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ORIGINAL ARTICLE

What can preoperative blood tests tell us about colorectal cancer?

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Summary

Purpose: *To study the diagnostic and/or prognostic role of preoperative blood tests in colorectal cancer.*

Methods: *Preoperative complete blood count tests and lactate dehydrogenase (LDH) serum levels of 167 patients with colorectal adenocarcinoma were examined for associations with clinicopathological parameters, disease-specific survival (DSS) and relapse-free survival (RFS).*

Results: *The following parameters showed high sensitivity (≥85%) in detecting these features: platelet to lymphocyte ratio (PLR) for T4 tumors, white blood cell count (WBC) and neutrophil count (NC) for distant metastases and lymphocyte count (LC) for high-grade tumors. The following parameters showed high specificity (≥85%) in excluding these features: lymphocyte percentage (LP) for tumors larger than 5 cm, LP, neutrophil to lymphocyte ratio (NLR), neutrophil to monocyte ratio (NMR), lymphocyte to monocyte ratio (LMR) and LDH for T4 tumors, platelet to monocyte ratio (PMR) for T2-T4 tumors, LDH for more than three infiltrated regional lymph nodes and distant metastases, LMR for high-grade tumors and neutrophil percentage (NP) for lymphovascular invasion. WBC and NLR were independent prognostic factors for DSS, whereas WBC, NP, LP and NLR were independent prognostic factors for RFS.*

Conclusions: *Preoperative complete blood count and LDH serum levels can provide valuable information about diagnosis and prognosis in colorectal cancer.*

Key words: *colorectal cancer, lactate dehydrogenase, leukocytes, platelets, preoperative blood tests, white blood cells*

Introduction

Colorectal cancer is the third most common malignant disease and the fourth most frequent cause of cancer-related death worldwide [1]. The fact that colorectal cancer is such a frequent disease makes the identification of new biomarkers necessary. Apart from carcinoembryonic antigen (CEA), which is the most studied and used biomarker for colorectal cancer, other blood biomarkers, such as cancer antigen (CA) 19-9, CA 72-4, CA 242 and cell-free nucleic acids, have been tested in regards to their diagnostic and/or prognostic role in this disease [2,3]. Various hematological and biochemical parameters, such as neutrophil to lymphocyte ratio (NLR) [4,5], lymphocyte to monocyte ratio (LMR) [6-8], platelet to lymphocyte ratio (PLR) [9,10], lactate dehydrogenase (LDH) [11-13], etc., have been tested as potential diagnostic and/or prognostic markers in a variety of malignant diseases during the last few years. Our aim was to study the potential role of various parameters of preoperative blood tests, specifically the complete blood count test and the biochemical blood test, as diagnostic and/or prognostic markers in colorectal cancer.

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Methods

Patients

One hundred and sixty-seven patients with newly diagnosed colorectal adenocarcinoma [102 men and 65 women, age: mean ± SD: 70.5 years ± 10.1, median (min-max): 71 years (42-94)] who had undergone complete excision of their primary tumor within a time period of 41 months in our department were included in this study. Their preoperative blood tests, specifically the complete blood count test and the biochemical blood test, were reviewed. The values of the following parameters were collected from them: white blood cell count (WBC), neutrophil count (NC), neutrophil percentage (NP), lymphocyte count (LC), lymphocyte percentage (LP), monocyte count (MC), monocyte percentage (MP), platelet count (PLT), mean platelet volume (MPV), platelet distribution width (PDW), plateletcrit (PCT), neutrophil to lymphocyte ratio (NLR), neutrophil to monocyte ratio (NMR), lymphocyte to monocyte ratio (LMR), platelet to neutrophil ratio (PNR), platelet to lymphocyte ratio (PLR), platelet to monocyte ratio (PMR) and lactate dehydrogenase (LDH). These parameters were examined in regards to their associations with various clinical and pathological parameters, as well as disease-specific survival (DSS) and relapse-free survival (RFS). Patients' clinicopathological parameters are listed in Table 1. Staging was performed using the 8th edition of the TNM Classification of Malignant Tumors according to the International Union Against Cancer (UICC) [14]. This study conformed to the Declaration of Helsinki and the guidelines of the Ethical Committee of our institution.

Measurement of complete blood count

Four ml of blood were collected in EDTA vacutainer tubes with lavender top. Blood samples were analyzed within 30 min from the blood drawn using the Sysmex XT-4000i automated hematology analyzer (Sysmex, Kobe, Japan).

Measurement of LDH serum levels

Four ml of blood were collected in serum-separating tubes. Blood samples were allowed to clot at room temperature for at least 30 min. Subsequently, the tubes were centrifuged at 2500 rpm for 15 min. The collected serum was processed using immunochemistry (Architect c16000 analyzer; Abbott Diagnostics, IL, USA) within 2 hrs from the blood drawn, in order LDH levels to be measured. The normal value range was 200-460 IU/L for this assay. As far as LDH levels are concerned, the inter-assay coefficient of variation was <12% and the intra-assay coefficient of variation was <10%.

Statistics

The Shapiro-Wilk test was used for the assessment of the normality of data distribution. Comparisons between two groups were performed with the Student's t-test, Welch test or Mann-Whitney U test, as appropriate. Comparisons between three or more groups were performed using analysis of variance (ANOVA) with the Bonferroni correction or the Kruskal-Wallis test with the

Table 1. Patient's clinicopathological data (n=167)

Data	*n*
Gender	
Male	102
Female	65
Age, years	
Mean ± SD	70.5 ± 10.1
Median (min-max)	71 (42-94)
Segment of the large intestine	
Right colon	50
Left colon	59
Rectum	58
Tumor diameter, cm	
Mean ± SD	4.1 ± 1.8
Median (min-max)	3.9 (0.7-12)
Stage	
0	10
I	37
II	49
III	52
IV	19
Direct extent of the primary tumor (T)	
Tis	10
T1	12
T2	38
T3	88
T4	19
Disease spread to regional lymph nodes (N)	
N0	100
N1	31
N2	36
Distant metastases (M)	
M0	148
M1	19
Histological grade	
Low grade	124
High grade	43
Lymphovascular invasion	
No	129
Yes	38
Perineural invasion	
No	153
Yes	14
Mucinous neoplasm	
No	151
Yes	16

Bonferroni correction, as appropriate. Correlations between two continuous variables were assessed using the Pearson's correlation coefficient or the Spearman's rank correlation coefficient, as appropriate. The receiver operating characteristic (ROC) curve was used in conjunction with the Youden's J statistic for the assessment of the optimal cut-off points for parameters that yielded significant differences. These optimal cut-off points were taken into account for the calculation of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy.

There were sufficient data for 113 patients in regards to DSS, of which the 23 (20.4%) died within the surveillance period [mean surveillance period ± SD: 50.1 months ± 30.3, median surveillance period (min-max): 48 months (0-99)] and for 107 patients in regards to RFS, of which the 26 (24.3%) had relapse of the disease within the surveillance period [mean surveillance period ± SD: 51.5 months ± 30.1, median surveillance period (min-max): 60 months (0-99)]. For the assessment of DSS and RFS, we divided patients into four groups, according to the levels of the tested parameter (group 1: ≤25th percentile, group 2: >25th and ≤50th percentile, group 3: >50th and ≤75th percentile, group 4: >75th percentile). Kaplan-Meier curves were used for the assessment of DSS and RFS and the log-rank test was used for comparison of survival among different groups. Multivariate survival analysis was performed using Cox regression with the forward conditional method.

All the tests were two-tailed. The level of statistical significance was set at p value less than 0.05. The statistical analyses were carried out using the 23rd edition of the Statistical Package for the Social Sciences (SPSS) (IBM, Armonk, NY, USA).

Results

Tumor diameter

There was a positive correlation between tumor diameter and NC (r=0.163, p=0.037), NP (r=0.233, p=0.003), PLT (r=0.245, p=0.002), PCT (r=0.189, p=0.015), NLR (r=0.249, p=0.001) and PLR (r=0.258, p=0.001), whereas there was a negative correlation between tumor diameter and LC (r=-0.196, p=0.011), LP (r=-0.234, p=0.002), PDW (r=-0.202, p=0.012) and LMR (r=-0.204, p=0.009). Various tumor diameters were tested as thresholds. Our analysis showed that tumors larger than 3 cm had increased WBC (p=0.009), NMR (p=0.03) and LDH (p=0.018) when compared with tumors up to 3 cm in diameter. In addition, tumors larger than 4 cm had decreased PDW (p=0.019) in comparison with tumors up to 4 cm in diameter. Furthermore, tumors larger than 5 cm had higher NC (p=0.018), NP (p=0.001), PLT (p=0.004), PCT (p=0.029), NLR (p=0.001), PLR (p=0.0001) and PMR (p=0.049), and lower LC (p=0.004), LP (p=0.001) and LMR (p=0.005) than tumors up to 5 cm in diameter. The exact results of comparisons between subgroups and ROC analysis concerning tumor diameter are shown in Table 2.

Direct extent of primary tumor (T)

Tumors infiltrating beyond submucosa (T2-T4 tumors) had increased PMR (p=0.027) when compared with tumors infiltrating up to submucosa (Tis-T1 tumors). Furthermore, tumors infiltrating beyond muscularis propria (T3-T4 tumors) had increased PLT (p=0.003) and PCT (p=0.027), and decreased PDW (p=0.002) in comparison with tumors infiltrating up to muscularis propria (Tis-T2 tumors). In addition, tumors penetrating to the surface of the visceral peritoneum or invading other adjacent organs or structures (T4 tumors) had higher WBC (p=0.006), NC (p=0.001), NP (p=0.000009), NLR (p=0.000005), NMR (p=0.016), PLR (p=0.00004) and LDH (p=0.006), and lower LC (p=0.001), LP (p=0.000007) and LMR (p=0.0003) than the rest tumors. The exact results of comparisons between subgroups and ROC analysis regarding the direct extent of primary tumor are listed in Table 2.

Disease spread to regional lymph nodes (N)

Patients with metastasis in four or more regional lymph nodes (N2 disease) had higher LDH serum levels than patients without lymph node metastasis (N0) or with up to three infiltrated lymph nodes (N1) (p=0.006). The exact results of comparisons between subgroups and ROC analysis in regards to the disease spread to regional lymph nodes are shown in Table 2.

Disease stage

Patients with stage II-IV disease had increased PLT (p=0.004) and PLR (p=0.01), and reduced PDW (p=0.004) when compared to patients with stage 0-I disease. Moreover, patients with stage IV disease, which corresponds to the presence of distant metastases (M1), had higher WBC (p=0.03), NC (p=0.003), NP (p=0.001), NLR (p=0.001), NMR (p=0.03) and LDH (p=0.000006), and lower LC (p=0.047), LP (p=0.001) and PNR (p=0.03) than patients without distant metastases (M0, stages 0-III). The exact results of comparisons between subgroups and ROC analysis in terms of the disease stage are listed in Table 2.

Histological grade of the neoplasm

Patients with high-grade neoplasms had higher PLR (p=0.017) and lower LC (p=0.046) and LMR (p=0.013) than patients with low-grade neoplasms. The exact results of comparisons between subgroups and ROC analysis concerning the histological grade of the neoplasm are shown in Table 2.

Table 2. Analysis according to clinicopathological parameters

Tumor diameter >3 cm										
Parameter	*≤3 cm*	*>3 cm*	*p-value*	*Cut-off point*	*AUC*	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*	*NPV (%)*	*Accuracy (%)*
WBC (cells/μl)	6700 (3750-10790)	7215 (3550-26330)	0.009	>6900	0.629	57.3	68.8	81.7	39.8	60.6
NMR	7.609 (3.25-47.5)	8.903 (2.727-33.014)	0.03	>10	0.607	38.5	81.3	83.3	35.1	50.9
LDH (IU/L)	314 (223-900)	363 (183-3506)	0.018	>326	0.626	68.7	64.3	81.9	46.6	67.4
LDH>460 IU/L				>460		18.2	92.9	85.7	32.5	40.4
Tumor diameter >4 cm										
Parameter	*≤4 cm*	*>4 cm*	*p-value*	*Cut-off point*	*AUC*	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*	*NPV (%)*	*Accuracy (%)*
PDW (%)	16.05 (9.6-19.4)	15.3 (0.6-20.9)	0.019	<16.1	0.61	70.1	50	52.2	68.3	58.8
Tumor diameter >5 cm										
Parameter	*≤5 cm*	*>5 cm*	*p-value*	*Cut-off point*	*AUC*	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*	*NPV (%)*	*Accuracy (%)*
NC (cells/μl)	4300 (1800-12100)	5600 (2300-24100)	0.018	>5700	0.632	52.9	80.2	40.9	86.8	74.5
NP (%)	63.7 ± 8.9	70.5 ± 10	0.001	>69.5	0.685	77.8	75.7	28	96.6	75.9
LC (cells/μl)	1600 (710-4140)	1380 (700-3170)	0.004	<1550	0.661	76.5	58.8	32.5	90.6	62.4
LP (%)	24.1 (7.3-47.2)	20.3 (5.5-34.4)	0.001	<16	0.684	41.2	88.6	48.3	85.4	78.9
PLT (cells/μl)	246000 (131000-510000)	303500 (163000-654000)	0.004	>295000	0.662	59.6	74.6	48.3	82.2	70.3
PCT (%)	0.231 (0.126-0.49)	0.305 (0.139-0.61)	0.029	>0.29	0.621	46.7	77.8	46.7	77.8	68.6
NLR	2.625 (0.789-11.268)	3.515 (1.586-16.507)	0.001	≥3	0.692	67.6	65.6	33.8	88.7	66.1
LMR	3.164 (1.067-7.708)	2.359 (1.077-6.667)	0.005	<2.285	0.656	50	80.9	40.5	86.2	74.5
PLR	147.778 (64.493-380.952)	226.148 (87.727-655.714)	0.0001	>178	0.713	70.6	66.4	35.3	89.7	67.3
PMR	467.5 (133.333-1841.667)	574.375 (203.846-1332.653)	0.049	>553	0.61	55.9	67.2	30.6	85.4	64.8
Direct extent of primary tumor (T): T2-T4 tumor										
Parameter	*Tis-T1*	*T2-T4*	*p-value*	*Cut-off point*	*AUC*	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*	*NPV (%)*	*Accuracy (%)*
PMR	421.667 (143-1067.5)	492.143 (133.333-1841.667)	0.027	>540	0.65	43.8	85.7	95.5	18.2	49.1
Direct extent of primary tumor (T): T3-T4 tumor										
Parameter	*Tis-T2*	*T3-T4*	*p-value*	*Cut-off point*	*AUC*	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*	*NPV (%)*	*Accuracy (%)*
PLT (cells/μl)	233500 (131000-510000)	270000 (134000-654000)	0.003	>281000	0.64	50	76.3	79.1	45.9	59.4
PDW (%)	16.1 (9.6-19.4)	15.2 (0.6-20.9)	0.002	<14.2	0.648	44.3	83.9	82.7	46.5	58.8
PCT (%)	0.22 (0.126-0.49)	0.262 (0.139-0.61)	0.027	>0.28	0.603	41.2	82.1	80	44.7	56.2

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Direct extent of primary tumor (T): T4 tumor										
Parameter	*Tis-T3*	*T4*	*p-value*	*Cut-off point*	*AUC*	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*	*NPV (%)*	*Accuracy (%)*
WBC (cells/μl)	6720 (3750-14500)	9160 (3550-26330)	0.006	>8200	0.698	66.7	75	24.5	94.9	74.1
NC (cells/μl)	4200 (1800-12100)	7200 (2300-24100)	0.001	>5900	0.749	66.7	83	32.4	95.3	81.2
NP (%)	63.8 ± 8.7	75.9 ± 8.4	0.000009	>69.3	0.822	77.8	75.7	28	96.6	75.9
LC (cells/μl)	1590 (800-4140)	1360 (700-1800)	0.001	<1465	0.751	77.8	66	21.9	96	67.3
LP (%)	24.1 (9.1-47.2)	13.4 (5.5-26.2)	0.000007	<18	0.825	72.2	85.1	37.1	96.2	83.7
NLR	2.658 (0.789-9.192)	5.714 (2.333-16.507)	0.000005	≥4	0.83	72.2	84.5	36.1	96.2	83.1
NMR	8.032 (2.727-47.5)	12 (6.846-33.014)	0.016	≥12	0.675	50	85.7	30	93.3	81.8
LMR	3.154 (1.067-7.708)	1.902 (1.077-4.048)	0.0003	<2.13	0.764	66.7	86.4	37.5	95.5	84.2
PLR	149.048 (64.493-621.212)	247.154 (147.778-655.714)	0.00004	>147	0.796	100	49.7	19.6	100	55.2
LDH (IU/L)	336 (183-1473)	441 (221-3506)	0.006	>470	0.686	50	90.4	40	93.4	85.8
LDH>460 IU/L				>460		50	89.6	38.1	93.3	85.1
Disease stage: II-IV disease										
Parameter	*Stage 0-I*	*Stage II-IV*	*p-value*	*Cut-off point*	*AUC*	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*	*NPV (%)*	*Accuracy (%)*
PLT (cells/μl)	232000 (143000-510000)	267000 (131000-654000)	0.004	>240000	0.643	66.4	60.9	81.4	41.2	64.8
PDW (%)	16.3 (9.6-19.4)	15.5 (0.6-20.9)	0.004	<16.4	0.647	75.2	50	78.8	44.9	68
PLR	136.25 (77.258-340)	169.88 (64.493-655.714)	0.01	>154.2	0.63	58.8	67.4	82.4	38.8	61.2
Disease stage: IV disease (M1 disease)										
Parameter	*Stage 0-III (M0)*	*Stage IV (M1)*	*p-value*	*Cut-off point*	*AUC*	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*	*NPV (%)*	*Accuracy (%)*
WBC (cells/μl)	6800 (3550-15960)	8135 (5300-26330)	0.03	>6000	0.653	94.7	29.9	14.9	97.8	37.3
NC (cells/μl)	4200 (1800-13200)	5200 (3900-24100)	0.003	>3900	0.712	94.7	43.5	17.8	98.5	49.4
NP (%)	64.3 ± 9.1	71.8 ± 9.9	0.001	>66	0.722	78.9	61.1	20.5	95.8	63.1
LC (cells/μl)	1565 (700-4140)	1400 (700-2620)	0.047	<1470	0.64	68.4	65.3	20.3	94.1	65.7
LP (%)	24.8 ± 7.9	17.6 ± 7.3	0.001	<22.3	0.746	73.7	64.9	21.2	95	65.9
NLR	2.667 (0.789-11.268)	3.593 (1.87-16.507)	0.001	≥3	0.74	73.7	63.3	20.6	94.9	64.5
NMR	8 (2.727-23.333)	9.692 (5.375-47.5)	0.03	>7.65	0.653	84.2	43.5	16.2	95.5	48.2
PNR	62.054 (25.672-261.2)	51.769 (9.668-74.75)	0.03	<57.5	0.653	73.7	54.4	17.3	94.1	56.6
LDH (IU/L)	331 (183-1007)	472 (280-3506)	0.000006	>435	0.824	68.4	87	44.8	94.7	84.5
LDH>460 IU/L				>460		52.6	91.1	47.6	92.6	85.9

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Disease spread to regional lymph nodes (N): N2 disease										
Parameter	*N0/N1*	*N2*	*p-value*	*Cut-off point*	*AUC*	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*	*NPV (%)*	*Accuracy (%)*
LDH (IU/L)	336 (196-819)	413.5 (183-3506)	0.006	>423	0.659	50	84.4	48.5	85.2	76.6
LDH>460 IU/L				>460		40.6	92.7	61.9	84.2	80.9
Histological grade of the neoplasm: High-grade neoplasm										
Parameter	*Low grade*	*High grade*	*p-value*	*Cut-off point*	*AUC*	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*	*NPV (%)*	*Accuracy (%)*
LC (cells/μl)	1560 (700-4140)	1460 (700-2500)	0.046	<1860	0.603	90.5	31.7	31.1	90.7	46.7
LMR	3.164 (1.143-7.375)	2.571 (1.067-7.708)	0.013	<1.91	0.628	33.3	91.9	58.3	80.1	77
PLR	150 (64.493-492.391)	190.525 (102.727-655.714)	0.017	>189	0.624	54.8	69.9	38.3	81.9	66.1
Lymphovascular invasion: Presence of lymphovascular invasion										
Parameter	*No*	*Yes*	*p-value*	*Cut-off point*	*AUC*	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*	*NPV (%)*	*Accuracy (%)*
NP (%)	64.4 ± 9	68 ± 10.7	0.026	>75	0.602	32.4	90.7	50	82.4	77.7

For abbreviations see text

Lymphovascular invasion

Tumors with lymphovascular invasion had higher NP than tumors without (p=0.026). The exact results of comparisons between subgroups and ROC analysis regarding lymhpovascular invasion are listed in Table 2.

Perineural invasion

There were no significant associations concerning perineural invasion.

Mucinous neoplasm

There were no significant associations regarding the presence or the absence of mucinous neoplasm.

Disease-specific survival (DSS)

Shorter DSS was observed in the following cases: WBC >7000/μl (p=0.045) (Figure 1), NC >4300/μl (p=0.038), NP >64% (p=0.002), LC <1300/μl (p=0.03), LP ≤24% (p=0.006), NLR ≥4 (p=0.001) (Figure 2) and PNR ≤44.4 (p=0.013). However, only WBC >7000/μl (HR: 3.05, 95% CI: 1.214-7.662, p=0.018) and NLR ≥4 (HR: 7.44, 95% CI: 2.631-21.044, p=0.0002) remained independent prognostic factors for worse DSS in the multivariate survival analysis. The exact results of survival analysis according to DSS are shown in Table 3.

Relapse-free survival (RFS)

Shorter RFS was observed in the following cases: WBC >7000/μl (p=0.049) (Figure 3), NC >4300/μl (p=0.044), NP ≥64% (p=0.002) (Figure 4), LP ≤24% (p=0.009) (Figure 5), PCT ≤0.197% (p=0.013), NLR >2.5 (p=0.035) (Figure 6) and PNR ≤44.4 (p=0.043). However, only WBC >7000/μl (HR: 2.258, 95% CI: 1.02-5.002, p=0.045), NP ≥64% (HR: 3.79, 95% CI: 1.536-9.355, p=0.004), LP ≤24% (HR: 2.87, 95% CI: 1.19-6.923, p=0.019) and NLR >2.5 (HR: 2.632, 95% CI: 1.068-6.488, p=0.035) remained independent prognostic factors for worse RFS in the multivariate survival analysis. The exact results of survival analysis according to RFS are listed in Table 3.

Discussion

The role of chronic inflammatory response in carcinogenesis has been suspected since Virchow proposed this interaction 150 years ago and it has begun to decipher during recent years. Inflammatory cells, such as neutrophils, lymphocytes, macrophages, dendritic cells, are part of tumor microenvironment. They are engaged in cross-talk with

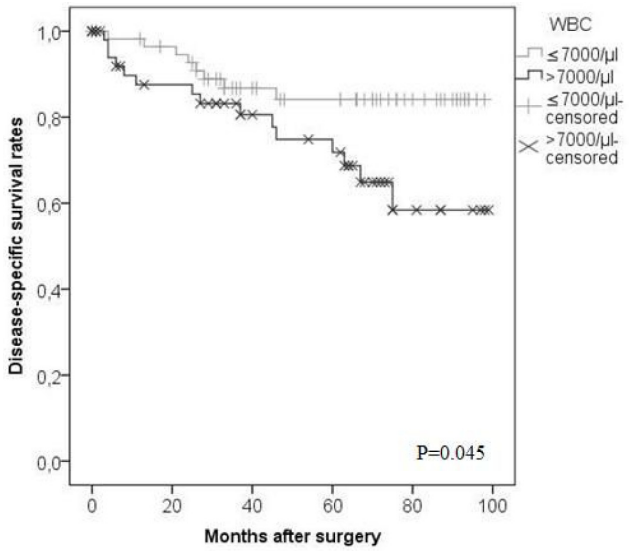

Figure 1. DSS according to WBC.

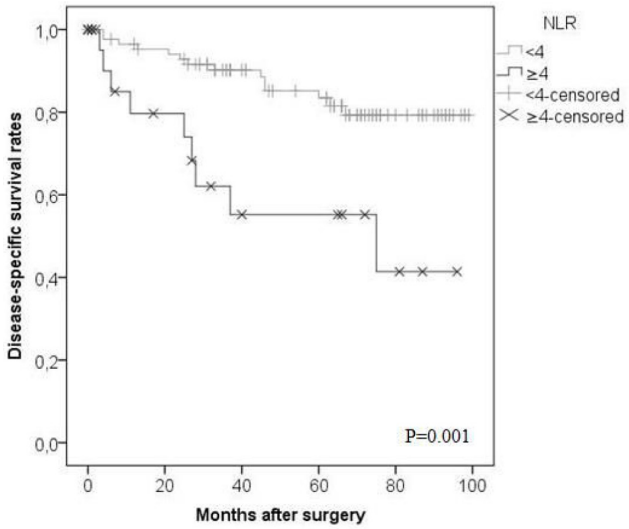

Figure 2. DSS according to NLR.

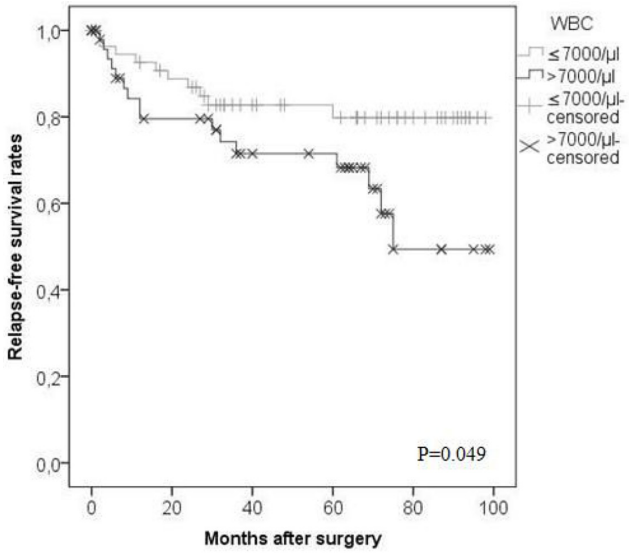

Figure 3. RFS according to WBC.

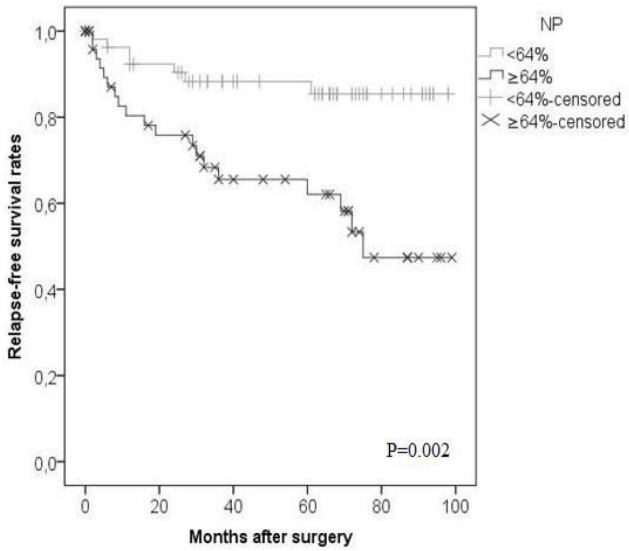

Figure 4. RFS according to NP.

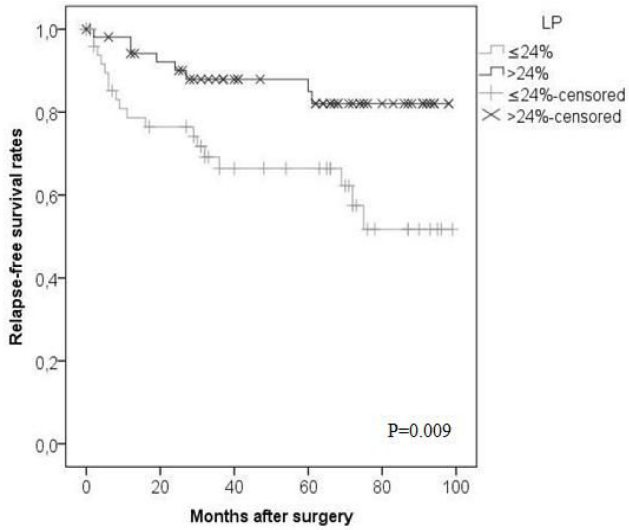

Figure 5. RFS according to LP.

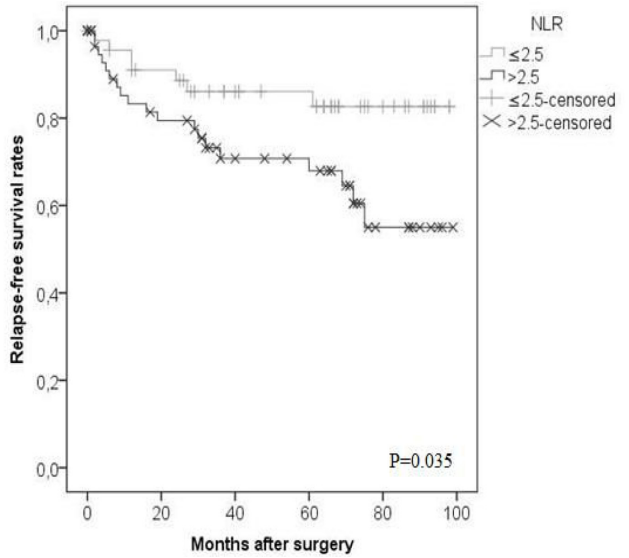

Figure 6. RFS according to NLR.

tumor cells, affecting tumorigenesis, tumor growth, angiogenesis, metastatic potential and escape from immune surveillance, and showing either tumor-promoting or tumor-suppressive properties [15-19]. Interleukin-1α (IL-1α), interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-10 (IL-10), interleukin-12 (IL-12), interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), transforming growth factor-β (TGF-β), CCL2 and CXCL8, are some out of the numerous cytokines that are released at the site of the tumor and are involved in the complicated cross-talk between the cells of the immune system and the neoplastic cells [15-20]. Apart from inflammatory cells, platelets are also involved in complicated cross-talks within tumor microenvironment, interacting with neoplastic cells, leuko-

Table 3. Survival analysis

Disease-specific survival (DSS)									
		Univariate analysis				*Multivariate analysis*			
Parameter	*Group*	*Mean DSS (months)*	*SE*	*95% CI*	*p value*	*Cut-off point*	*HR*	*95% CI*	*p value*
WB	≤7000	86.5	3.8	79.2-93.9	0.045	>7000	3.05	1.214-7.662	0.018
(cells/μl)	>7000	74.5	5.3	64.2-84.8					
NC	≤4300	86.6	3.7	79.4-93.9	0.038	>4300			0.135
(cells/μl)	>4300	74.2	5.3	63.8-84.7					
NP	≤64	90.1	3.1	84.1-96.1	0.002	>64			0.129
(%)	>64	70.7	5.5	59.8-81.6					
LC	<1300	67.2	7.7	52-82.3	0.03	<1300			0.167
(cells/μl)	≥1300	85.4	3.3	78.9-91.9					
LP	≤24	72.1	5.4	61.6-82.6	0.006	≤24			0.3
(%)	>24	89.7	3.2	83.4-96					
NLR	≤3.183	86	3.2	79.7-92.2	0.003	>3.183	2.79	1.103-7.059	0.03
	>3.183	61.6	8.6	44.7-78.4					
NLR	<4	86.2	3.1	80.1-92.4	0.001	≥4	7.44	2.631-21.044	0.0002
	≥4	58.6	9	40.9-76.3					
PNR	≤44.4	65.9	8.5	49.2-82.7	0.013	≤44.4			0.187
	>44.4	84.9	3.2	78.7-91.2					
Relapse-free survival (RFS)									
		Univariate analysis				*Multivariate analysis*			
Parameter	*Group*	*Mean RFS (months)*	*SE*	*95% CI*	*p value*	*Cut-off point*	*HR*	*95% CI*	*p value*
WBC	≤7000	82.6	4.4	74-91.3	0.049	>7000	2.258	1.02-5.002	0.045
(cells/μl)	>7000	68.6	6	56.8-80.4					
NC	≤4300	82.8	4.4	74.3-91.4	0.044	>4300			0.153
(cells/μl)	>4300	68.7	6	57-80.5					
NP	<64	87.1	3.9	79.5-94.7	0.002	≥64	3.79	1.536-9.355	0.004
(%)	≥64	64.8	6	53-76.6					
LP	≤24	66.6	6	54.8-78.4	0.009	≤24	2.87	1.19-6.923	0.019
(%)	>24	85.9	4	78.1-93.7					
PCT	≤0.197	55.2	8.3	38.9-71.6	0.013	≤0.197			0.089
(%)	>0.197	81.6	3.9	73.9-89.3					
NLR	≤2.647	87.1	3.9	79.5-94.7	0.002	>2.647	3.813	1.554-9.357	0.003
	>2.647	65	6	53.2-76.7					
NLR	≤2.5	85.1	4.5	76.2-94	0.035	>2.5	2.632	1.068-6.488	0.035
	>2.5	69.9	5.4	59.3-80.5					
PNR	≤44.4	62.6	9.2	44.7-80.6	0.043	≤44.4			0.064
	>44.4	80.4	3.8	72.9-87.8					

For abbreviations see text

cytes, endothelial cells and fibroblasts. Among the results of these interactions are the stimulation of angiogenesis, especially through the release of growth factors, such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), TGF-β and fibroblast growth factor (FGF), the facilitation of metastatic process, the release of cytokines that help tumor cells to sustain proliferative signals and resist cell death, and the formation of platelet-tumor cells aggregates, through interactions with selectins and other cell adhesion molecules, that help tumor cells to evade immune surveillance and protect them from the sheer force of the blood [21-26].

Many studies have tried to assess how the aforementioned activation of leukocytes and platelets is depicted in the complete blood count of patients in a variety of malignant diseases. A number of these studies concern colorectal cancer. First of all, increased NC has been associated with shorter overall survival [27]. Similarly, decreased LC and LP have been related to worse overall survival (OS) and progression-free survival (PFS) [28-30], larger tumors [28] and more locally advanced tumors [29]. Furthermore, elevated platelet count has been associated with poorer OS and disease-free survival (DFS) [31,32]. It has also been found that MPV is higher in patients with colorectal cancer than in healthy controls [33, 34] and is also higher in patients with distant metastases than in patients without distant metastases [35]. However, Włodarczyk et al. [36] reported that MPV is reduced in patients with rectal cancer when compared with healthy controls. In addition, various ratios, such as NLR, LMR and PLR have been tested in patients with colorectal cancer. Higher NLR has been associated with larger tumors [37], poorer differentiation [37,38] and worse OS, DFS and PFS [4,5,37-40]. Moreover, lower LMR has been related to the presence of distant metastases [8] and poorer OS, DFS and RFS [6-8,41,42], while elevated PLR has been associated with advanced stage [43], locally advanced tumors [44], poor differentiation [43,44] and shorter OS, DFS and RFS [9,10,42-47]. Finally, C-reactive protein (CRP) is a marker that has been studied in colorectal cancer, as well as in many other types of malignancies, as a depiction of the inflammatory processes that take place during the initiation and progression of tumorigenesis [48]. A meta-analysis conducted by Zhou et al. suggested that increased serum levels of CRP are associated with higher risk for colorectal cancer [49]. Another meta-analysis conducted by Pathak et al. concluded that OS and DFS of patients with colorectal cancer are shorter when there are high preoperative serum levels of CRP [50].

Apart from the indices of the complete blood count test, LDH is another common blood test that has been tested in colorectal cancer, as well as in many other types of malignant diseases. LDH is an enzyme that is located in the cytoplasm and catalyzes the final step of anaerobic glycolysis, which is the reversible conversion of pyruvate to lactate. It has a wide tissue distribution, being present in almost every type of cell in the body, and it can be found in five isoforms, which differ according to the type of tissue [13,51,52]. LDH is a biomarker of cell damage and cell death, because it is released in the bloodstream in these occasions. Thus, its serum levels are increased in many diseases, such as hemolytic anemia, myocardial infarction, pulmonary embolism, rhabdomyolysis, lymphomas, leukemia, seminomatous and non-seminomatous germ cell tumors [13,53]. In addition to its role to anaerobic glycolysis, on which tumors greatly rely, it has been found that LDH promotes tumor growth and proliferation and metastatic potential of neoplastic cells [13,52]. As far as colorectal cancer is concerned, increased serum levels of LDH were found in cases of T4, N2 and M1 tumors [54] and were related to poorer OS [11,12,55].

According to our findings, the various indices of the preoperative blood tests may be used as diagnostic or prognostic biomarkers. As far as diagnosis is concerned, we examined whether they can provide valuable information about the tumor diameter, the stage of disease, the direct extent of the primary tumor, the number of the infiltrated lymph nodes, the histological grade of the neoplasm and the presence or the absence of distant metastases, lymphovascular invasion, perineural invasion or mucinous neoplasm. First of all, it was found that the tumor diameter influenced WBC, NC, NP, LC, LP, PLT, PDW, PCT, NLR, NMR, LMR, PLR, PMR and LDH, providing either positive or negative correlations between the tumor diameter and the aforementioned parameters. When we tried to find a threshold in tumor diameter above which the values of these indices are altered, our analysis provided 3 cm and 5 cm as cut-off points. Moreover, the stage of disease had an impact on WBC, NC, NP, LC, LP, PLT, PDW, NLR, NMR, PNR, PLR and LDH. There was a significant difference when cases with distant metastases (stage IV disease) were compared with cases without distant metastases (stages 0-III) regarding most of these parameters, namely WBC, NC, NP, LC, LP, NLR, NMR, PNR and LDH. However, there was a significant difference when stages 0 and I were compared with stages II, III and IV, concerning PLT, PDW and PLR. Furthermore, the direct extent of the primary tumor seemed to affect WBC, NC, NP, LC, LP, PLT, PDW,

PCT, NLR, NMR, LMR, PLR, PMR and LDH. Most of these parameters, namely WBC, NC, NP, LC, LP, NLR, NMR, LMR, PLR and LDH, differed when T4 tumors were compared with the rest tumors (Tis-T3), but PLT, PDW and PCT differed when T3-T4 tumors were compared with Tis-T2 tumors, and PMR differed when T2-T4 tumors were compared with Tis-T1 tumors. The degree of disease spread to regional lymph nodes had an impact only on LDH serum levels and the presence of lymphovascular invasion affected only NP. Finally, the histological grade of the neoplasm, and therefore its differentiation, influenced only LC, LMR and PLR. On the other hand, there was no valuable information about the presence or the absence of perineural invasion or mucinous neoplasm, whereas no significant associations were observed between any tested parameter and MC, MP or MPV.

The optimal cut-off points, which were found after ROC analysis for the parameters that yielded statistically significant results, provided mediocre sensitivities and specificities in most cases. However, there were several cut-off points that provided high sensitivities or specificities (≥85%). In particular, the following parameters showed high sensitivities in detecting the presence of these features: PLR for T4 tumors, WBC and NC for distant metastases (M1 disease) and LC for high-grade tumors. Moreover, the following parameters showed high specificities in excluding the presence of these features: LP for tumors larger than 5 cm in diameter, LP, NLR, NMR, LMR and LDH for T4 tumors, PMR for T2-T4 tumors, LDH for more than three infiltrated regional lymph nodes (N2 disease) or distant metastases (M1 disease), LMR for high-grade tumors and NP for lymphovascular invasion. At this point, we should keep in mind that in regards to the preoperative computed tomography in colon cancer, the estimated sensitivities for T, N and M staging are about 77-90%, 70-76% and 85%, respectively, and the estimated specificities for T, N and M staging are about 69-78%, 55-78% and 98%, respectively [56-58]. Furthermore, in terms of the preoperative magnetic resonance imaging in rectal cancer, the estimated sensitivity and specificity for T staging are about 87% and 75%, respectively, and the estimated sensitivity and specificity for N staging are about 77% and 71-76%, respectively [59,60]. The aforementioned high (≥85%) sensitivities and specificities from our study point out that several parameters from preoperative blood tests could serve as an adjunct modality to the imaging studies for more accurate staging of colorectal cancer before treatment, which could be more meticulously planned.

We also examined whether the various indices of the preoperative blood tests can provide valuable information about survival. It was found that the values of WBC, NC, NP, LC, LP, NLR and PNR were associated with DSS. However, only WBC and NLR remained independent prognostic factors in the multivariate survival analysis. It was also found that the values of WBC, NC, NP, LP, PCT, NLR and PNR were associated with RFS. Nevertheless, only WBC, NP, LP and NLR remained independent prognostic factors in the multivariate survival analysis. On the other hand, no significant associations were documented between survival and MC, MP, PLT, MPV, PDW, NMR, LMR, PLR, PMR or LDH.

In conclusion, preoperative complete blood count and LDH serum levels can provide valuable information about diagnosis and prognosis in colorectal cancer. The aforementioned indices may be particularly helpful in informing about the tumor diameter, the stage of disease, the direct extent of the primary tumor, the number of infiltrated lymph nodes, the histological grade of the neoplasm and the presence or the absence of distant metastases and lymphovascular invasion and therefore they may serve as diagnostic markers. In addition, a number of these parameters may serve as prognostic markers about DSS and RFS. More studies are needed in order their diagnostic and prognostic role in colorectal cancer to become more explicit.

Conflict of interests

The authors declare no conflict of interests.

References

1. Brenner H, Kloor M, Pox CP. Colorectal cancer. Lancet 2014;383:1490-1502.
2. Gonzalez-Pons M, Cruz-Correa M. Colorectal Cancer Biomarkers: Where Are We Now? Biomed Res Int 2015;2015:149014.
3. Lech G, Slotwinski R, Krasnodebski IW. The role of tumor markers and biomarkers in colorectal cancer. Neoplasma 2014;61:1-8.
4. Paramanathan A, Saxena A, Morris DL. A systematic review and meta-analysis on the impact of pre-operative

neutrophil lymphocyte ratio on long term outcomes after curative intent resection of solid tumours. Surg Oncol 2014;23:31-9.

5. Bowen RC, Little NAB, Harmer JR et al. Neutrophil-to-lymphocyte ratio as prognostic indicator in gastrointestinal cancers: a systematic review and meta-analysis. Oncotarget 2017;8:32171-89.
6. Zhang J, Chen L, Zhou R, Sun H, Liao Y, Liao W. Pretreatment lymphocyte monocyte ratio predicts long-term outcomes in patients with digestive system tumor: a meta-analysis. Gastroenterol Res Pract 2016;2016:9801063.
7. Gu L, Li H, Chen L et al. Prognostic role of lymphocyte to monocyte ratio for patients with cancer: evidence from a systematic review and meta-analysis. Oncotarget 2016;7:31926-42.
8. Nishijima TF, Muss HB, Shachar SS, Tamura K, Takamatsu Y. Prognostic value of lymphocyte-to-monocyte ratio in patients with solid tumors: a systematic review and meta-analysis. Cancer Treat Rev 2015;41:971-8.
9. Templeton AJ, Ace O, McNamara MG et al. Prognostic role of platelet to lymphocyte ratio in solid tumors: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev 2014;23:1204-12.
10. Zhou X, Du Y, Huang Z et al. Prognostic value of PLR in various cancers: a meta-analysis. PLoS One 2014;9:e101119.
11. Petrelli F, Cabiddu M, Coinu A et al. Prognostic role of lactate dehydrogenase in solid tumors: a systematic review and meta-analysis of 76 studies. Acta Oncol 2015;54:961-70.
12. Zhang J, Yao YH, Li BG, Yang Q, Zhang PY, Wang HT. Prognostic value of pretreatment serum lactate dehydrogenase level in patients with solid tumors: a systematic review and meta-analysis. Sci Rep 2015;5:9800.
13. Miao P, Sheng S, Sun X, Liu J, Huang G. Lactate dehydrogenase A in cancer: a promising target for diagnosis and therapy. IUBMB Life 2013;65:904-910.
14. Brierley JD, Gospodarowicz MK, Wittekind C (Eds) Colon and Rectum. In: TNM classification of malignant tumours (8th Edn). Oxford,UK:Wiley-Blackwell 2016, pp 73-6.
15. Crusz SM, Balkwill FR. Inflammation and cancer: advances and new agents. Nat Rev Clin Oncol 2015;12:584-96.
16. Rodriguez-Vita J, Lawrence T. The resolution of inflammation and cancer. Cytokine Growth Factor Rev 2010;21:61-5.
17. Candido J, Hagemann T. Cancer-related inflammation. J Clin Immunol 2013;33:S79-S84.
18. Chow MT, Möller A, Smyth MJ. Inflammation and immune surveillance in cancer. Semin Cancer Biol 2012;22:23-32.
19. Wang K, Karin M. Tumor-elicited inflammation and colorectal cancer. Adv Cancer Res 2015;128:173-96.
20. Fernandes JV, Cobucci RN, Jatobá CA, Fernandes TA, de Azevedo JW, de Araújo JM. The role of the mediators of inflammation in cancer development. Pathol Oncol Res 2015;21:527-34.
21. Yan M, Jurasz P. The role of platelets in the tumor microenvironment: from solid tumors to leukemia. Biochim Biophys Acta 2016;1863:392-400.
22. Franco AT, Corken A, Ware J. Platelets at the interface of thrombosis, inflammation, and cancer. Blood 2015;126:582-8.
23. Sharma D, Brummel-Ziedins KE, Bouchard BA, Holmes CE. Platelets in tumor progression: a host factor that offers multiple potential targets in the treatment of cancer. J Cell Physiol 2014;229:1005-15.
24. Goubran HA, Stakiw J, Radosevic M, Burnouf T. Platelets effects on tumor growth. Semin Oncol 2014;41:359-69.
25. Menter DG, Tucker SC, Kopetz S, Sood AK, Crissman JD, Honn KV. Platelets and cancer: a casual or causal relationship: revisited. Cancer Metastasis Rev 2014;33:231-69.
26. Dovizio M, Alberti S, Guillem-Llobat P, Patrignani P. Role of platelets in inflammation and cancer: novel therapeutic strategies. Basic Clin Pharmacol Toxicol 2014;114:118-27.
27. Watt DG, Martin JC, Park JH, Horgan PG, McMillan DC. Neutrophil count is the most important prognostic component of the differential white cell count in patients undergoing elective surgery for colorectal cancer. Am J Surg 2015;210:24-30.
28. Iseki Y, Shibutani M, Maeda K et al. The impact of the preoperative peripheral lymphocyte count and lymphocyte percentage in patients with colorectal cancer. Surg Today 2017;47:743-54.
29. Liang L, Zhu J, Jia H et al. Predictive value of pretreatment lymphocyte count in stage II colorectal cancer and in high-risk patients treated with adjuvant chemotherapy. Oncotarget 2016;7:1014-28.
30. Cézé N, Thibault G, Goujon G et al. Pre-treatment lymphopenia as a prognostic biomarker in colorectal cancer patients receiving chemotherapy. Cancer Chemother Pharmacol 2011;68:1305-13.
31. Long Y, Wang T, Gao Q, Zhou C. Prognostic significance of pretreatment elevated platelet count in patients with colorectal cancer: a meta-analysis. Oncotarget 2016;7:81849-61.
32. Zhao JM, Wang YH, Yao N et al. Poor prognosis significance of pretreatment thrombocytosis in patients with colorectal cancer: a meta-analysis. Asian Pac J Cancer Prev 2016;17:4295-4300.
33. Kilincalp S, Çoban Ş, Akinci H 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;24:328-33.
34. Li JY, Li Y, Jiang Z, Wang RT, Wang XS. Elevated mean platelet volume is associated with presence of colon cancer. Asian Pac J Cancer Prev 2014;15:10501-04.
35. Tuncel T, Ozgun A, Emirzeoglu L, Celik S, Bilgi O, Karagoz B. Mean platelet volume as a prognostic marker in metastatic colorectal cancer patients treated with bevacizumab-combined chemotherapy. Asian Pac J Cancer Prev 2014;15:6421-3.
36. Włodarczyk M, Kasprzyk J, Sobolewska-Włodarczyk A et al. Mean platelet volume as a possible biomarker of

tumor progression in rectal cancer. Cancer Biomark 2016;17:411-7.

37. Tsai PL, Su WJ, Leung WH, Lai CT, Liu CK. Neutrophil-lymphocyte ratio and CEA level as prognostic and predictive factors in colorectal cancer: a systematic review and meta-analysis. J Cancer Res Ther 2016;12:582-9.
38. Li MX, Liu XM, Zhang XF et al. Prognostic role of neutrophil-to-lymphocyte ratio in colorectal cancer: a systematic review and meta-analysis. Int J Cancer 2014;134:2403-13.
39. Dong YW, Shi YQ, He LW, Su PZ. Prognostic significance of neutrophil-to-lymphocyte ratio in rectal cancer: a meta-analysis. Onco Targets Ther 2016;9:3127-34.
40. Malietzis G, Giacometti M, Kennedy RH, Athanasiou T, Aziz O, Jenkins JT. The emerging role of neutrophil to lymphocyte ratio in determining colorectal cancer treatment outcomes: a systematic review and meta-analysis. Ann Surg Oncol 2014;21:3938-46.
41. Song W, Wang K, Zhang RJ, Zou SB. Prognostic value of the lymphocyte monocyte ratio in patients with colorectal cancer: a meta-analysis. Medicine (Baltimore) 2016;95:e5540.
42. Guo YH, Sun HF, Zhang YB et al. The clinical use of the platelet/lymphocyte ratio and lymphocyte/monocyte ratio as prognostic predictors in colorectal cancer: a meta-analysis. Oncotarget 2017;8:20011-24.
43. Chen N, Li W, Huang K et al. Increased platelet-lymphocyte ratio closely relates to inferior clinical features and worse long-term survival in both resected and metastatic colorectal cancer: an updated systematic review and meta-analysis of 24 studies. Oncotarget 2017;8:32356-69.
44. Tan D, Fu Y, Su Q, Wang H. Prognostic role of platelet-lymphocyte ratio in colorectal cancer: a systematic review and meta-analysis. Medicine (Baltimore) 2016;95:e3837.
45. Min GT, Wang YH, Yao N et al. The prognostic role of pretreatment platelet-to-lymphocyte ratio as predictors in patients with colorectal cancer: a meta-analysis. Biomark Med 2017;11:87-97.
46. Gu X, Gao XS, Qin S et al. Elevated platelet to lymphocyte ratio is associated with poor survival outcomes in patients with colorectal cancer. PLoS One 2016;11:e0163523.
47. Peng HX, Lin K, He BS et al. Platelet-to-lymphocyte ratio could be a promising prognostic biomarker for survival of colorectal cancer: a systematic review and meta-analysis. FEBS Open Bio 2016;6:742-750.
48. Shrotriya S, Walsh D, Bennani-Baiti N, Thomas S, Lorton C. C-reactive protein is an important biomarker for prognosis tumor recurrence and treatment response in adult solid tumors: a systematic review. PLoS One 2015;10:e0143080.
49. Zhou B, Shu B, Yang J, Liu J, Xi T, Xing Y. C-reactive protein, interleukin-6 and the risk of colorectal cancer: a meta-analysis. Cancer Causes Control 2014;25:1397-1405.
50. Pathak S, Nunes QM, Daniels IR, Smart NJ. Is C-reactive protein useful in prognostication for colorectal cancer? A systematic review. Colorectal Dis 2014;16:769-776.
51. Storey KB. Comparative enzymology-new insights from studies of an "old" enzyme, lactate dehydrogenase. Comp Biochem Physiol B Biochem Mol Biol 2016;199:13-20.
52. Augoff K, Hryniewicz-Jankowska A, Tabola R. Lactate dehydrogenase 5: an old friend and a new hope in the war on cancer. Cancer Lett 2015;358:1-7.
53. Huijgen HJ, Sanders GT, Koster RW, Vreeken J, Bossuyt PM. The clinical value of lactate dehydrogenase in serum: a quantitative review. Eur J Clin Chem Clin Biochem 1997;35:569-79.
54. Kostakis ID, Vaiopoulos AG, Philippou A, Papavassiliou AG, Koutsilieris M, Kouraklis G. Preoperative serum lactate dehydrogenase levels in colorectal and gastric cancer: a hospital-based case-control study. Biomark Med 2013;7:131-7.
55. Li G, Wang Z, Xu J, Wu H, Cai S, He Y. The prognostic value of lactate dehydrogenase levels in colorectal cancer: a meta-analysis. BMC Cancer 2016;16:249.
56. Dighe S, Purkayastha S, Swift I et al. Diagnostic precision of CT in local staging of colon cancers: a meta-analysis. Clin Radiol 2010;65:708-19.
57. Leufkens AM, van den Bosch MA, van Leeuwen MS, Siersema PD. Diagnostic accuracy of computed tomography for colon cancer staging: a systematic review. Scand J Gastroenterol 2011;46:887-94.
58. Nerad E, Lahaye MJ, Maas M et al. Diagnostic accuracy of CT for local staging of colon cancer: a systematic review and meta-analysis. AJR Am J Roentgenol 2016;207:984-95.
59. Al-Sukhni E, Milot L, Fruitman M et al. Diagnostic accuracy of MRI for assessment of T category, lymph node metastases, and circumferential resection margin involvement in patients with rectal cancer: a systematic review and meta-analysis. Ann Surg Oncol 2012;19:2212-23.
60. Li XT, Sun YS, Tang L, Cao K, Zhang XY. Evaluating local lymph node metastasis with magnetic resonance imaging, endoluminal ultrasound and computed tomography in rectal cancer: a meta-analysis. Colorectal Dis 2015;17:O129-O135.