 19 patients (32.2%) were right sided. Of these patients, 17 with right-sided localization (89.5%) and 23 (57.5%) with left-sided localization had anemia. In colorectal cancer patients with right-sided localization, the incidence of anemia was significantly high (p<0.05). In the subgroup analysis, no significant association was detected in terms of NLR and PLR in colorectal cancer patients with right-sided and left-sided localization (p>0.05). However, RDW was significantly higher in patients with right-sided localization than in those with left-sided localization (p=0.032). Furthermore, when the non-anemic patients with colon cancer were compared with healthy participants, NLR and PLR were found to be significantly higher in the former (2.80 vs. 2.01, p<0.001; 122.2 vs. 118.5, p<0.05). According to ROC analysis, the cutoff value for NLR was 2.05 [area under the curve (AUC): 0.740, sensitivity: 78%, specificity: 66%]; the cutoff value for PLR was 130 (AUC: 0.702, sensitivity: 65%, specificity: 72%); and the cutoff value for RDW was 14 (AUC: 0.774, sensitivity: 68%, specificity: 73%) (Figure 1).

DISCUSSION

In our study, preoperative NLR, PLR, and RDW values were found to be significantly higher in patients with colon cancer than in healthy participants. In the subgroup analysis, NLR and PLR were significantly higher in non-anemic patients with colon cancer than in healthy participants. Therefore, these results indicate that NLR, PLR, and RDW obtained from simple and routine complete blood counts could be used as additional biomarkers for early detection and screening of patients with colon cancer.

Colorectal cancers are the most common causes of cancer-related deaths. Each year, an estimated 1.2 million new cases and approximately 600,000 deaths occur owing to colorectal cancer. The incidence of colorectal cancer increases after the age of 50, with the identified mean age being 70 years in developed countries (10). In developed countries such as Europe and North America, there is a high incidence of colorectal cancer, and its incidence tends to increase in developing countries. In epidemiological studies, the risk factors for colorectal cancer include high-fat and low-fiber diet, family history of colorectal cancer, inflammatory bowel disease, smoking, obesity, diabetes, and high red meat consumption (10, 11).

Inflammation contributes to the formation, progression, and metastasis of cancer. Chronic inflammation is known to cause many cancer types, such as hepatocellular carcinoma derived from hepatitis B and C, gastric cancer derived from *Helicobacter pylori*, and colon cancer derived from inflammatory bowel disease (10). In the literature, platelet, C-reactive protein (CRP), interleukin-6 (IL-6), NLR, PLR, and RDW, all of which are considered markers of systemic inflammation, provide important clues about the early diagnosis and prognosis of colon cancer (6, 11-13). The activation of neutrophils, platelets, and macrophages contribute to chronic inflammation and lead to the increase of reactive oxygen species and reactive nitrogen intermediates, both of which have high mutagenic activity. These molecules initiate tumor formation as a result of DNA damage and mutations in cells. p53, K-Ras, and B-raf gene mutations were particularly determined to cause gene mutations in colorectal cancer (11-13). Inflammatory cells lead to tumor progression by causing the increase of nuclear factor kappa B, signal transducers and activators of transcription, proinflammatory mediators related to factors such as B-catenin, cytokine, and chemokine, growth factors, and matrix metalloproteinases, which are transcription factors (12-14).

Platelet activation causes tumorigenesis and atherothrombosis owing to damage in epithelial and endothelial cells. Platelet inflammation plays a leading role in tumor mechanism by affecting several different steps. Under normal physiological conditions, cyclooxygenase (COX) enzyme expression is under strict control with transcriptional and posttranscriptional levels. There are two isoenzyme forms of the cyclooxygenase enzyme: COX-1 and COX-2. In chronic inflammation, the increase of active platelet COX-1 and COX-2 triggers intestinal tumorigenesis. Together with apoptosis resistance, the prostaglandin E_2 (PGE_2) and prostaglandin H_2, which increase in cells as a result of COX-1 and COX-2 increase, stimulate cell proliferation, migration, and angiogenesis. Furthermore, sTNF-α, IL-6, and IL- 8, which increase along with the inflammation, cause a change in the structure of microRNA-16 and microRNA-143 and thus increase the formation and proliferation of colon cancer (14). Activated platelet angiogenesis and vascular endothelial growth factor and colony-stimulating factor 1, which causes proliferation, increase platelet-derived growth factor

and transforming growth factor-β and leads to tumor invasion and metastasis (14, 15). Therefore, inflammation plays an important role in colorectal cancer. Antiinflammatory NSAI and aspirin reduce colon cancer and polyp formation by preventing numerous steps. With low-dose aspirin, the irreversible inactivation of the platelet thromboxane A2 synthesis and COX-1 activity reduces the risks of inflammation and the onset of colon cancer. Of the NSAI drugs, COX inhibitors have the effect of reducing polyp and cancer formation by suppressing COX-2 inhibitors PGE_2 (16, 17).

As lymphocytes regulate immune homeostasis during chronic inflammation and have an antiinflammatory effect, tumor formation and the proliferation of lymphocytes play an inhibitory role. However, the risk for colorectal cancer increase owing to increasing proinflammatory cytokines such as TNF-α, IL-6, and IL-17 and decreasing IL-10 because of the effect of T lymphocytes in chronic inflammation (18). RDW, which measures the complete blood count parameter and the size difference of red blood cells, increases with increases in interleukin, a proinflammatory mediator, and cytokines such as TNF-α. RDW increases in inflammation and in many cancer types, including colon, pancreas, and breast cancers, and it is accepted as a prognostic factor (13, 19, 20).

Early diagnosis and screening decrease mortality in colorectal cancer by approximately 53% (21). Therefore, early diagnosis and screening of colorectal cancer should be cost-effective measures (22). The most common tests used in clinical practice for the early diagnosis and screening of colon cancer are guaiac-based fecal occult blood tests (gFOBTs) and fecal immunochemical tests (FITs). While gFOBTs are able to detect hemoglobin in feces, they are not sensitive to cases of small hemorrhages. These tests return high levels of false-positive or -negative results when red meat, raw fruit and vegetables, and certain vitamins (vitamin C and E) are consumed (23). Thus, before performing gFOBTs, patients should avoid the drugs mentioned above and should follow a proper diet. The sensitivity and specificity for gFOBTs is 25-38% and 74%, respectively (24). However, these tests are currently no longer considered important, and their routine use has been discontinued.

Antibodies that are used for FITs are specific to hemoglobin in human blood. These tests are able to detect by binding monoclonal and polyclonal antibodies to the globin in hemoglobin. FITs provide cutoff value flexibility in terms of positivity, are more specific, and are less affected by factors such as diet and drugs. However, FITs require trained personnel and reliable laboratory conditions. Moreover, FITs are not specific to colorectal cancers, as the hemorrhage test in upper gastrointestinal hemorrhage and non-neoplastic and benign diseases may be positive and may not be able to distinguish between them. FITs should use two or more samples for maximum sensitivity. Despite the variations in the studies conducted, the sensitivity for FITs ranges between 61% and 91% and the specificity ranges between 91% and 98% (25, 26).

The fecal DNA test is used for patients with colorectal cancer because it is able to detect the specific cell mutations related to colorectal cancer that are excreted with stools. In studies conducted, the sensitivity and specificity of the fecal DNA test was 85% and 95%, respectively; however, this test is considerably more expensive than other tests (27). Capsule endoscopy is generally used as a diagnostic tool for small intestine examinations; however, there are very little data regarding their use for colon examinations. Data that are available regarding their use in colon cancer detection show a sensitivity of 76% and specificity of 75% (28). Virtual colonoscopy has high rates of sensitivity and specificity (95.7% and 100%, respectively). However, they have few major disadvantages, including radiation exposure, high cost, and the need for the patient to undergo another colonoscopy (29). Flexible sigmoidoscopy (for distal cancer) and colonoscopy sensitivities are both above 95%, and they decrease colorectal cancer incidence (31%-33%) and mortality rate (38%-43%). The disadvantages of this diagnostic tool are its inability to perform optimum intestinal cleaning, the low quality of the procedure, and its invasiveness (30). The screening methods in colorectal cancer vary according to the country, and the initial screening method recognized worldwide as the most reliable is FIT, followed by colonoscopies, when necessary (31). However, these methods are not easily accessible, and they are expensive and cause distress for the patient.

Recently, inflammatory markers have been used for the early diagnosis and determination of prognosis of patients with colorectal cancer. The most common inflammatory markers are CRP, platelets, NLR, PLR, and RDW. In the study by Chiang et al., NLR (>3) in patients with colorectal adenocarcinoma was detected as a poor prognostic factor (31). Galizia et al. (12) found that in early colon cancer, preoperative NLR served as a strong biomarker for estimating the independent prognosis factor and tumor relapse. In another study, the preoperative NLR value was statistically significant in patients with colorectal adenocarcinoma compared with the same value in the control group. In this study, the diagnostic sensitivity and specificity cutoff value was minimum 2.02 (sensitivity: 86%, specificity: 84%) (6). In our study, we found the diagnostic sensitivity and specificity cutoff value of NLR in patients with colon cancer to be minimum 2.05 (sensitivity: 78%, specificity: 66%). The NLR cutoff value in our study was the same as that determined by Kilincalp et al. in patients with colon cancer, and the NLR sensitivity and specificity ratios were similar.

In the study conducted by Sun et al. (32) on patients with colon cancer, preoperative high PLR was a poor prognostic factor. Similarly, Szkandera et al. (33) observed that preoperative high PLR (>176) was also detected to be a poor prognostic factor. The preoperative PLR values were statistically significant in patients with colorectal adenocarcinoma compared with the healthy participants in the study conducted by Kilincalp et al. (6). In this study, the diagnostic sensitivity and specificity cutoff value of PLR was minimum 135 (sensitivity: 70%, specificity: 90%) (6). In our study, we found the cutoff value for PLR to be minimum 130 (sensitivity: 65%, specificity: 72%). The PLR cutoff value in our study was the same as that determined by Kilincalp et al. (6) in patients with colon cancer, but the NLR sensitivity and specificity ratios were a little lower.

In the study by Beyazıt et al. (34), in which they aimed to distinguish between the benign and malign lesions that cause biliary obstruction, the RWD cutoff value was found to be 14.8%, and the sensitivity of the test was 72% and specificity was 69%. In the study by Ay et al., RDW as a biomarker for use in early diagnosis of colon cancers was found (13). In this study, the RDW cutoff value was 17.5%, and the sensitivity of the test was 53.3% and the

specificity was 91.4% (13). In our study, preoperative RDW values in TNM stage-independent patients with colorectal cancer were significantly higher than in healthy participants. The cutoff value for RDW was detected as 14% (sensitivity: 68%, specificity: 73%).

The primary limitation of this study was that it was a retrospective and single-center study design. In our patients with colorectal cancer, NLR, PLR, and RDW values, independent of TNM stage, were found to be significantly higher than those in the healthy participants. The sensitivity of NLR, PLR, and RDW values were higher than gFOBTs. To conclude, our study determined that NLR, PLR, and RDW parameters obtained from complete blood counts are easily accessible, simple, and inexpensive and can be recommended for use as additional biomarkers for early diagnosis and screening of patients with colorectal cancer.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethical committee of Cumhuriyet University's Faculty of Medicine (2015-07/01).

Informed Consent: N/A

Peer-review: Externally peer-reviewed.

Author Contributions: Conceived and designed the experiments or case: EÇ., SS., ÖY. Performed the experiments or case: EÇ., SS. Analyzed the data: EÇ., SS. Wrote the paper: EÇ., ÖY., AY. All the authors have read and approved the final manuscript.

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REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015; 136(5): 359-86. [CrossRef]
2. Siegel R, DeSantis C, Virgo K, et al. Cancer treatment and survivorship statistics, 2012. CA Cancer J Clin 2012; 62: 220-41. [CrossRef]
3. Pox CP. Controversies in colorectal cancer screening. Digestion. 2014; 89(4): 274-81. [CrossRef]
4. Lansdorp-Vogelaar I, Knudsen AB, Brenner H. Cost-effectiveness of colorectal cancer screening an overview. Best Pract Res Clin Gastroenterol 2010; 24(4): 439-49. [CrossRef]
5. Janakirama NB, Rao CV, Inflammation and Cancer. Adv Exp Med Biol 2014; 816: 25-52 [CrossRef]
6. Kilincalp S, Çoban Ş, Akinci H, Hamamc M, Karaahmet F, Coşkun Y, et al. Neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, and mean platelet volume as potential biomarkers for early detection and monitoring of colorectal adenocarcinoma. Eur J Cancer Prev 2015; 24(4): 328-33. [CrossRef]
7. Yildirim MA, Seckin KD, Togrul C, Baser E, Karsli MF, Gungor T, Gulerman HC. Roles of neutrophil/lymphocyte and platelet/lymphocyte ratios in the early diagnosis of malignant ovarian masses. Asian Pac J Cancer Prev 2014; 15(16): 6881-5. [CrossRef]
8. Spell DW, Jones DV Jr, Harper WF, David Bessman J. The value of a complete blood count in predicting cancer of the colon. Cancer Detect Prev 2004; 28(1): 37-42. [CrossRef]
9. Khusun H, Yip R, Schultink W, Dillon DH. World Health Organization hemoglobin cut-off points for the detection of anemia are valid for an Indonesian population. J Nutr 1999; 129(9): 1669-74.
10. Brenner H, Kloor M, Pox CP. Colorectal cancer. Lancet 2014; 26(383): 1490-502. [CrossRef]
11. Grivennikov SI. Inflammation and colorectal cancer: colitis-associated neoplasia. Semin Immunopathol 2013 Mar; 35(2): 229-44. [CrossRef]
12. Galizia G, Lieto E, Zamboli A, De Vita F, Castellano P, Romano C, et al. Neutrophil to lymphocyte ratio is a strong predictor of tumor recurrence in early colon cancers: A propensity score-matched analysis. Surgery 2015; 158(1): 112-20. [CrossRef]
13. Ay S, Eryilmaz MA, Aksoy N, Okus A, Unlu Y, Sevinc B. Is early detection of colon cancer possible with red blood cell distribution width? Asian Pac J Cancer Prev 2015; 16(2): 753-6. [CrossRef]
14. Vendramini-Costa DB, Carvalho JE. Molecular link mechanisms between inflammation and cancer. Curr Pharm Des 2012; 18(26): 3831-52. [CrossRef]
15. Ross JA, Potter JD, Severson RK. Platelet-derived growth factor and risk factors for colorectal cancer. Eur J Cancer Prev 1993; 2(3): 197-210. [CrossRef]
16. Guillem-Llobat P, Dovizio M, Alberti S, Bruno A, Patrignani P. Platelets, cyclooxygenases, and colon cancer. Semin Oncol 2014; 41(3): 385-96. [CrossRef]
17. Chan AT, Ogino S, Fuchs CS. Aspirin and the risk of colorectal cancer in relation to the expression of COX-2. N Engl J Med 2007; 356(21): 2131-42. [CrossRef]
18. Erdman SE, Poutahidis T. Roles for inflammation and regulatory T cells in colon cancer. Toxicol Pathol 2010; 38(1): 76-87. [CrossRef]
19. de Gonzalo-Calvo D, de Luxán-Delgado B, Rodríguez-González S, García-Macia M, Suárez FM, Solano JJ, et al. Interleukin 6, soluble tumor necrosis factor receptor I and red blood cell distribution width as biological markers of functional dependence in an elderly population: a translational approach. Cytokine 2012; 58(2): 193-8. [CrossRef]
20. Albayrak S, Zengin K, Tanik S, Bakirtas H, Imamoglu A, Gurdal M. Red cell distribution width as a predictor of prostate cancer progression. Asian Pac J Cancer Prev 2014; 15(18): 7781-4. [CrossRef]
21. Lieberman D. Colorectal cancer screening: what program is most effective? Gastrointest Endosc 2015; 81(3): 710-2. [CrossRef]
22. Cruzado J, Sánchez FI, Abellán JM, Pérez-Riquelme F, Carballo F. Economic evaluation of colorectal cancer (CRC) screening. Best Pract Res Clin Gastroenterol 2013; 27(6): 867-80. [CrossRef]
23. Young GP, Symonds EL, Allison JE, Cole SR, Fraser CG, Halloran SP, et al. Advances in Fecal Occult Blood Tests: the FIT revolution. Dig Dis Sci 2015; 60(3): 609-22. [CrossRef]
24. Burch JA, Soares-Weiser K, St John DJ, Duffy S, Smith S, Kleijnen J, et al. Diagnostic accuracy of faecal occult blood tests used in screening for colorectal cancer: a systematic review. J Med Screen 2007; 14(3): 132-7. [CrossRef]
25. Allison JE, Fraser CG, Halloran SP, Young GP. Population screening for colorectal cancer means getting FIT: the past, present, and future of colorectal cancer screening using the fecal immunochemical test for hemoglobin (FIT). Gut Liver 2014; 8(2): 117-30 [CrossRef]
26. Whitlock EP, Lin JS, Liles E, Beil TL, Fu R. Screening for colorectal cancer: a targeted, updated systematic review for the U.S. Preventive Services Task Force. Ann Intern Med 2008; 149: 638-58. [CrossRef]
27. Ahlquist DA, Zou H, Domanico M, Mahoney DW, Yab TC, Taylor WR, et all. Next generation stool DNA test accurately detects colorectal cancer and large adenomas. Gastroenterology 2012; 142(2): 248-56. [CrossRef]
28. Spada C, Hassan C, Marmo R, Petruzziello L, Riccioni ME, Zullo A, et al. Meta-analysis shows colon capsule endoscopy is effective in detecting colorectal polyps. Clin Gastroenterol Hepatol 2010; 8: 516-22. [CrossRef]
29. Singh K, Narula AK, Thukral CL, Singh NR, Singh A, Kaur H. Role of CT Colonography in Colonic Lesions and Its Correlation with Conventional Colonoscopic Findings.J Clin Diagn Res 2015; 9(4): 14-8. [CrossRef]
30. Lieberman D. Colorectal cancer screening: practice guidelines. Dig Dis 2012; 30(2): 34-8. [CrossRef]

31. Chiang SF, Hung HY, Tang R, Changchien CR, Chen JS, You YT, et al. Can neutrophil-to-lymphocyte ratio predict the survival of colorectal cancer patients who have received curative surgery electively? Int J Colorectal Dis 2012; 27(10): 1347-57. [CrossRef]
32. Sun ZQ, Han XN, Wang HJ, Tang Y, Zhao ZL, Qu YL, et al. Prognostic significance of preoperative fibrinogen in patients with colon cancer. World J Gastroenterol 2014; 20(26): 8583-91. [CrossRef]
33. Absenger G, Szkandera J, Stotz M, Postlmayr U, Pichler M, Ress AL, et al. Preoperative neutrophil-to-lymphocyte ratio predicts clinical outcome in patients with stage II and III colon cancer. Anticancer Res 2013; 33(10): 4591-4.
34. Beyazit Y, Kekilli M, Ibis M, Kurt M, Sayilir A, Onal IK, et al. Can red cell distribution width help to discriminate benign from malignant biliary obstruction? A retrospective single center analysis. Hepatogastroenterology 2012; 59(117): 1469-73.