Retrospective Study

Longitudinal changes in personalized platelet count metrics are good indicators of initial 3-year outcome in colorectal cancer

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Abstract

BACKGROUND
Platelet count or complete blood count (CBC)-based ratios including lymphocyte-to-monocyte (LMR), neutrophil-to-lymphocyte (NLR), hemoglobin-to-platelet (HPR), red blood cell count distribution width-to-platelet (RPR), and platelet-to-lymphocyte (PLR) ratio are good predictors of colorectal cancer (CRC) survival. Their change in time is not well documented, however.

AIM
To investigate the effect of longitudinal CBC ratio changes on CRC survival and their possible associations with clinicopathological properties, comorbidities, and anamnestic data.

METHODS
A retrospective longitudinal observational study was conducted with the inclusion of 835 CRC patients, who attended at Semmelweis University, Budapest. CBC ratios and two additional newly defined personalized platelet count metrics (pPLT_D and pPLT_S, the platelet counts relative to the measurement at the time of CRC diagnosis and to the one 4-6 wk after tumor removal surgery, respectively) were recorded.

RESULTS
The 835 CRC patients had a total of 4608 measurements (5.52 visits/patient, in average). Longitudinal survival models revealed that the increases/decreases in LMR [hazard ratio (HR): 0.4989, P < 0.0001], NLR (HR: 1.0819, P < 0.0001), HPR (HR: 0.0533, P = 0.0038), pPLT_D (HR: 4.9229, P < 0.0001), and pPLT_S (HR: 4.7568, P < 0.0001) values were poor prognostic signs of disease-specific survival. The same was obtained for all-cause mortality. Most abnormal changes occurred within the
first 3 years after the diagnosis of CRC. RPR and PLR had an only marginal effect on disease-specific ($P = 0.0675$) and all-cause mortality (Bayesian 95% credible interval: 0.90–186.05), respectively.

CONCLUSION
LMR, NLR, and HPR are good metrics to follow the prognosis of the disease. $p\text{PLT}_0$ and $p\text{PLT}_t$ perform just as well as the former, while the use of RPR and PLR with the course of the disease is not recommended. Early detection of the abnormal changes in $p\text{PLT}_0$, $p\text{PLT}_t$, LMR, NLR, or HPR may alert the practicing oncologist for further therapy decisions in a timely manner.

Key Words: Personalized platelet count; Lymphocyte-to-monocyte ratio; Neutrophil-to-lymphocyte ratio; Hemoglobin-to-platelet ratio; Platelet-to-lymphocyte ratio; Colorectal neoplasms

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INTRODUCTION
Colorectal cancer (CRC) is the third most commonly diagnosed cancer type with almost 1.9 million new cases and 916,000 deaths worldwide annually, being the second leading cause of cancer deaths, according to the GLOBOCAN 2020 data[1]. In the last decades, a large variety of molecular and routinely used biomarkers have been proposed as prognostic signs of the disease, including ratios computed from the parameters of complete blood count (CBC). The following ratios have been developed and their abnormal values have been associated with shorter survival times and worse prognosis in CRC: Lymphocyte-to-monocyte ratio (LMR)[2-5], neutrophil-to-lymphocyte ratio (NLR)[6-13], hemoglobin-to-platelet ratio (HPR)[14], platelet-to-lymphocyte ratio (PLR)[9,10,14-16], mean platelet volume-to-platelet ratio (MPV/PC)[17], red blood cell distribution width-to-platelet ratio (RPR)[18], and personalized platelet counts relative to a platelet count measured at a particular time point[19,20]. It has to be mentioned though, that almost all previous studies, except Sylman et al[19], investigated the effect of these ratios on CRC in only one of the following ways: (1) Only at a specific timepoint (e.g., pre- or post-operatively, or after the first set of chemotherapy, etc)[2-4,6-10,13-18]; or (2) Their change over time was investigated by the difference between two timepoints[11,12,20]. In contrast, Sylman et al[19] used a time-dependent statistical model-based approach and concluded that platelet changes over the course of the disease are strongly associated with the prognosis of CRC.

A retrospective longitudinal observational study was created to investigate the effect of CBC-related ratio-changes on CRC survival. The possible associations between the CBC ratios and various clinicopathological properties, comorbidities, and anamnestic data were further objectives of the investigations.

MATERIALS AND METHODS
This study was conducted in concordance with the WMA Declaration of Helsinki. It was approved by the Regional and Institutional Committee of Science and Research Ethics, Semmelweis University (SE TUKEB 21-14/1994, approval date of latest modification: February 23, 2021). Handling of patient data was in accordance with the General Data Protection Regulation issued by the European Union.
**Patients and study design**

A retrospective longitudinal observational study was conducted with the data available from the medical database of Semmelweis University, Budapest. List of possibly eligible patients was downloaded based on the International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes C18 (malignant neoplasm of the colon), C19 (malignant neoplasm of the rectosigmoid junction), and C20 (malignant neoplasm of the rectum). A total of 2150 CRC patients’ anonymous and de-identified data was retrieved, who attended at the outpatient clinics of the Department of Internal Medicine and Hematology, Semmelweis University, Budapest and at the Department of Internal and Medicine and Oncology, Semmelweis University, Budapest, between 2006 and 2018. The exclusion criteria included age <18 years, any previous malignancies, known hematologic disease, inflammatory bowel disease, systemic autoimmune disease, mental disease, and/or inadequately controlled thyroid diseases, the usage of systemic corticosteroids 90 d prior to baseline visit date, erythropoiesis-stimulating agents, and patients with an Eastern Cooperative Oncology Group (ECOG) performance status > 2. The criteria for inclusion in the study required laboratory results performed at Semmelweis University at least at the time of CRC diagnosis. After verification of the inclusion and exclusion criteria, 835 of the 2150 patients remained as the initial study population (Figure 1).

Of the 835 patients, a total of 4608 visits (5.52 visits/patient in average) had been processed as follows. Laboratory measurements of patients with a resectable tumor (n = 743, 88.98%) were recorded at the time of CRC diagnosis prior to any oncological procedures, 4-6 wk after but at least within 6 mo after the tumor removal surgery, and every 4-6 mo after the postoperative visit. Measurements of patients with an irresectable tumor (n = 92, 11.02%) were recorded every 4-6 mo after the initial laboratory measurements performed at the time of CRC diagnosis (Figure 1). If a patient had no visit within the optimal window, the next measurement was recorded as close as possible. If a recent blood transfusion was administered around the selected visit, another random visit was selected.

**Clinicopathological and laboratory data measurements**

Anamnestic data including co-morbidities and recent medications were collected for the baseline measurements, while fasting blood samples were recorded for every visit. CBC was measured at the laboratories of Semmelweis University, Budapest. Staging was given by histopathological examination of surgical specimens and imaging studies; the American Joint Committee on Cancer staging was used [21]. Location of colon tumor was described as rectal cancer; right-sided [22] if the tumor was originating from the cecum, ascending colon, and proximal two-third of the transverse colon; left-sided [22] if originating from the distal one-third of the transverse colon, descending colon, sigmoid colon; and multiplicity if tumor growth was found at more than one site. Chemotherapy was recorded as “adjuvant” if no distant metastasis by imaging was detected; and “metastatic” if metastasis was present. Furthermore, a “chemotherapy 2” grouping was also created, where the previous group “metastatic” was further divided into “First-line”, “Second-line”, and “Third-line and above”. The usage of biological agents and regorafenib / trifluridine-tipiracil was recorded as dummy variables. Survival times were calculated from the time of CRC diagnosis until patient’s death or until the termination of data collection (June 30, 2021). Tumor related and unrelated deaths were recorded as separate events, while patients alive were right-censored.

LMR, NLR, PLR, HPR, and RPR were calculated as described previously [5,14,18,23] and data was 88.15% (n = 4062), 69.73% (n = 3213), 70.05% (n = 3228), 100% (n = 4608), and 78.97% (n = 3639) available for every patient visit, respectively. In addition to the above, two newly developed personalized platelet measures were calculated: (1) The personalized platelet measure relative to the platelet count observed at the time of CRC diagnosis (pPLT<sub>t</sub>) was defined as the quotient of “the platelet count(s) at (a) later visit(s)” divided by “the platelet count at the time of CRC diagnosis”; while (2) The platelet count after the primary tumor removal surgery was used as the divisor for the other newly defined personalized platelet measure (pPLT<sub>t</sub>). The first could be determined for every, while pPLT<sub>t</sub> was only available for 3633 (78.84%) patient visits.

**Statistical analysis**

Statistical analyses were performed within the R for Windows version 4.1.0 environment (R Foundation for Statistical Computing, 2021, Vienna, Austria). Welch’s two sample t-test, one-way ANOVA with Tukey’s all-pair post-hoc test, and Fisher’s exact test were used for comparisons between groups. Receiver operating characteristic (ROC) analysis was performed with the R package “pROC” (Robin et al, version 1.17.0.1). Natural cubic spline adjusted random intercept linear mixed effect model was used to determine parameter changes with the course of the disease (R package “nlme”, developed by Pinheiro, Bates, DebRoy, Sarkar and the R Core Team, version 3.1-152). Survival models were calculated both for single-time-point and longitudinal data. Pre- and post-operative survival was determined with cause-specific competing risk survival model (R package “survival”, developed by Therneau and Grambsch, version 3.2-11), while longitudinal survival was analyzed using competing risk survival model with a time-dependent covariate and with Bayesian joint modeling (R package rstanarm, developed by Goodrich, Gabry, Ali and Brilleman, version 2.21.1). P < 0.05 was considered statistically
significant for frequentist methods, while Bayesian survival models were evaluated by the following method. If the 95% credible interval (CrI) – the equivalent to the frequentist confidence interval (CI) – contained the hazard ratio (HR) 1, the model was considered not significant. However, if the 95% CrI was under or over HR = 1, the effect of the parameter was considered clinically significant. Continuous data are reported as the mean ± SD, while the number of occurrences and their percentage in parentheses characterize frequency data. Longitudinal joint-model results were drawn using the built-in methods of “rstanarm” and forest plots with the ‘forestplot’ R package (Gordon Lumley, version 1.10.1).

**RESULTS**

**Baseline results and pre- and post-operative survival of CRC patients**

A total of 4608 CBC measurements of 835 patients were analyzed in this retrospective study, 5.52 ± 3.94 visits/patient (min: 1, max: 28) in average. Average age of patients was 65.31 ± 11.00 years at the time of CRC diagnosis, and 367 of the 835 study subjects (43.95%) were female. Detailed preoperative CBC measurements, anamnestic data, clinicopathological data, and medical history data are summarized in Table 1. The secondary chemotherapy grouping was not used during the longitudinal data analysis, as further breakdown of groups did not provide additional information.

The relationship between the various CBC ratios and anamnestic/clinicopathological data was analyzed. Higher preoperative LMR values were associated with female sex ($P = 0.0001$), more advanced stage ($P = 0.0036$), the presence of distant metastases ($P = 0.0231$), postoperative radiotherapy ($P = 0.0483$), the need for chemotherapy ($P = 0.0323$) and cholecystectomy in patient’s medical history ($P = 0.0483$). Similar to LMR, lower NLR values were associated with female sex ($P = 0.0214$), stage ($P < 0.0001$), distant metastases ($P < 0.0001$), postoperative radiotherapy ($P = 0.0207$), chemotherapy ($P = 0.0028$), and cholecystectomy in patient’s medical history ($P = 0.0217$). Furthermore, marginally different preoperative NLR values were found if a patient needed any biological agents at any point within the course of the disease ($P = 0.0673$). Basically, the same could have been found in the HPR, RPR, and PLR (Table 2) with the following additions. Lower HPR ($P = 0.0046$) and RPR ($P = 0.0352$) values were found in those patients with regional lymph-node metastases. Preoperative radiotherapy was associated with higher HPR ($P = 0.0129$). HPR ($P < 0.0001$) and PLR ($P = 0.0148$) were significantly different in right-sided and rectal tumors, respectively. Lower RPR and PLR values indicated the need for using regorafenib/trifluridine-tipiracil (RPR: $P = 0.0106$; PLR: $P = 0.0617$). Major cardiovascular (CV) event ($P = 0.0295$) and type 2 diabetes (T2DM, $P = 0.0695$) in a patient’s medical history was associated with higher RPR values (Table 2).

Approximately 73.17% of (611/835) the study participants had postoperative laboratory measurement (at least 4-6 wk, but max. 6 mo after the primary tumor removal surgery). Postoperative CBC ratios are summarized in Table 3. In previous findings [3,4,8-10,13-16,24], both pre- and post-operative CBC ratios have been associated with a worse survival of patients. Similar to those results [3,4, 8-10,13-16,24], we could also confirm that more abnormal pre- and post-operative LMR, NLR, HPR, and PLR values predicted a shorter disease-specific survival of CRC patients; however, the previously reported significant effect of RPR on survival[18] could not be confirmed. In addition, higher
Table 1 Baseline complete blood count measurements and anamnestic data of the 835 colorectal cancer patients

| Parameter                                              | mean ± SD or number of observations | Number of missing | Available |
|--------------------------------------------------------|-------------------------------------|------------------|-----------|
| Age (yr)                                               | 65.31 ± 11.00                       | 0                | 100%      |
| Male: Female                                           | 468:367 (56.05%: 43.95%)            | 0                | 100%      |
| White blood cell count (10³/µL)                       | 8.74 ± 3.55                         | 0                | 100%      |
| Neutrophil count (10³/µL)                             | 6.25 ± 3.37                         | 169              | 79.76%    |
| Eosinophil count (10³/µL)                             | 0.18 ± 0.37                         | 173              | 79.28%    |
| Basophil count (10³/µL)                                | 0.04 ± 0.03                         | 173              | 79.28%    |
| Monocyte count (10³/µL)                                | 0.56 ± 0.29                         | 147              | 82.40%    |
| Lymphocyte count (10³/µL)                              | 1.69 ± 0.78                         | 147              | 82.40%    |
| Red blood cell count (10¹²/µL)                        | 4.50 ± 0.58                         | 0                | 100%      |
| Hemoglobin (g/L)                                       | 122.34 ± 23.97                      | 0                | 100%      |
| Hematocrit (L/L)                                       | 0.38 ± 0.06                         | 0                | 100%      |
| Mean corpuscular volume (fL)                           | 83.45 ± 9.71                        | 0                | 100%      |
| Mean corpuscular hemoglobin (pg)                       | 27.15 ± 4.12                        | 0                | 100%      |
| Mean corpuscular hemoglobin concentration (g/L)        | 324.25 ± 24.05                      | 0                | 100%      |
| Red blood cell distribution width (%)                  | 14.95 ± 2.86                        | 62               | 92.57%    |
| Platelet count (10³/µL)                                | 341.19 ± 131.66                     | 0                | 100%      |
| AJCC stage[21]                                         |                                     |                  |           |
| I                                                      | 107 (12.81%)                        | 0                | 100%      |
| II                                                     | 214 (25.63%)                        | 0                | 100%      |
| III                                                    | 187 (22.40%)                        | 0                | 100%      |
| IV                                                     | 327 (39.16%)                        | 0                | 100%      |
| Regional lymph node metastasis                         | 445 (%)                             | 0                | 100%      |
| Distant metastasis                                     | 0 (%)                                | 0                | 100%      |
| At the time of diagnosis                               | 326 (39.04%)                        | 0                | 100%      |
| Later with the course of the disease                   | 102 (12.22%)                        | 0                | 100%      |
| Location of the tumor[22]                              |                                     |                  |           |
| Left-sided                                             | 273 (32.69%)                        | 0                | 100%      |
| Right-sided                                            | 246 (29.46%)                        | 0                | 100%      |
| Rectum                                                 | 297 (35.57%)                        | 0                | 100%      |
| Multiplex                                              | 19 (2.28%)                          | 0                | 100%      |
| Chemotherapy                                           | 0 (%)                                | 0                | 100%      |
| Adjuvant                                               | 248 (29.70%)                        | 0                | 100%      |
| Metastatic                                             | 331 (39.64%)                        | 0                | 100%      |
| First line                                             | 126 (15.09%)                        | 0                | 100%      |
| Second line                                            | 98 (11.74%)                         | 0                | 100%      |
| Third line or above                                    | 104 (12.46%)                        | 0                | 100%      |
| Radiotherapy                                           | 0 (%)                                | 0                | 100%      |
| Preoperative                                           | 63 (7.54%)                          | 0                | 100%      |
| Postoperative                                          | 64 (7.66%)                          | 0                | 100%      |
| Both                                                   | 5 (0.60%)                           | 0                | 100%      |
| Usage of                                               | 0 (%)                                | 0                | 100%      |
postoperative pPLT\textsubscript{D} values also predicted shorter survival times of study subjects (Figure 2).

In several previous studies, CRC ratios have been dichotomized based on ROC analysis results. ROC analyses investigating the relationship between all-cause mortality and CBC ratios had been performed and optimal thresholds were determined via Youden’s J statistic (Figure 3F). The cut-off values of 3.2214 [sensitivity (Se): 59.46%; specificity (Sp): 57.23%], 2.9383 (Se: 68.29%; Sp: 50.65%), 0.3190 (Se: 39.47%; Sp: 74.74%), 0.0438 (Se: 47.37%; Sp: 62.82%), and 67.2163 (Se: 70.17%; Sp: 40.45%) were determined for LMR, NLR, HPR, RPR, and PLR, respectively. Survival results of these dichotomized variables had been drawn (Figure 3A-E).

Changes of complete blood count ratios with the course of the disease
To determine whether the CBC ratio values change with respect to the course of CRC and how these affect patient survival, we chose two approaches. First, random intercept linear mixed effect models were constructed, where all 4608 measurements from all the 835 study participants were used. To gather information on whether survivors and patients who died during the study had different changes within the parameters, censoring data was included in all models as an explanatory variable. A total of 451 patients (54.01%) died until the termination date of our data collection, of which 367 (43.95%) and 84 (10.06%) were related to CRC and other non-cancer related causes, respectively. The data obtained from the model predictions can be summarized in general as follows. Change in CBC ratios of survivors and patients who died due to non-cancer related causes did not differ: pPLT\textsubscript{D}, pPLT\textsubscript{E}, NLR, and PLR slowly, but constantly decreased, LMR was basically constant, and HPR and RPR increased (Figure 4C). In contrast, the observed parameters moved in the opposite directions in those patients who died of CRC. The most significant change in pPLT\textsubscript{D}, pPLT\textsubscript{E}, LMR, and NLR values occurred within the first 36 mo after the diagnosis of the tumor, which coincided with the observation that the highest proportion of deceased patients (262/367, 71.39%) died within this period. A generalizable pattern that a slow decrease was followed by a sudden, fast increase was observable (Figure 4A and B). In contrast to the former four ratios, the different change-directions in HPR, RPR, and PLR values were observed in later periods of the disease (> 36 mo observation time), meaning that the abnormal change in these parameters was more common in those patients who died after a long illness. Data was further stratified by clinicopathological and anamnestic parameters, and a significant effect of tumor stage (pPLT\textsubscript{D}, pPLT\textsubscript{E}, LMR, HPR, and RPR: P < 0.0001; Figure 5 and Supplementary Figure 1), tumor location (pPLT\textsubscript{D} and LMR: P < 0.0001; Supplementary Figure 2), presence of distant (NLR: P = 0.0354; HPR: P = 0.0380; Supplementary Figure 3) or lymph-node metastasis (pPLT\textsubscript{D}: P = 0.0019; pPLT\textsubscript{E}: P = 0.0421; Supplementary Figure 4), used oncological therapy (pPLT\textsubscript{D}, pPLT\textsubscript{E}, HPR, and RPR: P < 0.05; LMR and NLR: P ≤ 0.0013; Supplementary Figure 5-9), sex (LMR, HPR, and PLR: P < 0.0001; NLR: P = 0.0186; RPR: P = 0.0043; Supplementary Figure 10), cholecystectomy (pPLT\textsubscript{D}: P = 0.0434; HPR: P = 0.0479; PLR: P = 0.0455; Supplementary Figure 11), hypertension (pPLT\textsubscript{D}: P = 0.0454; LMR: P = 0.0378; Supplementary Figure 12), and T2DM (pPLT\textsubscript{D}: P = 0.0643; LMR: P = 0.0229; PLR: P = 0.0244; Supplementary Figure 13) on the parameter changes was observed. Although we found more abnormal values in those patients with any comorbidities and clinically more advanced CRC cases, in general, the presence of comorbidities was associated with less abnormal values of CBC ratios.

Second, specific survival models were constructed, with which the effect of longitudinal changes in CBC ratios on patient survival could also be analyzed. Univariate Bayesian joint-models and univariate and multivariate competing risk models with a time-dependent covariate (CR\textsubscript{D}) were used to analyze all-cause and disease specific mortality, respectively. Based on the results of joint models, all CBC ratios,
Table 2 Comparison of the different baseline complete blood count ratios by anamnestic and clinicopathological data

| Grouping factor                  | LMR       | NLR       | HPR       | RPR       | PLR       |
|---------------------------------|-----------|-----------|-----------|-----------|-----------|
| **Sex**                         |           |           |           |           |           |
| Male                            | 3.30 ± 2.22$^c$ | 4.69 ± 3.94$^d$ | 0.45 ± 0.21$^d$ | 0.051 ± 0.020$^d$ | 58.96 ± 30.01$^d$ |
| Female                          | 3.90 ± 1.88 | 4.05 ± 3.14 | 0.38 ± 0.18 | 0.047 ± 0.025 | 66.87 ± 25.68 |
| **Location of the tumor**       |           |           |           |           |           |
| Left-sided                      | 3.64 ± 2.50 | 4.55 ± 3.48 | 0.43 ± 0.21$^d$ | 0.049 ± 0.027 | 61.06 ± 32.31 |
| Right-sided                     | 3.34 ± 1.96 | 4.54 ± 3.09 | 0.35 ± 0.19 | 0.048 ± 0.020 | 67.49 ± 28.98 |
| Rectum                          | 3.64 ± 1.81 | 4.24 ± 4.21 | 0.47 ± 0.19$^d$ | 0.050 ± 0.019 | 59.19 ± 22.49$^d$ |
| Multiplex                       | 4.03 ± 1.42 | 2.69 ± 1.05 | 0.45 ± 0.17 | 0.056 ± 0.014 | 68.17 ± 32.28 |
| **AJCC stage**                  |           |           |           |           |           |
| I                               | 4.12 ± 2.10$^{b,d}$ | 3.42 ± 2.99 | 0.49 ± 0.22$^d$ | 0.054 ± 0.026$^{b,d}$ | 63.22 ± 26.54 |
| II                              | 3.47 ± 1.55 | 4.23 ± 3.13 | 0.43 ± 0.17 | 0.051 ± 0.018 | 61.18 ± 23.52 |
| III                             | 3.82 ± 2.53 | 3.82 ± 2.29 | 0.42 ± 0.18 | 0.049 ± 0.015 | 63.47 ± 25.45 |
| IV                              | 3.29 ± 2.11 | 5.21 ± 4.50 | 0.39 ± 0.22$^d$ | 0.047 ± 0.027 | 62.60 ± 33.47 |
| **Regional lymph node metastasis** |           |           |           |           |           |
| No                              | 3.59 ± 1.78 | 4.17 ± 3.64 | 0.44 ± 0.20$^b$ | 0.051 ± 0.021$^b$ | 62.58 ± 25.96 |
| Yes                             | 3.52 ± 2.35 | 4.59 ± 3.57 | 0.40 ± 0.20 | 0.048 ± 0.023 | 62.38 ± 30.47 |
| **Distant metastasis**          |           |           |           |           |           |
| None                            | 3.76 ± 2.14$^{a,b}$ | 3.83 ± 2.71$^{a,b}$ | 0.45 ± 0.19$^a$ | 0.051 ± 0.020$^a$ | 62.38 ± 24.59 |
| At the time of diagnosis        | 3.29 ± 2.11 | 5.21 ± 4.51 | 0.39 ± 0.22 | 0.047 ± 0.027 | 62.69 ± 33.51 |
| Later with the course of the disease | 3.62 ± 1.80 | 4.23 ± 3.27 | 0.42 ± 0.17 | 0.049 ± 0.016 | 62.51 ± 26.06 |
| **Radiotherapy**                |           |           |           |           |           |
| None                            | 3.48 ± 2.15$^{a,b}$ | 4.55 ± 3.72$^{a,b}$ | 0.40 ± 0.20$^a$ | 0.048 ± 0.022 | 62.94 ± 29.18 |
| Preoperative                    | 3.73 ± 2.06 | 4.11 ± 3.67 | 0.53 ± 0.24$^b$ | 0.055 ± 0.033 | 56.41 ± 23.60 |
| Postoperative                   | 4.29 ± 1.38 | 3.00 ± 1.43 | 0.48 ± 0.16 | 0.051 ± 0.015 | 61.32 ± 22.12 |
| Both                            | 4.17 ± 1.55 | 2.53 ± 0.94 | 0.52 ± 0.10 | 0.049 ± 0.010 | 87.02 ± 18.13 |
| **Chemotherapy**                |           |           |           |           |           |
| None                            | 3.29 ± 1.89$^{a,b}$ | 5.06 ± 5.01$^{a,b}$ | 0.42 ± 0.23 | 0.050 ± 0.023 | 60.61 ± 33.77 |
| Adjuvant                        | 3.82 ± 2.30 | 3.86 ± 2.57 | 0.44 ± 0.18 | 0.050 ± 0.017 | 63.73 ± 24.96 |
| Metastatic                      | 3.57 ± 1.89 | 4.29 ± 2.77 | 0.40 ± 0.20 | 0.047 ± 0.026 | 63.14 ± 25.95 |
| **Usage of biological agents**  |           |           |           |           |           |
| No                              | 3.52 ± 2.16 | 4.53 ± 3.87 | 0.42 ± 0.21 | 0.050 ± 0.025$^a$ | 61.96 ± 28.46 |
| Yes                             | 3.67 ± 1.93 | 4.03 ± 2.66 | 0.41 ± 0.17 | 0.046 ± 0.014 | 64.16 ± 28.26 |
| **Usage of regorafenib/trifluridine-tipiracil** |           |           |           |           |           |
| No                              | 3.58 ± 2.12 | 4.38 ± 3.66 | 0.42 ± 0.21 | 0.049 ± 0.023$^a$ | 62.96 ± 28.66 |
| Yes                             | 3.21 ± 1.66 | 4.67 ± 2.85 | 0.41 ± 0.17 | 0.045 ± 0.012 | 55.65 ± 23.33 |
| **Type 2 diabetes mellitus**    |           |           |           |           |           |
| No                              | 3.58 ± 2.09 | 4.41 ± 3.70 | 0.42 ± 0.20 | 0.048 ± 0.019 | 63.62 ± 29.85 |
| Yes                             | 3.47 ± 2.13 | 4.41 ± 3.38 | 0.43 ± 0.21 | 0.052 ± 0.031 | 58.87 ± 23.31 |
| **History of major CV event**   |           |           |           |           |           |
| No                              | 3.60 ± 2.19 | 4.44 ± 3.78 | 0.42 ± 0.20 | 0.048 ± 0.023$^a$ | 62.68 ± 29.21 |
| Yes                             | 3.38 ± 1.67 | 4.24 ± 2.82 | 0.43 ± 0.23 | 0.053 ± 0.022 | 61.80 ± 24.86 |
### History of cholecystectomy

|                | Mean ± SD          | Number of missing | Available % |
|----------------|--------------------|-------------------|-------------|
| No             | 3.49 ± 2.03        | –                 | –           |
| Yes            | 4.02 ± 2.47        | 107               | 82.49%      |

*P < 0.05.

*P < 0.01.

*P < 0.001.

*P < 0.0001.

1 Right-sided vs left-sided tumors.

2 Right-sided tumors vs rectal cancer.

3 Stage I vs Stage IV.

4 Stage I vs Stage III.

5 None vs at the time of diagnosis.

6 None vs postoperative radiotherapy.

7 None vs preoperative radiotherapy.

8 None vs adjuvant chemotherapy.

LMR: Lymphocyte-to-monocyte ratio; NLR: neutrophil-to-lymphocyte ratio; HPR: Hemoglobin-to-platelet ratio; RPR: Red blood cell distribution width-to-platelet ratio; PLR: Platelet-to-lymphocyte ratio; AJCC: American Joint Committee on Cancer; CV: Cardiovascular. Of the total 835 study subjects, 82.40%, 79.04%, 92.57%, and 79.76% of LMR, NLR, RPR, and PLR were only available for statistical analysis, respectively.

### Table 3 Complete blood count ratios at least 4-6 weeks after primary tumor removal surgery (n = 644)

| Parameter                                               | Mean ± SD          | Number of missing | Available % |
|---------------------------------------------------------|--------------------|-------------------|-------------|
| Time since tumor removal surgery (mo)                   | 2.21 ± 1.88        | –                 | –           |
| Lymphocyte-to-monocyte ratio                            | 4.01 ± 1.95        | 107               | 82.49%      |
| Neutrophil-to-lymphocyte ratio                          | 3.59 ± 2.82        | 273               | 55.32%      |
| Hemoglobin-to-platelet ratio                            | 0.48 ± 0.19        | 0                 | 100%        |
| Red blood cell distribution width-to-platelet ratio     | 0.058 ± 0.023      | 212               | 65.30%      |
| Platelet-to-lymphocyte ratio                            | 67.60 ± 28.82      | 266               | 56.46%      |
| Personalized platelet count, relative to “at-diagnosis” | 0.91 ± 0.27        | 0                 | 100%        |

except RPR, had a clinically significant effect on all-cause mortality. Higher pPLT_D, pPLT_S, and NLR, and lower LMR, HPR, and PLR values predicted a shorter survival of the study subjects (Figure 6 and Supplementary Figure 14). Similar to the results obtained from joint models, disease-specific results of CR_TD models strengthened the observations on pPLT_D, pPLT_S, LMR, NLR, and HPR; however, here it was not RPR, but PLR, that was not significant (Figure 7). In all the multivariate CR_TD models, all CBC ratios, except PLR, had significant effect, while PLR had only marginal effect (P values between 0.0664 and 0.0766). Study subjects with more advanced disease stages had more abnormal pPLT_D, (Figure 8B), LMR, and RPR values, which were associated with a higher risk of earlier disease-specific death. Furthermore, a marginal effect of tumor stage on pPLT_S (Figure 8A), tumor location on pPLT_D, and HPR (Supplementary Figure 15A and B), previous major CV event on pPLT_D (Supplementary Figure 15C), sex on LMR, T2DM on NLR, the use of anti-hypertensive agents on NLR and HPR (Supplementary Figure 15D), and previous cholelithiasis on NLR was observed.

### DISCUSSION

CRC has been associated with several risk factors in recent years, including various genetic factors, routine laboratory parameters, co-morbidities, etc. Abnormal values of CBC indices and ratios calculated from those are associated with a shorter survival of CRC patients[2-4,6-20]. These changes are thought to be caused by tumor-specific background mechanisms like paraneoplastic thrombocytosis[25] or the interaction between the microenvironment of the tumor and the immune system leading to various systemic effects[26]. Clinically, hemoglobin and hematocrit values, platelet count, white blood cell count, and red blood cell counts decrease with age[27-29], while in various forms of cancer, including CRC, the opposite has been observed[19,20,30]. Without going into too much detail, the following observations are known within the literature regarding the relationship between CRC and platelets and CBC-based ratios. Qualitative and quantitative changes in platelets in gastrointestinal cancers are known for more than 100 years[31], and a significant platelet increase can be observed within the last 1-4
Herold Z et al. Longitudinal platelet changes in colorectal cancer

Table 1

| Data type          | HR     | 95%CI             | P value |
|--------------------|--------|-------------------|---------|
| Preoperative data: |        |                   |         |
| LMR                | 0.8416 | 0.7665 - 0.9239   | 0.0003  |
| NLR                | 1.0766 | 1.0496 - 1.1040   | < 0.0001|
| HPR                | 0.3148 | 0.1567 - 0.6326   | 0.0012  |
| RPR                | 0.0002 | 0.0000 - 4.7620   | 0.0973  |
| PLR                | 0.9942 | 0.9896 - 0.9989   | 0.0153  |
| Postoperative data:|        |                   |         |
| LMR                | 0.8523 | 0.7767 - 0.9353   | 0.0007  |
| NLR                | 1.2194 | 1.1257 - 1.3210   | < 0.0001|
| HPR                | 0.1824 | 0.0791 - 0.4210   | < 0.0001|
| RPR                | 0.0035 | 0.0000 - 72.6800   | 0.2640  |
| PLR                | 0.9898 | 0.9824 - 0.9973   | 0.0080  |
| pPLT<sub>D</sub>   | 1.9031 | 1.1559 - 3.1330   | 0.0114  |

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Figure 2 Forest plot of univariate competing risk survival models. Colorectal cancer-specific hazard was higher if a patient had a lower lymphocyte-to-monocyte ratio, hemoglobin-to-platelet ratio, or platelet-to-lymphocyte ratio and higher neutrophil-to-lymphocyte ratio or personalized platelet count relative to “at-diagnosis”. Red blood cell distribution width-to-platelet ratio did not affect neither pre- nor post-operative survival. CI: Confidence interval; HR: Hazard ratio; LMR: Lymphocyte-to-monocyte ratio; PLR: Platelet-to-lymphocyte ratio; NLR: Neutrophil-to-lymphocyte ratio; HPR: hemoglobin-to-platelet ratio; RPR: red blood cell distribution width-to-platelet ratio; pPLT<sub>D</sub>: Personalized platelet count relative to “at-diagnosis”.

years prior to the diagnosis of CRC[19]. Platelet count over the upper normal range (known as thrombocytosis) at the time of CRC diagnosis or postoperatively is associated with an increased risk for shorter survival times[25]. It must be mentioned though that the definition of elevated platelet counts varies within publications[25]; some authors have defined thrombocytosis cut-off values even within the normal range[32,33], while others set higher values than the upper normal range[34]. It has been suggested that using hard cut-off points of single-time-point measurements may introduce erroneous findings and personalized/relative platelet counts may more accurately describe the true risk of patients [19,20,35]. Furthermore, the following problem can also introduce significant bias not finding high risk patients using the single-time threshold methods. If hypothetical “Patient 1” and “Patient 2” have a baseline platelet count of 180 × 10<sup>9</sup>/L increasing to 386 × 10<sup>9</sup>/L due to CRC and 390 × 10<sup>9</sup>/L to 405 × 10<sup>9</sup>/L, respectively, using the single-time-point thrombocytosis cut-offs, the true higher risk of “Patient 1” would be probably unnoticed, even if his/her relative increase is much higher (114% vs 4%). A higher increase is usually accompanied with an elevated risk of shorter survival times[19,20]. Previous findings of relative platelet ratios have shown that the higher the increase in the platelet counts, the worse the expected survival, and higher values are possibly good indicators of more advanced stages with the presence of regional lymph node or distant metastases[19,20]. In the current study, we defined two new personalized relative platelet measures, pPLT<sub>D</sub> and pPLT<sub>S</sub>, which could show us how a patient’s platelet count changed in relation to two specific timepoints. With these, the following patterns could have been observed: Survivors were basically the patients who are in complete remission, in whom pPLT<sub>D</sub> and pPLT<sub>S</sub> values decreased slowly, like those observed within the healthy population[27-29], while a sudden, fast increase within the last months prior to cancer-related death could be observed. Both parameters could be associated with various oncological parameters, including the location of the tumor, tumor stage, the presence of lymph-node metastasis, and the usage of radiotherapy, biological therapy, and various chemotherapies. As an expected result from previous reports[19,20,25] and the current study’s observed pattern-changes, the increase in pPLT<sub>D</sub> and pPLT<sub>S</sub> values was accompanied with a higher risk for a shorter survival.
Figure 3 Naïve Kaplan-Meier survival curves of preoperative complete blood count ratios of colorectal cancer patients, which were
dichotomized based on optimal thresholds available from receiver operating characteristic models. AUC: Area under curve; CI: Confidence interval; RDW: Red blood cell distribution width.

Adjustment of platelet counts with other CBC indices (MPV/PC, HPR, and PLR)[9,10,14-18] can further increase its potential predictive power on finding CRC patients[17,36] and the abnormally increased/decreased values of these ratios are usually related to more advanced clinicopathological factors and are poor prognostic signs[9,10,14-16,18,24,37]. We found that higher HPR values predicted a better survival of patients and its lower values were usually found more likely in those patients with more advanced disease, inversely proportional to those of personalized platelet ratios. The longitudinal analysis of HPR revealed that its decrease was more prominent in patients with a longer illness. The relationship between the clinicopathological parameters and PLR and RPR was also verifiable, but the effect of their changes on survival with the course of the disease was somewhat controversial. The effect of PLR and RPR changes on disease-specific and all-cause mortality was found to be only marginal, respectively, which suggests that therapy-decisions based on these two parameters should be avoided, compared to the other CBC ratios. Partial longitudinal data - pre-chemotherapy and 3-mo after chemotherapy - on PLR has been described in the paper of Nemoto et al[11], where, similarly to our results, no significant effect of delta-PLR changes on survival has been found. Single time-point analysis of pre- and post-operative HPR, RPR, and PLR data did not differ from those previously reported[3,4,8-10,13-16,24]. Due to the low number of available measurements, longitudinal modeling of MPV/PC was unfeasible.

The relationship between CRC and white blood cell type ratios is also a popular research area. Most studies have investigated NLR and just like with platelets and platelet-related ratios, abnormal NLR has been associated with a poorer progression-free and overall survival of patients[3,8,13,24,37], higher clinical stages, tumor location, and regional lymph-node and distant metastases[3,8,10,24]. Several studies have found NLR of ~3.0 as a good threshold to distinguish patient with possibly good and bad life expectancies[8-10]. A few studies have evaluated NLR changes over time and it has been found that patients with a lower or no decrease in NLR were at a greater risk[11,12,38]. We could also confirm and strengthen this relationship between NLR changes and patient survival, and higher NLR levels throughout the course of the disease increased the risk of a shorter disease-specific and all-cause mortality. Most NLR increase occurred within the first 36 mo of our observation, like that of pPLTp and pPLTg. LMR, also a much studied white blood cell ratio, is considered a poor prognostic sign if its value is low[2,3]. Low LMR occurs if the monocyte count is greater than lymphocyte count. Longitudinal LMR changes were good indicators of disease progression and like in the case of NLR, the majority of significant LMR decrease were observed within the first 3 years after the diagnosis of CRC. The similarities in the patterns of platelet- and lymphocyte-related ratios suggest that the changes in these two CBC parameters are most likely related to more advanced CRC and disease progression may be well-characterized using pPLTp, pPLTg, LMR, or NLR, while in longer-lasting disease, the late decrease in hemoglobin levels may predict the worsening of a patients’ condition and HPR will be the better marker to be used.

The strong relationship between CRC and other comorbidities in a patient’s medical history, such as T2DM[39], hypertension[40], major CV events[41-43], appendectomy[44,45], and cholecystectomy[46], is well known. The population suffering from these conditions are at a greater risk of developing CRC than healthy people, and several common risk factors between CRC and the other conditions have been found[39,42,47]. Studies investigating CBC ratios in non-cancer populations having the comorbidities listed above have found similar results to those reported in CRC-related studies that the abnormal values of the various CBC ratios are associated with an increased risk of more advanced illness and faster disease progression[48-52]. Despite the large number of studies examining the relationship between CBC ratios and CRC, there are only a few that have investigated the combined effect of CBC ratios and comorbidities in CRC. One of the reasons behind this tendency might be that most observational studies were designed in a similar way to randomized clinical trials, and the various comorbidities will increase the heterogeneity of patients, and to avoid bias, comorbidities are very often included in exclusion criteria (e.g., including, but not limited to[14,36]). The following is known about the combined relationship of CRC, CBC ratios, and comorbidities. Lower body mass index and marginally less obese patients can be found with a preoperative PLR > 160[53]. NLR of patients with T2DM or hypertension do not differ from those without the two conditions[54]. LMR combined with carbohydrate antigen 19-9 has good predictive value on postoperative recurrence in CRC + T2DM patients[55], and PLR is significantly higher in CRC patients with metabolic syndrome[56]. Furthermore, colorectal adenoma, which has a high risk to develop into CRC[57], has an increased prevalence in metabolic syndrome patients with higher NLR values[23], and higher NLR at the diagnosis of CRC may be a sign of stroke within 2 years after cancer diagnosis[58]. We found that preoperative RPR was marginally and significantly higher in those CRC patients with T2DM and previous major CV event in their medical history, respectively. Cholecystectomy in medical history was associated with significantly higher LMR, significantly lower NLR, and marginally higher PLR. Some of the longitudinal changes in CBC ratios were affected by cholecystectomy (pPLTg, HPR, and PLR),
Herold Z et al. Longitudinal platelet changes in colorectal cancer

Figure 4 Characteristic changes of complete blood count ratios in patients who died or were alive at the end of our observation. Dotted vertical line represents time of death. pPLT$_D$: Personalized platelet count relative to “at-diagnosis”; pPLT$_S$: Personalized platelet count relative to “after-surgery”; LMR: Lymphocyte-to-monocyte ratio; NLR: Neutrophil-to-lymphocyte ratio; HPR: Hemoglobin-to-platelet ratio; RPR: Red blood cell distribution width-to-platelet ratio; PLR:

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Platelet-to-lymphocyte ratio.

Figure 5 All recorded personalized platelet count relative to “at-diagnosis” (pPLT\textsubscript{D}), lymphocyte-to-monocyte ratio, and platelet-to-lymphocyte ratio values of the 835 study participants, which have been stratified by American Joint Committee on Cancer staging[21].

For better view, the remaining complete blood count ratios are drawn on Supplementary Figure 1. Regression curves are not drawn from the actual spline adjusted mixed effect model, but the automatic smoothing curve of the plotting process.

hypertension (pPLT\textsubscript{S} and LMR), and T2DM (pPLT\textsubscript{D}, LMR and PLR); furthermore, marginally lower hazard ratios within the longitudinal survival models were observed for pPLT\textsubscript{D} with CV events, for NLR with T2DM, and for NLR and HPR with medically treated hypertension. Platelet aggregation inhibition had no effect neither on single-time-point nor on longitudinal survival. These observations suggest that the known and well-managed comorbidities as well as the regular medical supervision can decrease the increased risk for this subset of patients, which ultimately leads to a conclusion that the appropriate treatment for any known or emerging comorbidities observed during routine oncology care should be resolved with proper patient education and by finding the appropriate specialist if necessary. In addition to the above, the subset of CRC patients with any controlled thyroid diseases (in euthyroid state) did not show differentiation in any of the CBC ratios, which might be in connection with the lower risk of developing CRC in thyroid illnesses[59], despite the known relationship between non-cancer and cancer originated thyroid disorders and NLR[60].

Routine follow-up of CRC patients is currently done according to the scheme, recommended, e.g., by the European Society for Medical Oncology[61,62] or by others[63]. In general, the current gold standards are the measurement of the tumor marker carcinoembryonic antigen (CEA) and imaging studies, which are recommended to be performed every 3-6 mo and 3-6-12 mo depending on the stage, presence of metastases, current treatment, etc., of the disease, respectively. Although the superiority of...
Herold Z et al. Longitudinal platelet changes in colorectal cancer

Table 1

| Metric                        | HR     | 95% CI           | Clinically relevant? |
|-------------------------------|--------|------------------|----------------------|
| LMR                           | 0.6090 | 0.5406 - 0.6771  | Yes                  |
| NLR                           | 1.1320 | 1.1052 - 1.1630  | Yes                  |
| HPR                           | 0.4538 | 0.2976 - 0.6676  | Yes                  |
| RPR                           | 15.1046| 0.8967 - 186.0471| No                   |
| PLR                           | 0.9871 | 0.9812 - 0.9930  | Yes                  |
| pPLT_D                        | 1.9387 | 1.4614 - 2.5574  | Yes                  |
| pPLT_S                        | 2.3187 | 1.6905 - 3.2027  | Yes                  |

**Figure 6 Forest plot of univariate Bayesian joint-models.** Higher risk of all-cause mortality was associated with a lower lymphocyte-to-monocyte ratio, hemoglobin-to-platelet ratio, and platelet-to-lymphocyte ratio and higher neutrophil-to-lymphocyte ratio, personalized platelet count relative to “at-diagnosis”, and personalized platelet count relative to “after-surgery”. Red blood cell distribution width-to-platelet ratio did not affect all-cause mortality of study participants. CrI: Credible interval; HR: Hazard ratio; LMR: Lymphocyte-to-monocyte ratio; PLR: Platelet-to-lymphocyte ratio; NLR: Neutrophil-to-lymphocyte ratio; HPR: hemoglobin-to-platelet ratio; RPR: red blood cell distribution width-to-platelet ratio; pPLT_D: Personalized platelet count relative to “at-diagnosis”; pPLT_S: Personalized platelet count relative to “after-surgery”. Bayesian statistical methods do not give P values, and evaluation of results was detailed in methods.

**Figure 7 Forest plot of univariate competing risk models with time-dependent covariate.** Higher risk of disease-specific mortality was associated with a lower lymphocyte-to-monocyte ratio, hemoglobin-to-platelet ratio, and platelet-to-lymphocyte ratio, and higher red blood cell distribution width-to-platelet ratio, personalized platelet count relative to “at-diagnosis”, and personalized platelet count relative to “after-surgery”. Neutrophil-to-lymphocyte ratio did not affect disease-specific mortality of study participants. CI: Confidence interval; HR: Hazard ratio; LMR: Lymphocyte-to-monocyte ratio; PLR: Platelet-to-lymphocyte ratio; NLR: Neutrophil-to-lymphocyte ratio; HPR: hemoglobin-to-platelet ratio; RPR: red blood cell distribution width-to-platelet ratio; pPLT_D: Personalized platelet count relative to “at-diagnosis”; pPLT_S: Personalized platelet count relative to “after-surgery”.

**Limitations**
A major limitation of the current research was its retrospective design, which, e.g., prevented testing whether any intervention in the case of an observable CBC metric increase/decrease could change the tumor markers and imaging studies is not questioned, our results suggest that frequent CBC measurements may extend the current routine follow-up arsenal of medical tests. The application of CBC metrics is easy and cost-effective; however, a prospective clinical trial – similar to that of the COLOFOL randomized clinical trial[64] and its retrospective counterpart[65] – is required to properly address its everyday usefulness in routine CRC follow-up. The two aforementioned studies[64,65] have found that there is no connection between CEA/imaging surveillance intensity and overall survival or frequency of tumor recurrence for stages II and III CRC.

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Figure 8 Survival curves for two competing events, stratified by American Joint Committee on Cancer staging[21], in colorectal cancer patients. Solid and dashed lines represent disease-specific death and non-cancer related death, respectively. A: The effect of the stage on patient survival was marginal in the case of personalized platelet count relative to “at-diagnosis” ($pPLT_D$, Stage I vs Stage II: $P = 0.0847$); B: A significant difference was found in personalized platelet count relative to “after-surgery” ($pPLT_S$, Stage I vs Stage II: $P = 0.0314$; Stage I vs Stage III: $P = 0.0594$; Stage I vs Stage IV: $P = 0.0335$). $pPLT_D$: Personalized platelet count relative to “at-diagnosis”; $pPLT_S$: Personalized platelet count relative to “after-surgery”.

CONCLUSION

Summarizing the results of our study, our results strengthened the previous observations that LMR,
NLR, and HPR are good indicators of disease progression, but the usefulness of RPR and PLR is in question as they had only marginal effect on all-cause and disease specific mortality, respectively. We had introduced two additional platelet-related personalized metrics, pPLT_D and pPLT_S and our result suggested that their usage is equivalent to that of LMR, NLR, and HPR. Most abnormal changes in pPLT_D, pPLT_S, LMR, and NLR suggestive of progressive disease are expected within the first 3 years after CRC diagnosis, whereas those of HPR are in the subsequent interval.

Most important message of our results is that the early detection of the described patterns above, as auxiliary indicators accompanying tumor markers and imaging studies, may ultimately bring the attention of the practicing oncologist for further therapy decisions in a timely manner. However, to properly address these questions, a prospective randomized clinical trial is required.

**ARTICLE HIGHLIGHTS**

**Research background**
Abnormal pre- and/or post-operative platelet count, lymphocyte-to-monocyte ratio (LMR), neutrophil-to-lymphocyte ratio (NLR), hemoglobin-to-platelet ratio (HPR), red blood cell count distribution width-to-platelet ratio (RPR), and platelet-to-lymphocyte ratio (PLR) values are associated with shorter overall and progression free survival times of colorectal cancer (CRC) patients. However, only a limited number of former studies have investigated how these parameters change during disease progression.

**Research motivation**
It was hypothesized that platelet count, LMR, NLR, HPR, RPR, and PLR of CRC patients with shorter or longer survival times do change differently.

**Research objectives**
The aim of the study was to identify tendencies within the longitudinal changes of platelet count, LMR, NLR, HPR, RPR, and PLR of CRC patients with different disease outcomes and clinicopathological properties.

**Research methods**
A retrospective observational study was conducted with the inclusion of 835 CRC patients. Platelet counts, LMR, NLR, HPR, RPR, and PLR were recorded as follows: (1) At the time of CRC diagnosis; (2) After primary tumor removal surgery; and (3) Every 6 mo postoperatively. In addition to LMR, NLR, HPR, RPR, and PLR, two newly defined personalized platelet count metrics was also introduced: pPLT_D and pPLT_S, which were defined as the platelet count ratio relative to the one measured at the time of CRC diagnosis and the one measured after tumor removal surgery, respectively.

**Research results**
Although the single time-point measurement of all complete blood count metrics had been associated with a worse survival of CRC patients, only the longitudinal changes of LMR, NLR, HPR, and the personalized platelet metrics showed a significant effect on patient survival. Most abnormal changes were observed in the first 3-year period after the diagnosis of CRC, which coincided with most of the CRC-related deaths. Different patterns in the investigated metrics could have been identified in those patients who died or survived.

**Research conclusions**
pPLT_D, pPLT_S, LMR, NLR, and HPR are good markers for patient survival, and their change to abnormal values are effective markers of disease progression. Therefore, their use in the routine oncology care may alert the practicing oncologist for further therapy decisions in a timely manner.

**Research perspectives**
The current study provided enough evidence for a future prospective study, which should investigate the usefulness of pPLT_D, pPLT_S, LMR, NLR, and HPR in routine oncology care, as potential markers for disease progression.

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FOOTNOTES

Author contributions: Herold Z, Somogyi A, and Dank M built the study design; Herold Z and Herold M were involved in the collection of data; Herold Z performed the statistical analysis of data; Herold Z, Herold M, and Szasz AM interpreted the data; Lohinszky J and Dank M were involved in patient selection; Herold Z prepared the draft of the manuscript; all authors were involved in manuscript editing and reviewing; Herold Z and Dank M received funding; Somogyi A supervised the study; all authors have read and agreed to the published version of the manuscript.

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Informed consent statement: Patient data was retrieved anonymously from the medical database of Semmelweis University in a retrospective manner. A general consent form for academic assessment studies of all admitted patients was signed upon their treatment back in those years. Signed patient informed consent for further research at that time was not required given the anonymized, de-identified data.

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