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Predictive model using hemoglobin, albumin, fibrinogen, and neutrophil-to-lymphocyte ratio to distinguish patients with colorectal cancer from those with benign adenoma

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Colorectal cancer (CRC) is associated with inflammation, activation of coagulation, and mild anemia. Hematological parameters reflecting ongoing cancer may have the potency to be effective for early diagnostics of CRC. The aim of this study was to examine the validity and relationship between some biochemical and hematological parameters for the early diagnosis of CRC. We designed a prospective observational cohort study to analyze whether these laboratory markers have the potency to distinguish benign tumors from malignant before planned surgery. The clinical data were collected from 208 patients with suspected benign or malignant colorectal tumors who were eligible for elective surgery between September 2018 and January 2020. Blood samples were collected one day before surgery, examined parameters included: complete blood count, hemoglobin (HGB) concentration, albumin (ALB), C-reactive protein (CRP), interleukin-6 (IL-6), and fibrinogen (FG). Absolute neutrophil and lymphocyte counts were used for the calculation of the neutrophil-to-lymphocyte ratio (NLR). The diagnosis was confirmed by histopathological examination. The 197 patients were divided into the group of benign (B group = 52 patients) or malignant tumors (CRC group = 145 patients). ROC curves and cut-off values of NLR, HGB, FG, and ALB concentration, serum CRP and IL-6 levels. In the cohort of 197 adult patients submitted for the elective colorectal surgery, the complete blood samples drawn one day before surgery showed significant differences between patients with benign tumors and colorectal carcinoma: HGB (mean 139.9 g/l vs. 129.9; p<0.001), FG (mean 3.36 g/l vs. 3.94 g/l; p<0.001), ALB (mean 43.4 g/l vs. 41.1 g/l; p=0.001), NLR (mean 2.73 vs. 3.88; p=0.016), respectively. CRP (mean 2.9 mg/l vs. 4.4 mg/l; p=0.011), thrombocyte count (mean 235×10^9/l vs. 265×10^9/l; p<0.029). Differences in IL-6 concentrations were not significant (2.9 pg/ml vs. 4.15 pg/ml; p=0.052). Using multivariable logistic regression analysis, four valid parameters (HGB, FG, ALB, and NLR) were suitable for the construction of a diagnostic predictive model for the identification of CRC. In conclusion, a panel of routinely examined blood parameters like HGB, FG, ALB, and NLR has the potency to distinguish patients with benign tumors from malignant by applying a diagnostic predictive model for early laboratory detection of CRC.

Key words: neutrophil-to-lymphocyte ratio, hemoglobin, albumin, fibrinogen, colorectal cancer, predictive model

Colorectal cancer (CRC) is one of the most common gastrointestinal malignancies and represents the fourth most common cause of cancer-related death globally. CRC represents a heterogenous spectrum of oncological diseases, and predictive models such as the Duke classification or the Tumor Nodal Metastasis (TNM) system are not always sufficient for guiding anticancer therapy. Although TNM or Duke classification is cornerstones of cancer prognosis, there is an increasing recognition that patient-related factors, in particular, decline of functional, nutritional, and immune status is associated with impaired outcome independent of tumor stage. There is growing and consistent evidence that the systemic inflammatory response syndrome due to cancer disease is a key factor for patient deterioration [1–5]. The mediators and cellular effectors of inflammation are important constituents of the local tumor environment. Regardless of its origin, inflammation in the tumor microenvironment has many tumor-promoting effects. Inflammation promotes

proliferation, angiogenesis, tumor invasion metastasis, subverts adaptive immune response, and alters the response to hormones [6]. This cancer-related inflammation seems to be crucial for better understanding the pathophysiology of cancer and the possibilities of management and therapy of solid malignancies [4]. Cancer-associated inflammation was adopted as a seventh of the 12 hallmarks of cancer [5, 7]. Hannahan and Weinberg [5] clearly defined that cancer as very heterogeneous disease, manifested with a cluster of typical clinical symptoms and laboratory findings. Development of cancer is associated with marked anemia [8, 9], thrombocytosis [10], and high level of plasma fibrinogen – FG [11, 12], dysbalance between innate and adaptive immune cellular response manifesting as an increase of neutrophil-to-lymphocyte ratio (NLR) [13], increased synthesis and concentration of positive acute-phase proteins (C-reactive protein (CRP), fibrinogen), and a decrease of a negative one-albumin [3, 14–16]. Thus, complete blood count investigation, acute-phase proteins, and coagulation parameters concentration may bring valuable information about the presence and course of cancer disease. We asked a simple question whether these parameters may have the potency to differentiate patients with benign adenoma and colorectal adenocarcinoma.

Most colorectal carcinomas develop from a preclinical state of adenoma, which takes years to progress to advanced cancer-adenocarcinoma [17, 18]. Many challenges remain in current practices of CRC screening and stratification, such as expensive cost, difficult logistics, low compliance, and specificity. There were epidemiological studies using regular health check-up data for valid screening for CRC using complete blood count [19]. Blood has a specific properties and functions in the human body [20]. Blood comes into direct contact with cancer cells, and/or the microenvironment of malignant tumors. The blood as a part of the immune system reacts and responds to cancer and may warn the host organism. Blood cells: erythrocytes, leukocytes, thrombocytes (PLT) [21], markers of inflammation: erythrocyte sedimentation rate (ESR) and humoral factors: interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), tumor markers, and acute-phase proteins: albumin (ALB), FG, CRP are activated during oncogenesis and significant changes of their levels and function are observed [10, 22–24]. We designed a prospective observational single-center study to follow up the basic hematological parameters, complete blood count with differential including NLR [13, 15, 25] together with a marker of inflammation IL-6 [16] and acute-phase proteins (ALB, CRP, and FG) with histopathological findings in adult oncological patients submitted for elective colorectal surgery. The goal of our study was to explore the statistical differences of hematological parameters, NLR, and acute-phase proteins on the day of admission (up to two days before surgery) between patients with benign adenoma and adenocarcinoma (CRC) confirmed by definite histopathological findings.

Patients and methods

Patients and study design. After approval by the Hospital ethics committee (2018), we examined 228 patients who were diagnosed with CRC or benign colorectal adenoma and admitted for CRC surgery from September 2018 to January 2020. Patients agreed with the participation in the pivotal observational single-center study. After hospital admission a day before CRC surgery, we withdrew blood for a complete blood count and differential investigation of the following seven parameters: platelet count (PLT), hemoglobin (HGB), and plasma FG concentration, ALB, CRP, IL-6, absolute neutrophil and lymphocyte count to calculate NLR. All parameters were examined using standard laboratory protocols. Complete blood count was measured on an automated hematology analyzer UniCel DxH 800 (Beckman-Coulter, USA). Plasma FBG levels were determined using the Clauss method and the ACL TOP 550 system (Instrumentation Laboratory, USA). ALB and CRP were determined using an automated chemistry analyzer and an IL-6 on immunoassay analyzer (Beckman-Coulter, USA).

Exclusion criteria included: infection 2 weeks before admission to the hospital, known additional malignancies, neoadjuvant chemotherapy, and blood transfusion 6 weeks before surgery. A total of 20 patients were excluded from the study. The remaining 208 were analyzed; age, sex, tumor localization, surgical procedure, preoperative blood parameters, and postoperative histopathology were assessed prior to the enrollment (Table 1). Next 11 patients were excluded due to the missing data or unclear histopathology (cancer *in situ* and or high-grade adenoma) and 197 patients were submitted for final analysis. We were interested in which of the following blood parameters had the statistical power to discriminate patients with benign adenoma from patients with CRC (mostly adenocarcinoma) and use this information to develop a predictive model for the risk of CRC.

Statistical analysis. Demographic and clinical data were obtained from our institutional electronic health record system and summarized using descriptive statistics. Continuous variables are presented as the means with the respective standard deviations (SD) for the normally distributed variables or as median and interquartile ranges for data showing departures from normality. The assumption of normality was assessed using histograms and the Shapiro-Wilk test. Categorical variables are presented as counts and relative frequencies.

A two-sample t-test or alternatively the Mann-Whitney test was used to test for differences between groups. Simple bivariate correlations (Pearson's parametric or Kendall's/Spearman's nonparametric) for all pair-wise combinations of the variables were computed to indicate the existence and degree of mutual relationships.

The ROC analysis was conducted to evaluate the discriminative power of each variable associated with CRC in the bivariate analysis. Finally, a multivariable binary logistic

regression model was established to identify the independent risk factors for CRC.

Statistical analyses were performed using StatsDirect 3.0.191 software (Stats Direct Ltd., Cheshire, UK) and Statistica 13.1 software (TIBCO Software Inc., US). All reported p-values were two-sided, and significance was set at $p<0.05$.

Results

A total of 208 patients were enrolled, eleven were excluded due to the uncertainty of histopathological findings. After the exclusion of eleven patients in this prospective pilot study with retrospective analysis, we analyzed the records of 197 adult patients. The mean age was 66.6±10.2 years. There were 88 (45.3%) males and 109 (55.3%) females. Family history of CRC was positive in 15 patients (7.4%). After obtaining histopathological results, we enrolled the patients into the group of benign tumors (B group of 52 patients) or into the group of CRC (145 patients). The basic demographic and clinical data are summarized in Table 1.

We examined seven hematological or biochemical parameters (HGB, PLT, FG, NLR, ALB, CRP, and IL-6) from peripheral venous blood sample collected one day before the elective surgery. We tested distribution, mean (+/– standard deviation), and median values in the whole cohort of 197 patients (Table 2) and in each B and CRC group (Table 3).

Table 1. Demographical, hematological, and laboratory parameters characteristics of 197 patients grouped by outcome.

Characteristics	Total	Malign	Benign	Probability
Count	197 (100%)	145 (100%)	52 (100%)	n.a.
Sex				
male	88 (44.7%)	62 (42.8%)	26 (50.0%)	0.337
female	109 (55.3%)	83 (57.2%)	26 (50.0%)	
Age (years)	66.6±10.20	66.8±10.59	66.0±9.10	0.608
Tumor stage				
T1	n.a.	28	n.a.	
T2	n.a.	31	n.a.	
T3	n.a.	61	n.a.	
T4	n.a.	25	n.a.	
Hemoglobin	129.9±20.41	126.3±20.91	139.9±15.13	<0.001
Platelets	256.6±83.15	264.3±84.20	235.12±76.90	0.029
NLR median (Q1–Q3)	2.9 (2.12–4.11)	3.18 (2.13–4.38)	2.60 (1.83–3.45)	0.016
Albumin	41.9±4.08	41.1±3.96	44.0±3.94	<0.001
CRP median (Q1–Q3)	3.5 (1.7–8.4)	4.4 (2.0–10.2)	2.9 (1.6–5.7)	0.011
IL-6	4.0 (2.6–7.2)	4.15 (2.0–10.2)	2.9 (1.6–5.7)	0.052
Fibrinogen	3.79±1.18	3.94±1.20	3.36±1.02	<0.001

Abbreviations: NLR-neutrophil-to-lymphocyte ratio; CRP-C reactive protein; Q1-lower quartile; Q3-upper quartile; n.a.-not applicable

Table 2. Selected parameters for early laboratory pre-diagnosis and risk of colorectal cancer. Related hematological ratios for reliable prediction of the risk of colorectal cancer.

Parameter(s) related to the presence of cancer and/ or cancer-associated inflammation	Response to the presence and advanced course of CRC, and *suggested* cut–off value(s)	Reference range-normal physiological values
Hemoglobin mild to moderate anemia	<129 g/l	131–160 g/l
Platelet's count	≥285×10^9/l	151–280×10^9/l
PLR	<80, or ≥200 and ≥300	100–200
ALB	<41.9 g/l	43.0–49.0 g/l
PNI	<45–47	≥48–50
CRP	≥4.5 mg/l	0.1–3.0 mg/l
CLR (CRP/lymphocyte count ratio)	≥4.0	1–4
Fibrinogen	≥3.79 g/l	1.9–3.5 g/l
NLR (neutrophil-to-lymphocyte ratio)	≥3.0 (2.45–3.45), or <0.7	1.0–2.3 (NLR)
Lymphocyte count	<1.8×10^9/l	1.9–3.2×10^9/l
Interleukin-6	≥7.5–8.0 pg/ml	1.0–7.0 pg/ml

Note: hematological and biochemical parameters suggested for early detection and stratification of colorectal cancer with potential to differentiate it from benign affliction. Abbreviations: CRP-C-reactive protein; CLR-CRP to lymphocyte count ratio; NLR-neutrophil-to-lymphocyte ratio; PLR-platelet-to-lymphocyte ratio; PNI-prognostic nutrition index (PNI = albumin + 5× absolute lymphocyte count)

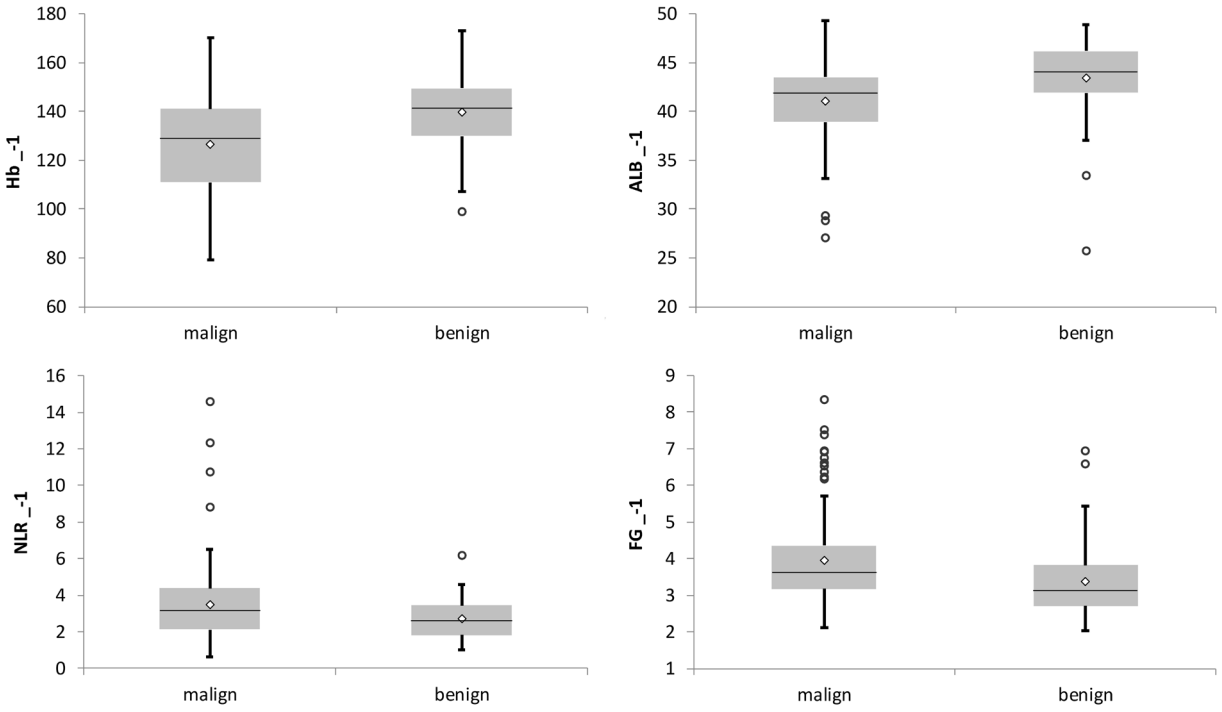

Figure 1. Box-plot graphs of the selected laboratory parameters between the malign (CRC) and benign groups. Data are presented as the median (horizontal line) and mean (diamond sign), the lower-upper quartile range, minimal, and maximal values. Data points that fell outside of the presumed normal distribution (i.e., 1.5 times of the interquartile range above the 3rd quartile and below the 1st quartile) are depicted as red circles. A non-parametric Mann-Whitney test was used to test the between-group differences in the parameters: HGB-hemoglobin (p<0.001), ALB-albumin (p<0.001), NLR-neutrophil-to-lymphocyte ratio (p=0.016), and FG-plasma fibrinogen levels (p<0.001).

Table 3. Cumulative data of the selected seven hematological parameters measured before planned colorectal surgery in the cohort of 197 adult patients using descriptive statistics.

Variable	Valid N	Mean	SD	Median	IQR (25–75%)	Min	Max
HGB g/l]	197	129.9	20.4	131	117–144	79	173
PLT [1 × 10^9/l]	197	256	83.1	248	200–305	54	541
NLR	197	2.90	1.8	2.95	2.13–4.11	0.62	14.56
ALB [g/l]	197	41.77	4.1	42.3	39.7–44.4	25.7	48.9
CRP [mg/l]	197	3.59	2.87	3.57	1.6–8.4	0.30	162
IL-6 [ng/l]	196	4.08	13.6	3.95	2.48–7.2	0.01	390
FG [g/l]	195	3.79	1.18	3.56	2.97–4.19	2.03	8.91

Abbreviations: N-valid number; mean-SD and median; IQR-25–75%, minimal and maximal values; HGB-hemoglobin; NLR-neutrophil-to-lymphocyte ratio; PLT-platelets; Min-minimum; Max-maximum

Table 4. Aggregative data of the selected parameters in the group of patients with benign tumors (B group) and in the group of patients with colorectal carcinoma (CRC group).

Variable parameter	Valid number B vs. CRC	Mean value B vs. CRC	Median B P-v CRC	IQR 25–75% B-benign	IQR 25–75% CRC-cancer
HGB [g/l]	52 vs. 145	139.4 vs. 126.3	141–***129	130–149	111–141.5
PLT [1×10^9/l]	52 vs. 145	235 vs. 264	232–*265	183–275	205–317
NLR	52 vs. 145	2.75 vs. 3.48	2.60–**3.18	1.84–3.47	2.13–4.38
ALB [g/l]	52 vs. 145	43.4 vs. 41.1	44.0–***41.9	41.9–46.2	38.9–43.6
CRP [mg/l]	52 vs. 145	2.9 vs. 4.4	2.85–**4.4	1.4–5.7	1.95–10.2
IL-6 [pg/ml]	51 vs. 145	4.7 vs. 9.6	2.9–ns.4.15	2.11–5.86	2.66–8.18
FG [g/l]	50 vs. 145	3.32 vs. 3.98	3.12–***3.61	2.7–3.71	3.18–4.36

Notes: statistical significance p-values *p=0.029, **p=0.016, ***p=0.001. ns-non-significant Six paremeters were significant: HGB (p<0.001), ALB (p<0.006), and FG (***p<0.001), PLT*, CRP** and NLR (**p=0.016). Four parameters were selected according statistical power for diagnostic model building in the logistic regression: HGB, ALB, FG, and NLR

We did not find statistical differences when comparing concentrations of IL-6 between B group 2.9 pg/ml (benign tumors) and CRC group 4.15 pg/ml (p=0.052). We observed significant differences between groups (benign adenoma versus colorectal carcinoma) in the following parameters (Table 4): CRP (mean values 2.9 mg/l vs. 4.4 mg/l, p=0.011), PLT (235×10^9/l vs. 264×10^9/l, p=0.029), and NLR (mean 2.73 vs. 3.18, p=0.016). Interestingly the most significant differences between B group and CRC group were observed in HGB concentration (mean 139.9 vs. 126.3 g/l, p=0.001), ALB (mean value 43.4 g/l vs. 41.1 g/l, p=0.001), and FG (mean value 3.36 vs. 3.94 g/l, p=0.001).

We tested the potential of these routinely used parameters to differentiate between benign tumors and CRC by means of multivariable logistic regression analysis. Four parameters have significant statistical power for a predictive model: HGB, ALB, FG, and NLR (Figure 1, Table 5). The performance of the selected diagnostic four-parameters model for CRC: logit = ln(p/(1–p)) = 6.543–0.030 × Hb+0.267 × NLR–0.088 × ALB+0.371 × FG, was calculated using multivariable logistic regression analysis, by means of the receiver operating curve (ROC) method and area under the curve (AUC 74.4%), at the different p=(0.5; 0.6) (Figure 2, Table 5).

Discussion

We tested a hypothesis of whether routinely available hematological and biochemical parameters may have the potential to be effective for early detection, diagnosis, and/or stratification of CRC. We designed a prospective observational single-center study to follow up seven routinely investigated blood parameters for the evaluation of subclinical inflammation (NLR, CRP, ALB, IL-6), activation of coagulation (FG), thrombocytosis (PLT), and anemia (HGB) (Figure3). Blood is a unique fluid, which carries information about ongoing pathological processes like infection, inflammation, stress, and cancer [20, 26–28]. We tried to find the answers to two questions: 1) which of the commonly used hematological parameters are the most effective and reliable for the detection of ongoing cancer disease (CRC), 2) which of these parameters are valid to create an equation for a predictive model for the detection of CRC.

Regarding many studies which provide huge amounts of evidence that inflammation has contributed significantly to the carcinogenesis and progression of the cancer [1, 2, 5], we have chosen several trials dealing with different hematological parameters with significant impact on the clinical outcome and prognosis. Walsh et al. [29] first showed that pre-operative NLR >5 correlated with overall and cancer-specific survival in univariate analyses. Pre-operative NLR may represent a simple method of identifying CRC patients with poor

Table 5. Multivariable logistic model suggested for early detection of patients with CRC.

Variable	Coefficient	OR	95% CI Lower	95% CI Upper	p-value
Intercept	6.543	n. a.	1.244	n. a.	n. a.
Hb	–0.030	0.971	0.948	0.994	0.0135
NLR	0.267	1.306	1.002	1.703	0.0482
ALB	–0.088	0.916	0.807	1.040	0.1753
FG	0.371	1.449	0.972	2.161	0.0686

Notes: Logit model: Deviance (likelihood ratio) χ^2=32.24; p<0.001; deviance goodness of fit χ^2; p=0.368. Predictors: Hb-hemoglobin; NLR-neutrophil-to-lymphocyte ratio; ALB-albumin; and FG-plasma fibrinogen levels. Age and sex did not significantly improve classification performance of the model. Diagnostic performance at probability cut-off at 0.5: correctly classified = 75% of the patients; sensitivity = 93.0%; specificity = 25.0%, +ve-predictive value = 77.3%, -ve-predictive value = 56.5%, and AUC = 74.6%. Equation of the four-parameter model for calculation the odds of CRC in adult patients: logit (CRC) = 6.543–0.030 × Hb + 0.267 × NLR – 0.088 × ALB + 0.371 × FG. The logit function is the natural logarithm of the odds that a patient would be classified as having CRC. The odds can be easily converted to the probability of CRC. Abbreviations: p-probability value (the achieved significance level); OR-odds ratio; CI-confidence interval; AUC-area under ROC curve

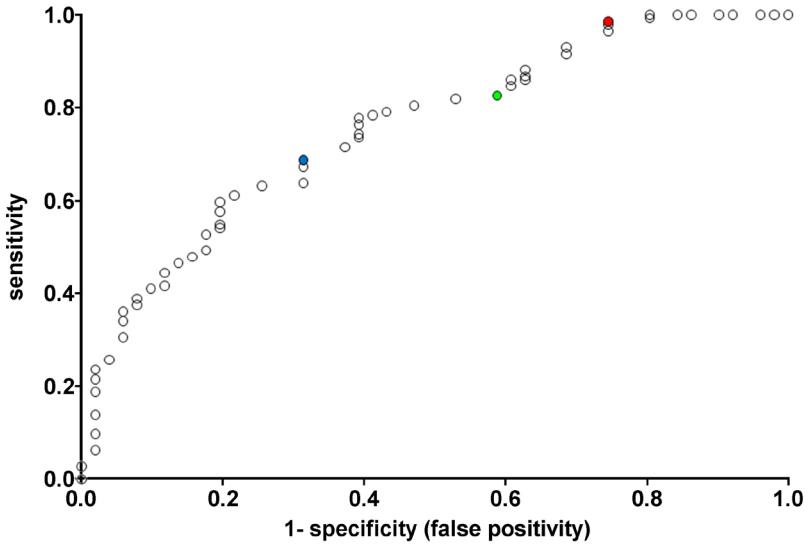

Figure 2. Receiver operating characteristic curve for the predictive power of the classifier based on the logistic regression. The performance of the multivariable diagnostic model in distinguishing patients with colorectal cancer from those with benign adenoma. The area under the curve (AUC=0.746; 74.6%) was calculated to evaluate the overall performance of the classifier based on receiver operating characteristic (ROC) curve analysis. Diagnostic performance at the cut-offs points for selected probability (p) of the event) is depicted in the ROC curve: p=0.5 as the red circle, p=0.6 as the green circle, and p=0.7 as the blue circle. Using logit (CRC)=6.543–0.030×Hb+0.267×NLR–0.088×ALB+0.371×FG.

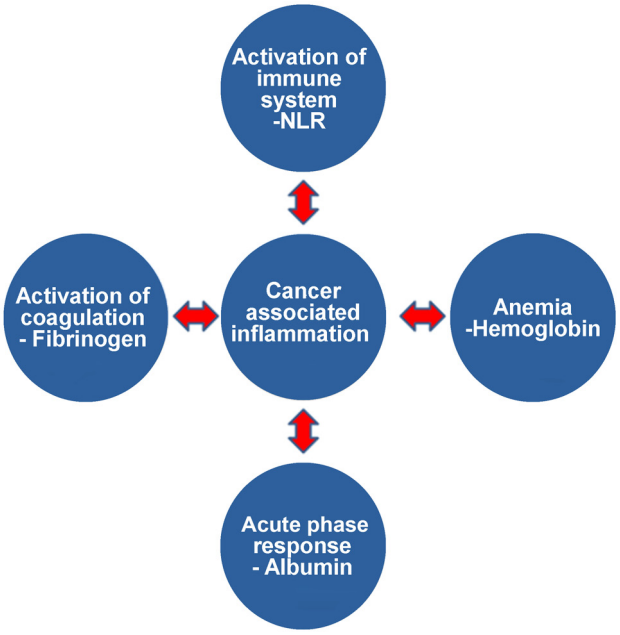

Figure 3. Hematologic parameters valid for early detection, monitoring, and stratification of colorectal cancer associated with cancer-associated inflammation. Cancer-associated systemic inflammation is related to activation of the immune system (NLR), anemia (HBG), acute phase response (ALB, CRP), and activation of coagulation (FB, platelets count).

prognosis even before surgery [29]. Since then, a number of trials confirmed the role and importance of NLR for early detection and risk evaluation with variable cut-off values of NLR = 2.5–5.0 [15, 30–33]. The noteable trials showed that systemic inflammation has a strong impact on the survival of CRC after surgery. High NLR is an independent predictor of poor outcome in advanced CRC, based on high neutrophils count (≥6×10^9/l) and low serum ALB <39 g/l [34].

Pinato et al. (2014) observed that hematological ratios like NLR and platelets-to-lymphocyte ratio (PLR) are associated with anemia (HGB <120 g/l) and hypoalbuminemia (<35 g/l). They suggested inflammation-based scores for monitoring and stratification of advanced malignant solid tumors including NLR, PLR, HGB, and ALB concentration [35]. Seong [36] showed that many parameters of inflammation may be used to evaluate ongoing inflammation during the course of CRC cancer disease including NLR, ESR, CRP, and total leukocyte count. After univariate analyses of clinical and laboratory results of 265 patients suffering from CRC, together with clinical severity and outcome, they suggested a prognostic inflammation score (PIS) based on the two most valid parameters: NLR and CRP [36]. An interesting finding was that even small or mild elevations of hematological (NLR ≥2.4, ESR ≥15 mm/h, leukocyte counts ≥7.5×10^9/l), and inflammation parameters (CRP ≥5 mg/l) have an impact on the clinical course, morbidity, and mortality of CRC measured as disease-free survival (DFS) or cancer-specific death. PIS is constructed with a combination of CRP and NLR, it is a potentially significant prognostic variable associated with poor survival in patients with CRC after curative resection [36].

We came to similar results: simple parameters obtained from complete blood count, may be useful to give a warning for the risk of CRC: mild decrease of albumin and hemoglobin (ALB<41 g/l, HGB<129 g/l) or mild increase of NLR≥2.45, FG≥3.7 g/l, CRP≥5 mg/l, and thrombocytosis PLT≥285-300×10^9/l (see Tab. 2). The role of the immune system in cancer pathogenesis has been given an increasingly prominent role [37]. In the cohort of 358 patients who underwent curative resection for CRC, authors studied the impact of high NLR (≥5) on the clinical outcome. 88 patients had an NLR >5, which predicted lower overall survival (OS) and greater cancer disease recurrence. A high NLR was associated with advanced CRC, higher pT- and pN-stage, and greater extramural venous invasion. A pronounced lymphocytic reaction at the invasive margin of resectable tumors indicated a better prognosis and was associated with the lower NLR. They concluded that NLR predicts disease-free and OS and is associated with a more aggressive tumor phenotype. NLR as a simple parameter has a strong position for the evaluation of cancer disease, especially the stage of cancer-associated inflammation [37]. The best studies were done on gastrointestinal cancers. Bowen et al. [30] analyzed 144 studies comprising 45,905 patients. The mean, median, and mode cut-offs for NLR reporting overall survival from multivariate models were 3.4, 3.0, and 5.0 (IQR 2.5–5.0), respectively. The association between NLR value and OS and DFS was observed in all subgroups based on tumor site, stage, and region. Evidence suggests that NLR greater than the cut-off (median NLR >3.0), IQR 2.5–5.0 reduces OS independently of gastrointestinal cancer type or stage of cancer [30]. Howard et al. [33] explored group-specific cut-off values of NLR in different types of cancer for precise clinical validation as a tool for risk stratification. The eight cancer types including CRC were selected from 228 published studies and over 75,000 patients. A total of 5,363 patients were included in the final analysis with 1,024 cases of CRC. They proposed an optimal cut-off value of NLR <3.22 for OS. For each type of cancer, authors measured the median of NLR value and compared the OS and DFS between patients with lower NLR than the median and higher NLR than median [33]. The outstanding position of CRP and ALB, which both reflect an ongoing chronic systemic inflammation during cancer, has been extensively studied by the research group from the University of Glasgow [38]. 20 years ago they concluded that systemic inflammatory response predicts the survival following curative resection of CRC. The systemic inflammation prognostic score was based on the serum levels of CRP and ALB, termed the Glasgow Prognostic score-GPS [3, 14]. GPS arbitrarily evaluates the concentration of CRP >10 mg/l, or low ALB concentration <35 g/l. Many trials adopted the HGB, CRP, and ALB as basic parameters for the evaluation

of systemic inflammatory response in cancer patients [3, 14–16, 35, 36]. Our results show that both ALB and CRP are valid and reliable markers to discriminate CRC and benign adenoma, but should be assessed very carefully with clinical context. The cut-off values are 41.9 g/l for ALB and 4.5 mg/l for CRP (Table 2). A few experiments have shown that some coagulation factors can facilitate the dissemination of cancer cells. Among all the effects of coagulation factors on tumor progression, the role of PLT and FG has been investigated for more than 20 years [12, 21, 39, 40]. By the experiments of malignant melanoma on the mice model, Zheng et al. [41] showed that FG enhances the interaction between tumor cells and PLTs. Tumor cells adhere to FG and then to PLT. The exact role of PLTs is to provide thrombin for FG. In other words, aggregation of dense fibrin(-ogen) around tumors cells depends on the thrombin formation by PLT [41]. The formation of thrombin around tumor cells is essential for the fate of cancer cells during the hematogenous phase. From the results of our trial even mild thrombocytosis (PLT≥285–300×10^9/l) and increased concentration of FG (≥3.68–3.8 g/l) may contribute significantly to the progression of cancer disease [41, 42]. High levels of FBG in oncological patients are associated with progression of the disease, higher stages of cancer disease (stage III or IV), lymphatic invasion and positive lymph nodes, and poor OS in gastric cancer patients [11, 42]. Both PLT and FG are involved in the pathogenesis of cancer and are associated with poor clinical outcomes, DFS, and OS.

We expected the null hypothesis that parameters of NLR, ALB, and CRP will deteriorate in CRC patients even before planned surgery. To our surprise, the most significant differences between the benign B group and the CRC group were high FG levels ($p<0.001$) and low HGB-mild to moderate anemia ($p<0.001$). Anemia in cancer is a well-known multifactorial phenomenon but clinically underestimated and overlooked. Anemia is associated with lower treatment effectiveness, worse clinical outcome, and lower survival rate [8, 9, 43]. The causes of anemia in cancer included: low synthesis of HGB, altered metabolism of iron, low secretion of erythropoietin, the shorter life span of red blood cells, higher rate of erythrocyte destruction in reticuloendothelial systems [26, 44].

We tested perspective routine hematological and biochemical parameters, which have the potency to discriminate patients with CRC from those with benign adenoma using a diagnostic model, which consists of four measured valid parameters: HGB, ALB (both decreased in cancer), and FG and NLR (both are significantly increased in patients with CRC). Stepwise logistic multivariate analyses identified four key parameters that had the statistical power to detect CRC and discriminate it from benign adenoma with high probability. We suggested an equation logit for the evaluation of CRC to be determined with probability. The panel of seven biomarkers for early detection of cancer-associated inflammation has a special biological, pathophysiological, and clinical background. All of these parameters are very sensitive determinants of cancer development, progression, and OS.

Cancer is a multifactorial biological phenomenon with high activation of neuroendocrine systems, altered function of reticuloendothelial systems, and metabolism, deterioration of systemic immune-inflammatory response, and profound activation of coagulation systems [45–47]. Each of the biomarkers reflects one system involved in the pathogenesis of the cancer disease. Immune response and chronic systemic inflammation are characterized mostly by increased platelet count (thrombocytosis, PLT≥285×10^9/l), high NLR≥2.5–3.0 [48], and acute-phase proteins (increased concentrations of CRP≥4.5 mg/l and FG≥3.8 g/l), and lower/decreased concentrations of ALB <41.9 g/l. Dysfunction of the hematologic and reticuloendothelial system is characterized by the anemia of cancer with a low concentration of HGB<129 g/l (Table 1) and high neutrophils count (mild neutrophilia, relatively more than 65% of total WBCs, or absolute ≥5.6×10^9/l) and mild, but significant lymphocytopenia <1.8×10^9/l. All of these biomarkers provide evidence that host response has a major role in CRC development (Table 2). The limitations of our study: it was a single-center study with a relatively low number of patients. Our contribution is that we suggested a panel of biomarkers for CRC evaluation (detection, monitoring, stratification, and prognosis). The panel should be validated on a larger cohort of cancer patients. We designed a diagnostic predictive model using multivariable Cox regression analysis, which consists of four parameters valid for the CRC identification: HGB level, ALB, FG concentration, and NLR (Table 5, Figure 3). Shi et al. [19] designed a trial to identify the high-risk groups for CRC from a general population by their routine laboratory test biomarkers based on the regression trees (CART) model. The final, best CART model consisted also of only four biomarkers: age, ALB, hematocrit/HGB, and relative lymphocyte count (%). The CART model showed a high AUC (0.88), the sensitivity of 62.2% at the high 99% specificity, in a multivariate CRC enrichment model [19]. It is in agreement with the results of our study and the idea that routinely used complete blood count may provide valuable information and an early warning for the detection of cancer (CRC).In conclusion, the complete blood count has been for a long time an integral component for the diagnosis of sepsis, systemic infection, and cancer. Many parallels have been recognized between cancer, inflammation, and sepsis on the molecular, cellular/tissue, organ, and systemic level [6]. A complete blood count may provide plenty of worthwhile information, which can be used for the early detection, diagnosis, stratification, and prognosis of cancer. We have observed that four of seven parameters (HGB, ALB, NLR, and FBG) (Figure 3) have significant statistical power to create a predictive model and nomogram to predict the risk of CRC in patients with colorectal tumors. The predictive model should be validated in a prospective trial on a larger cohort of patients to confirm or ule out its validity.

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