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Evaluating the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) as prognostic and treatment response biomarkers in stage IV colorectal cancer patients

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ABSTRACT

Introduction. Stage IV colorectal cancer presents significant challenges in prognosis and treatment response. Reliable biomarkers are critical for predicting outcomes and guiding treatment choices. This study evaluated the efficacy of the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) as such biomarkers.

Material and methods. Conducted at a hematology department in Mashhad, Iran, this study involved 105 patients diagnosed with stage IV colorectal cancer. Participants underwent complete blood count analysis before chemotherapy to determine the NLR and PLR. Clinical information was collected, including tumor size, location, and *KRAS*/*NRAS*/*CEA* levels. Post-treatment categorization followed the RECIST guidelines.

Results. Median values for the NLR and PLR were 4.8 and 169.0, respectively. A higher NLR and PLR were significantly associated with progressive disease post-treatment. ROC analysis demonstrated the prognostic accuracy of the NLR (AUC 0.95) and PLR (AUC 0.90) at specific cutoffs. These markers also showed predictive accuracy for treatment response. Correlation analysis indicated a strong positive correlation between initial and post-treatment CEA levels and both the NLR and PLR.

Conclusions. The NLR and PLR are significant predictors of clinical outcomes in stage IV colorectal cancer, with potential utility in routine clinical practice for prognosis and treatment response prediction. Their high sensitivity and specificity suggest a role in guiding clinical decision-making. Further research is needed to refine their application in CRC management.

Keywords: colorectal neoplasms, biomarkers, prognosis, neutrophil, platelet

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Introduction

Colorectal cancer presents a major challenge in public health, evidenced by rising cases and deaths [1]. Patients with stage IV colorectal cancer often have a difficult prognosis because of the increased risk of local recurrence and the spread of the disease [2]. Consequently, there is a critical need for dependable biomarkers that can accurately predict outcomes and assist in making informed treatment choices [3].

The role of systemic inflammation in the advancement of cancer, especially colorectal cancer, has been recognized [4]. Markers based on inflammation, including the Glasgow prognostic score (GPS),

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neutrophil-to-lymphocyte ratio (NLR), and C-reactive protein (CRP), are associated with poorer colorectal cancer outcomes [5, 6]. Additionally, these indicators are useful in forecasting responses to chemotherapy and tracking tumor growth in patients with inoperable metastatic colorectal cancer [6]. These ratios are easily obtainable from routine blood tests, making them practical for clinical use. However, their predictive value in the context of stage IV colorectal cancer (CRC) and in relation to treatment response remains insufficiently explored.

The primary objective of this study was to evaluate the efficacy of the NLR and PLR as prognostic biomarkers for clinical outcomes in patients with stage IV colorectal cancer.

Material and methods

Study setting

This study was conducted between the years 2022 and 2023 at a hematology department of a tertiary medical center in Mashhad, Iran.

Study participants and data collection

This study involved patients diagnosed with stage IV colorectal cancer. Before initiating a chemotherapy regimen, these patients underwent complete blood count (CBC) analysis to determine the NLR and the PLR. We also gathered pertinent clinical information from their medical records, including the size and location of the tumor, levels of *KRAS*, NRAS, and carcinoembryonic antigen (CEA) markers, along with demographic details. Following the completion of treatment, the patients were classified into one of four categories — complete response, partial response, stable disease, or progressive disease — following the Response Evaluation Criteria in Solid Tumors (RECIST) [7] guidelines.

Inclusion and exclusion criteria

The inclusion criteria were patients diagnosed with stage IV colorectal cancer, aged over 18 years, with no prior chemotherapy for stage IV disease. The exclusion criteria included active urinary infection, leukocytosis, leukopenia, diabetes, chronic kidney disorder, nephrotic syndrome not caused by diabetes, steroid use for any reason, chronic cardiac, liver, and kidney diseases, and autoimmune diseases.

Statistics

The quantitative data were presented as medians (P25, P75). The associations between various quantitative variables with the NLR and PLR were assessed using the Spearman test (due to the non-normal distribution of the quantitative variables). The Kruskal-Wallis test was employed for comparing the medians of the NLR and PLR in qualitative variables with more than two categories. Receiver operating characteristic (ROC) analysis was used to determine cutoff points for both variables. A p-value of < 0.05 was considered statistically significant. Data analysis was performed using the 'gtsummary' package in R and SPSS version 26.

Ethical considerations

Patient information was anonymized and coded during collection, analysis, and reporting to ensure confidentiality. The study protocol was approved by the Ethics Committee of the Mashhad University of Medical Sciences (IR.MUMS.MEDICAL.REC.1402.362).

Results

Clinical characteristics

In this study, we evaluated 105 patients diagnosed with stage IV colorectal cancer at a median age of 60 years (51–67 years). The group demonstrated median values of the NLR 4.8 (3.10–7.5) and PLR 169.0 (131.00––199.0). The distribution of tumor locations in patients showed a higher prevalence in the sigmoid colon (30 patients, 29%), followed closely by the ascending colon (25 patients, 24%) and the rectum (24 patients, 23%). The least prevalent location was the transverse colon, accounting for 3 patients (2.9%) (Tab. 1).

KRAS mutations were present in nearly half of the patients, with 55 patients (52%) having wild-type *KRAS* and 50 patients (48%) showing *KRAS* mutations. For NRAS, a similar pattern was observed. The wild-type NRAS were found in 59 patients (56%), whereas 46 patients (44%) had NRAS mutations (Tab. 1).

The post-treatment outcomes varied in the cohort. The largest group included patients with progressive disease, accounting for 37 patients (35%). Partial response to treatment was observed in 26 patients (25%), while stable disease was noted in 21 patients (20%). Additionally, 21 patients (20%) achieved a complete response to the treatment (Tab. 1).

Comparative analysis of the NLR and PLR in relation to clinical variables and treatment response

When comparing the mean NLR and PLR across different tumor locations (sigmoid, ascending, rectum, descending, cecum, rectosigmoid, transvers), and the *KRAS* and *NRAS* mutation status, no statistically significant differences were observed ($p > 0.05$).

Table 1. Patient characteristics

Variable	N = 105[1]
Age [years]	60.0 (51.00–67.0)
Tumor location	
Sigmoid colon	30 (29%)
Ascending colon	25 (24%)
Rectum	24 (23%)
Descending colon	10 (9.5%)
Cecum	7 (6.7%)
Rectosigmoid junction	6 (5.7%)
Transverse colon	3 (2.9%)
Pre-treatment CEA Level [ng/mL]	44.0 (7.00–180.0)
Post-treatment CEA Level [ng/mL]	8.0 (2.10–71.0)
KRAS mutation status	
Wild type	55 (52%)
Mutant	50 (48%)
NRAS mutation status	
Wild type	59 (56%)
Mutant	46 (44%)
Clinical outcome	
Progressive	37 (35%)
Partial response	26 (25%)
Complete response	21 (20%)
Stable	21 (20%)
Outcome categorial	
Non-responsive	58 (55%)
Responsive	47 (45%)

[1]Median [interquartile range (IQR)] or frequency (%); CEA — carcinoembryonic antigen

However, a significant difference in the NLR and PLR was noted in relation to treatment outcomes. Patients with progressive disease exhibited a notably higher NLR [8.1 (7.20–9.0)] compared to those with partial response [4.1 (3.20–5.1)], stable disease [4.4 (3.00–6.1)], or complete response [3.1 (1.80–4.1)] ($p < 0.01$). Also, patients with progressive disease had the highest PLR [200.5 (185.00––324.0)], significantly different from those in other response categories including partial response [135.0 (121.00––150.8)], stable disease [159.0 (121.00–179.0)], or complete response [132.0 (121.00–150.0)] ($p < 0.01$) (Fig. 1).

In addition to the comparative analysis of the NLR and PLR, we also performed correlation analysis to understand the relationships between these biomarkers and various clinical variables, including initial and post-treatment CEA levels and patient age.

The correlation analysis indicated a strong positive correlation between initial CEA levels and the NLR ($r^2 = 0.71$, $p < 0.01$). Similar findings were observed between initial CEA levels and the PLR ($r^2 = 0.618$, $p < 0.01$). Post-treatment CEA levels also showed a strong positive correlation with the NLR ($r^2 = 0.72$, $p < 0.01$) and PLR ($r^2 = 0.63$, $p < 0.01$).

The correlation between patient age and the NLR was relatively weak and not statistically significant ($r^2 = 0.14$, $p = 0.13$). Similarly, the correlation between age and the PLR was weak and not statistically significant ($r^2 = 0.11$, $p = 0.23$).

ROC analysis

The NLR demonstrated significant predictive accuracy for prognosis with an area under curve (AUC)

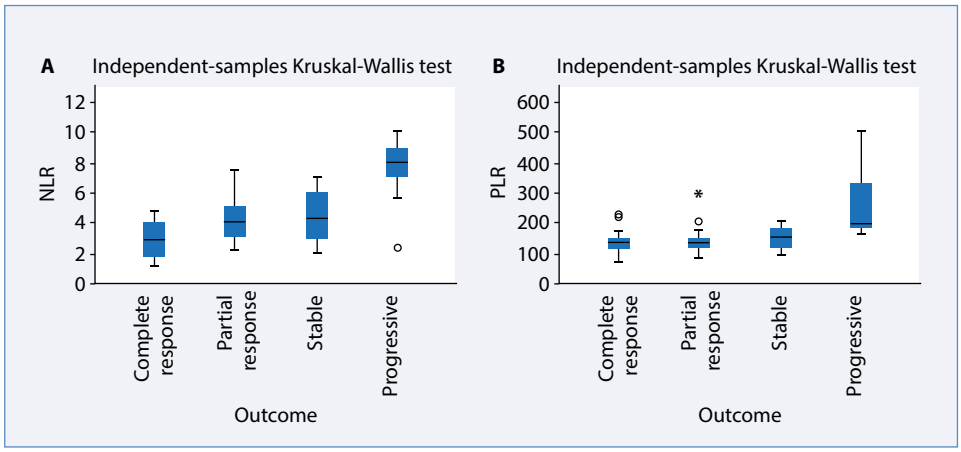

Figure 1. Distribution of the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) vs. treatment outcomes [Response Evaluation Criteria in Solid Tumors (RECIST)]; **A.** Comparison of the NLR across various RECIST criteria; **B.** Comparison of the PLR across various RECIST criteria

Table 2. Diagnostic accuracy of biomarkers in prognosis and treatment response

Biomarker	Outcome	Cutoff Value	AUC	Sensitivity [%]	Specificity [%]	p-value
NLR	Prognosis	6.05	0.95	94	86	< 0.01
PLR	Prognosis	164	0.90	100	75	< 0.01
CEA	Prognosis	90.5	0.85	85	70	< 0.01
NLR	Treatment Response	5.45	0.84	91	75	< 0.01
PLR	Treatment Response	155	0.80	80	84	< 0.01
CEA	Treatment Response	84.5	0.82	91	60	< 0.01

CEA — carcinoembryonic antigen; NLR — neutrophil-to-lymphocyte ratio; PLR — platelet-to-lymphocyte ratio

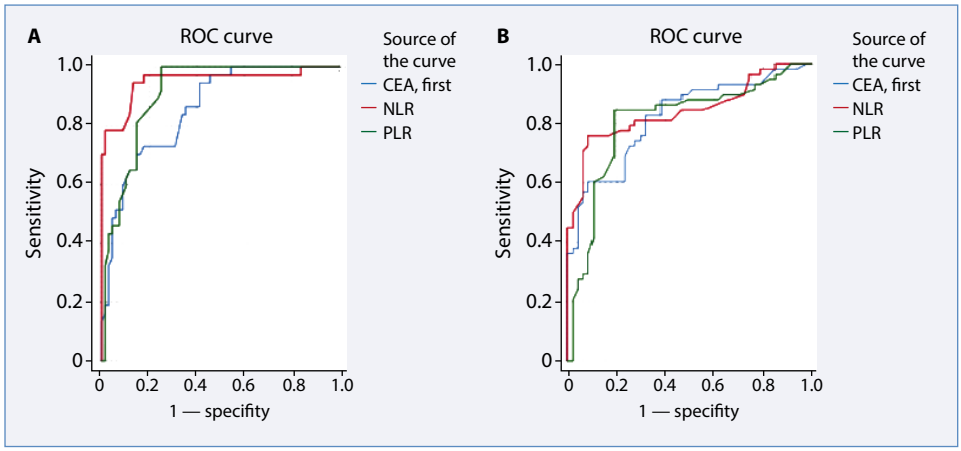

Figure 2. Diagnostic accuracy of neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and carcinoembryonic antigen (CEA) in predicting prognosis and treatment response in colorectal cancer; **A.** Focuses on the prognostic value of NLR, PLR, and CEA, displaying for prognosis; **B.** Focuses on the prognostic value of NLR, PLR, and CEA, displaying for treatment response; ROC — receiver operating characteristic

of 0.95 at a cutoff of 6.05. Platelet-to-lymphocyte ratio also showed high diagnostic utility with an AUC of 0.90 at a cutoff of 164. CEA, at a cutoff of 90.5, exhibited moderate prognostic predictive ability with an AUC of 0.85 (Tab. 2, Fig. 2).

In predicting treatment response, the NLR with a cutoff of 5.45 had an AUC of 0.84, indicating substantial accuracy. The PLR had an AUC of 0.80 at a cutoff of 155, demonstrating good predictive value. The initial level of CEA at a cutoff of 84.5 showed an AUC of 0.82 (Tab. 2, Fig. 2).

Discussion

Our study evaluated 105 patients with metastatic colon cancer, focusing on the prognostic and treatment response prediction capabilities of the NLR and PLR. The median age was 60.0 years, with a median NLR of 4.8 and a PLR of 169.0. Our findings show that both NLR and PLR are significant predictors of clinical outcomes in metastatic colon cancer. Notably, an NLR cutoff of 6.05 demonstrated high sensitivity (94%) and specificity (86%), while a PLR cutoff of 164 showed sensitivity of 100% and specificity of 75%.

Our findings corroborate those of Chan et al. [8] and Li et al. [9], who also recognized the NLR as a reliable predictor of overall survival (OS) and disease-free survival (DFS) in CRC patients. Jiang et al. [10] found that a higher NLR (> 3.0) was associated with worse OS in CRC patients, which aligns with our findings. Similarly, Kim et al. [11] suggested that higher NLR and PLR values are independent predictors of long-term outcomes in advanced CRC stages. These studies underscore the utility of the NLR and PLR as prognostic markers in CRC, even though variations in optimal cutoff values across the studies are noteworthy. Ying and Choi [12, 13] found NLR to be a better prognostic predictor than derived neutrophil-to-lymphocyte ratio (dNLR), PLR, and lymphocyte-to-monocyte ratio (LMR) in CRC although the reasons for the NLR's superiority over other inflammatory markers remain

unclear. This further supports the NLR's role in reflecting pre-operative inflammatory and immune status in CRC patients.

In comparison with similar studies, the prognostic value of the PLR in CRC has been extensively studied, yielding varied but informative results. Pedrazzani et al. conducted a study on 603 CRC patients, demonstrating that an elevated platelet count ($> 350 \times 10^9$/L) could be a reliable predictor of poor OS. Similarly, Ishizuka found that platelet counts $> 300 \times 10^9$/L were associated with a poor prognosis in CRC patients in all stages [14, 15].

These findings align with the broader understanding that a high PLR, indicative of increased platelet counts and decreased lymphocyte counts, correlates with poorer prognosis in CRC patients. This is further corroborated by studies suggesting a relationship between thrombocytosis (high PLR) and systemic inflammation due to cancer, with thrombosis potentially indicating systemic inflammatory activity and tumor presence [16].

Zou et al. [17] found an AUC for the PLR of 0.69 at a cutoff of 246.36, associating a high PLR with larger tumor diameter, higher tumor classification (T classification), and worse 5-year OS rates compared to patients with a lower PLR ($\leq$ 246.36). Acikgoz [16] explored the prognostic value of the PLR and its relationship with tumor location in 229 CRC patients, determining an AUC of 0.69 for a PLR cutoff of 196.5, with significant correlations between a high PLR and *BRAF* mutations, treatment response, tumor location, and tumor progression.

Jia et al.'s [18] univariate analysis showed that, unlike the NLR, the PLR was associated with OS and DFS in CRC patients, suggesting greater prognostic significance of high PLR values ($>$ 154.31) especially in patients receiving neoadjuvant chemotherapy (NAC).

Recent studies indicate that combining inflammatory parameters and tumor markers provides a high diagnostic value in invasive tumors. Peng et al., after a comparative analysis of ROC curves, showed that the diagnostic efficiency of combining the NLR and PLR (AUC = 0.83) was significantly higher than that of either the NLR or PLR alone, or CEA alone, and even higher than any combination of two of these three biomarkers [19, 20].

Our emphasis on metastatic colon cancer adds to the existing literature by specifically addressing the prognostic relevance of the NLR and PLR in this subgroup. The consistent findings across studies highlight the potential of these markers in guiding clinical decision-making and stratifying patient risk.

The high sensitivity and specificity of NLR and PLR in our study suggest their potential role in routine clinical practice for prognosis and treatment response prediction in metastatic colon cancer. The association of higher NLR and PLR values with worse prognoses could reflect underlying systemic inflammatory responses.

Interestingly, our study, along with others, indicates that the predictive power of these markers may vary depending on cancer stage and patient demographics, suggesting a tailored approach to their application. This aspect underscores the necessity for clinicians to consider stage-specific cutoffs and patient characteristics when interpreting NLR and PLR values.

While our study contributes valuable insights, it is essential to acknowledge its limitations. The relatively small sample size may limit the generalizability of the findings. Additionally, as with all observational studies, the potential for confounding factors cannot be entirely ruled out.

Conclusions

In conclusion, our study underscores the prognostic significance of the NLR and PLR in patients with metastatic colon cancer. These easily obtainable markers could serve as valuable tools in predicting patient outcomes and tailoring treatment strategies. However, further research is warranted to refine their application and understand their role within the broader context of CRC management.

Article Information and Declarations

Data availability statement

Data will be available upon reasonable request from the corresponding author.

Ethics statement

This study was conducted in full accordance with ethical principles, including the World Medical Association Declaration of Helsinki (version 2008). The research protocol was reviewed and approved by the Ethics Committee of Mashhad University of Medical Sciences under the ethical approval code: IR.MUMS.MEDICAL.REC.1402.362.

Author contributions

A.A.: conceptualization, methodology, writing — review and editing, supervision; F.F.: data curation, investigation, writing — original draft; P.B.T.: investigation, data curation, visualization, writing — original draft; S.P.T: data curation, writing — review and editing; M.M.V: software, validation, formal analysis, writing — review and editing; M.M.N: resources, project administration, funding acquisition, writing — review and editing; M.K.: data curation, formal analysis, writing — original draft, writing — review and editing; A.N.: methodology, validation, writing — review and editing, supervision, conceptualization, final approval of the version to be published.

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Conflict of interest

The authors have no conflicts of interest to disclose.

Supplementary material

None.

References

1. Sawicki T, Ruszkowska M, Danielewicz A, et al. A Review of Colorectal Cancer in Terms of Epidemiology, Risk Factors, Development, Symptoms and Diagnosis. Cancers (Basel). 2021; 13(9), doi: 10.3390/cancers13092025, indexed in Pubmed: 33922197.
2. Feria A, Times M. Effectiveness of Standard Treatment for Stage 4 Colorectal Cancer: Traditional Management with Surgery, Radiation, and Chemotherapy. Clin Colon Rectal Surg. 2024; 37(2): 62–65, doi: 10.1055/s-0043-1761420, indexed in Pubmed: 38322607.
3. Koncina E, Haan S, Rauh S, et al. Prognostic and Predictive Molecular Biomarkers for Colorectal Cancer: Updates and Challenges. Cancers (Basel). 2020; 12(2), doi: 10.3390/cancers12020319, indexed in Pubmed: 32019056.
4. Lam M, Tie J, Lee B, et al. Systemic inflammation–impact on tumor biology and outcomes in colorectal cancer. J Clin Cell Immunol. 2015; 6(377): 2.
5. Rossi S, Basso M, Strippoli A, et al. Are Markers of Systemic Inflammation Good Prognostic Indicators in Colorectal Cancer? Clin Colorectal Cancer. 2017; 16(4): 264–274, doi: 10.1016/j.clcc.2017.03.015, indexed in Pubmed: 28412137.
6. Shibutani M, Maeda K, Nagahara H, et al. Significance of Markers of Systemic Inflammation for Predicting Survival and Chemotherapeutic Outcomes and Monitoring Tumor Progression in Patients with Unresectable Metastatic Colorectal Cancer. Anticancer Res. 2015; 35(9): 5037–5046, indexed in Pubmed: 26254405.
7. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009; 45(2): 228–247, doi: 10.1016/j.ejca.2008.10.026, indexed in Pubmed: 19097774.
8. Chan JCY, Diakos CI, Chan DLH, et al. A Longitudinal Investigation of Inflammatory Markers in Colorectal Cancer Patients Perioperatively Demonstrates Benefit in Serial Remeasurement. Ann Surg. 2018; 267(6): 1119–1125, doi: 10.1097/SLA.0000000000002251, indexed in Pubmed: 28394869.
9. Li Y, Jia H, Yu W, et al. Nomograms for predicting prognostic value of inflammatory biomarkers in colorectal cancer patients after radical resection. Int J Cancer. 2016; 139(1): 220–231, doi: 10.1002/ijc.30071, indexed in Pubmed: 26933932.
10. Jiang H, Li H, Li A, et al. Preoperative combined hemoglobin, albumin, lymphocyte and platelet levels predict survival in patients with locally advanced colorectal cancer. Oncotarget. 2016; 7(44): 72076–72083, doi: 10.18632/oncotarget.12271, indexed in Pubmed: 27765916.
11. Kim JH, Lee JY, Kim HK, et al. Prognostic significance of the neutrophil--to-lymphocyte ratio and platelet-to-lymphocyte ratio in patients with stage III and IV colorectal cancer. World J Gastroenterol. 2017; 23(3): 505–515, doi: 10.3748/wjg.v23.i3.505, indexed in Pubmed: 28210087.
12. Choi WJ, Cleghorn MC, Jiang H, et al. Preoperative Neutrophil-to-Lymphocyte Ratio is a Better Prognostic Serum Biomarker than Platelet-to--Lymphocyte Ratio in Patients Undergoing Resection for Nonmetastatic Colorectal Cancer. Ann Surg Oncol. 2015; 22 Suppl 3: S603–S613, doi: 10.1245/s10434-015-4571-7, indexed in Pubmed: 25900206.
13. Ying HQ, Deng QW, He BS, et al. The prognostic value of preoperative NLR, d-NLR, PLR and LMR for predicting clinical outcome in surgical colorectal cancer patients. Med Oncol. 2014; 31(12): 305, doi: 10.1007/s12032-014-0305-0, indexed in Pubmed: 25355641.
14. Pedrazzani C, Mantovani G, Fernandes E, et al. Assessment of neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio and platelet count as predictors of long-term outcome after R0 resection for colorectal cancer. Sci Rep. 2017; 7(1): 1494, doi: 10.1038/s41598-017-01652-0, indexed in Pubmed: 28473700.
15. Ishizuka M, Nagata H, Takagi K, et al. Preoperative thrombocytosis is associated with survival after surgery for colorectal cancer. J Surg Oncol. 2012; 106(7): 887–891, doi: 10.1002/jso.23163, indexed in Pubmed: 22623286.
16. Acikgoz O, Cakan B, Demir T, et al. Platelet to lymphocyte ratio is associated with tumor localization and outcomes in metastatic colorectal cancer. Medicine (Baltimore). 2021; 100(44): e27712, doi: 10.1097/MD.0000000000027712, indexed in Pubmed: 34871263.
17. Zou ZY, Liu HL, Ning N, et al. Clinical significance of pre-operative neutrophil lymphocyte ratio and platelet lymphocyte ratio as prognostic factors for patients with colorectal cancer. Oncol Lett. 2016; 11(3): 2241–2248, doi: 10.3892/ol.2016.4216, indexed in Pubmed: 26998156.
18. Jia W, Yuan L, Ni H, et al. Prognostic Value of Platelet-to-Lymphocyte Ratio, Neutrophil-to-Lymphocyte Ratio, and Lymphocyte-to-White Blood Cell Ratio in Colorectal Cancer Patients Who Received Neoadjuvant Chemotherapy. Technol Cancer Res Treat. 2021; 20: 15330338211034291, doi: 10.1177/15330338211034291, indexed in Pubmed: 34308689.
19. Peng HX, Yang L, He BS, et al. Combination of preoperative NLR, PLR and CEA could increase the diagnostic efficacy for I-III stage CRC. J Clin Lab Anal. 2017; 31(5), doi: 10.1002/jcla.22075, indexed in Pubmed: 27686880.
20. Liu XF, Zhou LY, Wei ZH, et al. The diagnostic role of circulating inflammation-based biomarker in gallbladder carcinoma. Biomark Med. 2018; 12(10): 1095–1103, doi: 10.2217/bmm-2018-0049, indexed in Pubmed: 30191731.