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Research Article

The role of hematological inflammation markers in predicting survival in metastatic colorectal cancer

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Abstract. Introduction. In the context of multiple systemic treatment options and of a multidisciplinary management of the metastatic colorectal cancer patients, there is a continuous need for identifying accessible, predictive biomarkers, in order to perform an adequate selection of patients for various treatments. Material and method. We performed a retrospective analysis on 189 metastatic colorectal cancer patients treated in the Oncology Institute "Prof. Dr. Ion Chiricuță", Cluj-Napoca, Romania and analyzed the predictive value for survival of hematological inflammation markers before the start of first-line chemotherapy, together with other clinical, pathological and therapeutic features of our colorectal cancer patients. Results. Among the analyzed hematological inflammation markers tested, the COP-NLR score showed a significant predictive value for overall survival. In multivariate analysis, a COP-NLR score of 2 increased the likelihood of death along with the presence of lung and peritoneal metastases, while the surgery of the primary tumor and the surgery or radiofrequency ablation of metastases were associated with a decreased risk of death. Conclusion. COP-NLR is an inflammatory hematological score that showed a predictive value for overall survival in metastatic colorectal cancer prior to the administration of first-line systemic treatment.

Key Words: prediction, hematological markers, COP-NLR, inflammation, colorectal cancer

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Introduction

In the nineteenth century scientists observed that tumors appear at the site of chronic inflammation. This corroborated with the observation that inflammatory cells were present in biopsied samples of tumors, led to the connection between cancer and inflammation. The tumor microenvironment is vast and plays an important role in all stages of carcinogenesis (Mantovani et al 2008). Cancer cells are complex and one of their features is the ability to promote inflammation (Hanahan & Weinberg 2011), which stimulates tumor growth and progression, angiogenesis and metastasis. There is a continuous interplay between the tumor cell and its microenvironment, leading to dynamic interactions that promote and sustain cancer development and progression. Leukocytes, neutrophils, lymphocytes, platelets and acute phase proteins are the hallmarks of an inflammatory microenvironment and their evaluation is affordable and inexpensive. The predictive role of hematological markers for the survival of patients has been studied in various types of neoplasms. Thrombocytosis, neutrophilia, and lymphopenia are associated with an unfavorable prognosis in cancer. There is evidence that an increased level of inflammatory markers is associated with chemoresistance (de Visser et al 2009; Olive et al 2017).

Starting from the currently available data in the literature, the present study has aimed to investigate the role of circulating hematological inflammatory markers in predicting survival of patients with metastatic colorectal cancer (mCRC). The main objective was to evaluate their predictive role for overall survival (OS) and to integrate them in the analyses of other clinical, pathological, therapeutic variables potentially associated with the duration of survival in mCRC patients.

Material and method

This study is a retrospective analysis that initially included a number of 208 patients consecutively diagnosed and treated within the Oncological Institute "Prof. Dr. Ion Chiricuță" Cluj-Napoca between January 2005 and December 2017 with mCRC who met all the inclusion criteria and none of the exclusion ones among those applied and stated below. Due to incomplete information, 20 patients were excluded and 189 patients remained eligible for the final analysis. This study was approved by the Ethics Committee of the Institute of Oncology "Prof. Dr. Ion

Table 1. Inflammatory markers derived from complete blood count

SCORE	SIGNIFICANCE	CALCULATION FORMULA
NLR	neutrophil to lymphocyte ratio	neutrophils ÷ lymphocytes
PLR	platelet to lymphocyte ratio	platelets ÷ lymphocytes
dNLR	NLR- derived ratio	neutrophils ÷ [leukocytes- neutrophils]
PNLR (SII)	systemic inflammatory immune index	platelets x neutrophils ÷ lymphocytes
LMR	lymphocyte to monocyte ratio	lymphocytes ÷ monocytes
COP-NLR	combination of platelet count and neutrophil to lymphocyte ratio	0 neither platelets > 300 x 10^9/L, nor NLR > 3
		1 platelets > 300 x 10^9/L or NLR > 3
		2 platelets > 300 x 10^9/L and NLR > 3

Chiricuță" Cluj-Napoca, No 42/8th December 2015. All data were obtained from the Institutional Cancer Registry.

The inclusion criteria were: age ≥ 18 years; confirmed anatomopathological diagnosis of metastatic colonic or rectal adenocarcinoma, either from the initial diagnosis or after recurrence; K-RAS exon 2 wild-type or all-RAS exon 2,3,4 wild-type status, depending on the national and institutional testing recommendations in effect at the time of treatment for each patient, as predictive factors for response to cetuximab or panitumumab; systemic treatment for metastatic disease performed within the Oncological Institute "Prof. Dr. Ion Chiricuță "Cluj-Napoca; no medical contraindications for the administration of chemotherapy and targeted molecular treatments, as appropriate; available information in terms of clinical, pathological, laboratory characteristics, treatment performed, type of response to treatment, disease progression and date of death. The exclusion criteria were: unknown K-RAS status or K-RAS mutated; patients with uncontrolled comorbidities, ineligible for systemic treatment according to standards; patients with acute inflammatory processes or proven infections before the start of the first line of chemotherapy for metastatic disease or other associated conditions that may alter the values of the parameters in the blood counts; patients with multiple synchronous neoplasms; patients under chronic treatment with anti-inflammatory and/or immunosuppressive drugs.

All parameters that could influence survival under treatment were analyzed. The complete blood counts considered for analysis were collected up to 5 weeks before the start of first line systemic treatment for metastatic disease. The mutational status of K-RAS or all-RAS genes was assessed according to the recommendations in effect at the time of treatment of patients with anti-EGFR agents. Metastases were considered metachronous when they occurred more than 6 months after the initial diagnosis. Tumors having a right colon localization were defined as those located proximal to the splenic flexure, while those with left localization were tumors distal to the splenic flexure, including rectal tumors.

As this was a retrospective study, the therapeutic decisions for the administration of chemotherapy and targeted molecular treatments belonged to the treating physicians, in accordance with the institutional and international therapeutic guidelines at the time of treatment. Chemotherapy protocols consisted of fluoropyrimidines (5-fluorouracil (5-FU), capecitabine) alone or in combination with irinotecan (FOLFIRI or XELIRI) or oxaliplatin (FOLFOX or XELOX). The combinations with 5-FU were administered at 2 weeks, those with capecitabine at 3 weeks, according to standard treatment protocols. Where administered, targeted molecular treatment (cetuximab, panitumumab, bevacizumab) was associated with the first line mCRC chemotherapy protocol.

Statistical analysis

For the statistical analysis, OS was defined as the interval from the first administration of chemotherapy for metastatic disease to death, if it occurred by 30.06.2019. Regarding the prognostic hematological indices and scores based on inflammation, they were defined as shown in Table 1, in accordance with other investigators (Wu et al 2017; Ishizuka et al 2013; Passardi et al 2016). The classification of the COP-NLR score was taken from existing and widely used data in the literature, as shown in Table 1 (Olive et al 2017).

For the parameters or inflammatory indices with a statistically significant predictive value for survival in univariate analysis, cut-offs were calculated and applied to allow stratification of patients. The variables that maintained, after the application of these cut-offs a significant or close to significance predictive value were included in the multivariate analysis of survival. Along with the hematological markers, tumor and disease characteristics, laboratory tests, patient-related characteristics and treatment variables were also included in the univariate analysis of OS.

The statistical analysis was performed using the program "MedCalc Statistical Software" version 19.1.5 (MedCalc Software bv, Ostend, Belgium; https://www.medcalc.org; 2020). Quantitative data were described by medians and 25-75 percentiles, while nominal data were expressed by frequency and percentages. Comparisons between groups were performed by the Man-Whitney test or the hi-square test, as appropriate. The univariate analysis of survival was performed by the Kaplan-Meier method. Multivariate survival analysis was performed according to Cox regression. The value of $p < 0.05$ was considered to be of statistical significance.

Results

Patients` characteristics and administered treatments are presented in Table 2. Of all the patients included in the study, 77.80% died by the time the study was completed. The median age at the diagnosis of metastatic disease was of 58 years. In 81% of the cases, tumors were located on the left colon and the majority of patients (82%) had only one metastatic site involved at the diagnosis, most commonly liver (67.70%). All patients were K-RAS wild-type, while the complete all-RAS status was

Table 2. Patients characteristics

PATIENT CHARACTERISTICS	No OF PATIENTS	%
Age (years)		
<58	99	52.38%
≥58	90	47.62%
Sex		
Male	107	56.60%
Female	82	43.40%
Body mass index		
<25	87	46.00%
25-30	67	35.40%
>30	35	18.50%
Degree of tumor differentiation		
G1	23	12.90%
G2	117	65.70%
G3	38	21.30%
Primary tumor location		
Right	36	19.00%
Left	153	81.00%
Number of metastatic sites		
<2	155	82%
≥2	34	18%
Liver metastases at diagnosis	128	67.70%
Lung metastases at diagnosis	41	21.70%
Peritoneal metastases at diagnosis	35	18.50%
Ovarian metastases at diagnosis	9	4.80%
Bone metastases at diagnosis	5	2.60%
Pleural collection at diagnosis	2	1.10%
Loco-regional recurrence without metastases	7	3.70%
Type of metastases		
Metachronous	62	32.80%
Synchronous	127	67.20%
RAS mutational status		
all-RAS wild type	126	66.70%
K-RAS wild-type	189	100%
Surgery of the primary tumor	102	80.30%
Surgery/ ablation of metastases	40	21.20%
5-FU / Capecitabine chemotherapy in first line	6	3.20%
Irinotecan-based first line chemotherapy	37	19.60%
Oxaliplatin-based first line chemotherapy	147	77.80%
Bevacizumab in first line	54	28.60%
Cetuximab/Panitumumab in first line	94	49.70%
Death		
Yes	147	77.80%
COP-NLR		
0	60	31.70%
1	85	45%
2	44	23.30%

Table 3. Patient characteristics based on complete blood counts and derived inflammatory scores

PARAMETER	MEDIAN (25,75 PERCENTILES)
Lymphocytes	1.88 x 10^9L^{-1}(1.42, 2.30)
Monocytes	0.65 x 10^9L^{-1} (0.5, 0.84)
Neutrophils	4.75 x 10^9L^{-1}(3.82, 6.18)
Leukocytes	7.54 x 10^9L^{-1}(6.31, 9.38)
Platelets	294 x 10^9L^{-1} (230.5, 384)
Mean platelet volume (MPV)	9.7fL (9.3, 10.4)
NLR	2.72 (1.78, 3.81)
dNLR	1.80 (1.20, 2.30)
PLR	168.70 (113.04, 229.13)
LMR	2.82 (2.10, 3.62)
PNLR	774.64 (516.01, 1319.79)

Table 4. Statistically significant variables in the univariate analysis of OS

VARIABLE		DECEASED (N=147)	SURVIVORS (N=42)	HR* (95% CI)	P
Number of metastatic sites	<2	28(19%)	6(14.3%)	1.765(1.162-2.679)	0.008
	>=2	119(81%)	36(85.7%)		
Lung metastases	Yes	37 (25.2%)	4 (9.5%)	1.882 (1.287- 2.752)	0.001
	No	110 (74.8%)	38 (90.5%)		
Peritoneal metastases	Yes	29 (19.7%)	6 (14.3%)	1.610 (1.070 - 2.422)	0.022
	No	118 (80.3%)	36 (85.7%)		
Primary tumor surgery (synchronous tumors)	Yes	78(77.2%)	24(92.3%)	0.470 (0.292-0.758)	0.002
	No	23 (22.8%)	2 (7.7%)		
Metastases resection / ablation	Yes	29 (19.7%)	11 (26.2%)	0.526 (0.337 – 0.799)	0.003
	No	118 (80.3)	31 (73.8)		
COP-NLR	0	40 (27.2%)	20 (47.6%)		
	1	69 (46.9%)	16 (38.1%)	1.311 (0.887-1.937)	0.174
	2	38 (25.9%)	6 (14.3%)	1.645 (1.049-2.579)	0.03

Table 5. Univariate analysis of OS in terms of scores from complete blood counts

VARIABLE	DECEASED (N=147) median (percentile 25-75)	SURVIVORS (N=42) median (percentile 25-75)	P
Platelets	315 x 10^9L^{-1}(241, 403)	246.5 x 10^9L^{-1}(204, 325.5)	0.005
MPV	9.6fL (9.3, 10.4)	10fL (9.5, 10.55)	0.032
PLR	180.66 (118.90, 243.36)	126.08 (101.44, 205.98)	0.012
PNLR	873.33 (567.6, 1376.64)	601.98 (423.98, 1175.98)	0.043

evaluated and proved to be wild-type in 66.70%. 86.20% of the patient had surgery for the primary tumor, which was performed in all cases of synchronous disease and in 80.30% of metachronous disease. The resection or radiofrequency ablation of metastases was performed in 20% of all patients.

The medians values of the parameters and scores derived from complete blood count are given in Table 3.

The median OS was of 26.20 months. Table 4 presents the statistically significant results of the univariate survival analysis. The patients with lung, peritoneal and more than two sites of metastases had a significantly higher probability of death. The patients for whom the surgery of the primary tumor was performed and the patients that had the resection/ablation of metastases had a significantly better survival. Also, the patients having a COP-NLR score of 2 had a higher probability of death. There were no other statistically significant differences regarding OS with respect to other variables studied (age, sex, body mass index, degree of differentiation, primary tumor location, other sites of metastases except the previously mentioned, locoregional recurrence without metastases, type of metastases, all-RAS wild-type, first line bevacizumab/anti-EGFR, first-line based on irinotecan/oxaliplatin/5-FU/capecitabine).

Table 5 presents the statistically significant results of predictive value of hematological markers for OS in univariate analysis. There were no statistically significant differences for survival with respect to other variables studied (lymphocytes, monocytes, neutrophils, leukocytes, NLR, dNLR, LMR).

Table 6. Cut-off values for inflammatory parameters

VARIABLE		DECEASED (N=147)	SURVIVORS (N=42)	HR* (95% CI)	P
Platelets cut-off	<249	20 (27.2%)	22 (52.4%)	1.391 (0.965-2.005)	0.077
	>249	107 (72.8%)	20 (47.6%)		
MPV cut-off	>9.8	58 (39.5%)	25 (59.5%)	1.208 (0.886-1.685)	0.267
	<9.8	89 (60.5%)	17 (40.5%)		
PLR cut- off	<150	52 (35.4%)	25 (59.5%)	1.202 (0.856-1.688)	0.287
	>150	95 (64.6%)	17 (40.5%)		
PNLR cut-off	<697.5	55 (37.3%)	26 (61.9%)	1.393 (1-1.952)	0.05
	>697.5	92 (62.6%)	16 (38.1%)		

Table 7. The multivariate survival analysis

VARIABLE	P	HR	95.0% CI for HR	
			Min	Max
All-ras wild-type status	0.158	0.78	0.553	1.101
Primary tumor surgery	0.017	0.559	0.347	0.902
Metastases resection / ablation	0.031	0.608	0.387	0.956
Lung metastases	< 0.001	2.28	1.51	3.443
Peritoneal metastases	0.005	1.839	1.202	2.814
PNLR cutoff	0.695	0.919	0.604	1.399
COPNLR (0)	0.084			
COPNLR (1)	0.05	1.551	1.002	2.429
COPNLR (2)	0.036	1.846	1.041	3.274

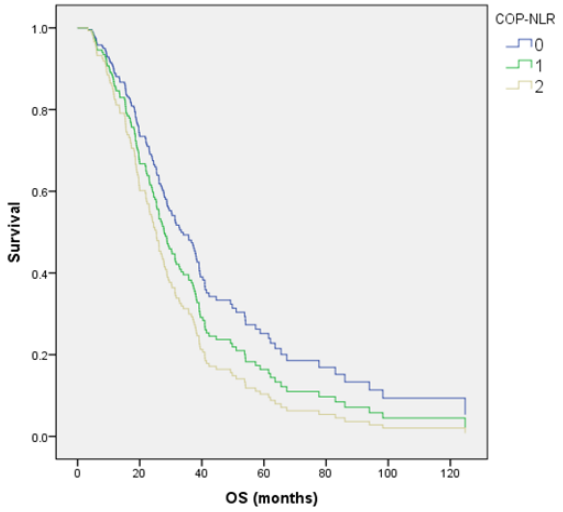

Figure 1. Overall survival according to COP-NLR

For the hematological parameters that showed a significant impact on survival in univariate analyses, we calculated cut-off values, as seen in Table 6. After applying these cut-offs, only PNLR > 697.5 was marginally significantly (p=0.05), associated in univariate analyses with a higher probability of death. The multivariate analyses of survival, as shown in Table 7 included variables from the univariate analysis that reached or approached the threshold of statistical significance. The surgery of the primary tumor and the resection/ablation of metastases were independently and significantly associated with a better OS, while the presence of lung and peritoneal metastases, as well as a COP-NLR of 2 were independently associated with a worse OS.

Discussion

Cancer therapy implies a multidisciplinary approach. The OS of mCRC patients reaches today approximately 30 months when applying all feasible treatment options in various sequences (chemotherapy, targeted treatments, local treatments for the primary tumor, resection/ablation of metastases). The patients included in our study were treated during a 13-year period of time, starting with the year 2005. At the time, doctors were facing limited therapeutic resources as well as unsatisfactory predictive biomarkers for the response to therapies and survival, thus deficient patient selection criteria. The median OS for our patients was 26 months, close to what is reported today.

Each of the hematological inflammatory indices analyzed in this study contributes to carcinogenesis, tumor progression and/or the immune response (Grivennikov et al 2010; Neal et al 2015). In our study, an increased platelet count was associated with a lower OS, while the values above the calculated threshold of 249*103 /μL (AUC=0.642) were also associated with a shorter survival, without reaching, instead, the statistical significance. These results are consistent with a meta-analysis of 9 retrospective studies that included 3413 patients with CRC, regardless the stage (including completely resected stage IV) for which surgery was performed with negative resection margins. In this meta-analysis, the OS was lower in the patients with increased pre-therapeutic platelet count versus normal counts and increased platelet count was also associated with a shorter PFS. (Rao et al 2018).

MPV is a surrogate marker for platelet activation and there are studies that have shown its association with the presence of malignancies and prognosis of certain neoplasms. Another team

(Li et al, 2017)included in their study 509 CRC patients, among which 266 were stage III-IV and they were able to show that an elevated MPV (>8.6 fL) was significantly associated with a higher grade of tumor differentiation, but also with a poorer OS, both in univariate and multivariate analyses. Our findings are in line with theirs, but also with other researchers' results (Chang et al, 2019), confirming the association between an increased MPV and a lower OS ($p = 0.032$) in the univariate analyses, although the values above the calculated threshold of 9.8 fL (AUC = 0.608), did not show an association statistically significant with a lower OS.

We found that PLR and PNLR scores were significantly associated with the OS in univariate analyses, but as with the above discussed parameters (platelet count, MPV), they did not reach statistical significance after applying the calculated cut-off value, although PNLR reached the limit of significance ($p=0.05$). Their role was also investigated by other researchers (Chen et al 2017) in a study that included 1183 CRC radically operated patients, regardless the stage and showed that both OS and disease-free survival were significantly better in patients with low NLR, PLR and PNLR and the latter also had a discriminatory value for the TNM stage. Another analyses (Passardi et al 2016) on 289 mCRC patients included in the ITACa prospective clinical trial, performed on complete blood counts collected prior the administration of first-line chemotherapy plus bevacizumab showed that both OS and progression-free survival (PFS) were significantly higher in the patients having a low PNLR, NLR and PLR.

COP-NLR is an inflammatory score, less studied in mCRC compared to other malignancies. As our results show, it is the only inflammatory score which maintained the statistically significant predictive value for OS in multivariate analyses, along with other clinical-pathological and therapeutic characteristics (Table 4, Table 7). We did not identify studies to analyze the predictive role of COP-NLR for survival in mCRC prior to the administration of first-line chemotherapy. A research team (Neal et al 2015) studied the prognostic value of six inflammatory markers (NLR, dNLR, PLR, LMR, COP-NLR and nutritional prognostic index) on 302 mCRC patients with resectable liver metastases and showed that only a high NLR was significantly associated with better survival after metastases resection. We identified, however, a study in metastatic gastric cancer (Wang et al 2017) that included 273 patients and showed that a pretreatment COP-NLR score of 0 was associated with better response rates and overall survival than patients with COP-NLR 1 and 2. In the final model, the surgery of primary tumor and metastases resection/ablation were independently significantly associated with better overall survival, while the presence of pulmonary, peritoneal metastases and a COPNLR index of 2 independently determined a poor prognosis.

The main limitations of our study are its retrospective nature, the heterogeneity of treatments administered without a pre-planned sequence of therapies; due to the limited number of patients, some other variables with known impact on patients` survival (e.g. all-RAS wild-type status)did not show a significant association with the OS.

Conclusions

The present study showed the predictive value for OS of COP-NLR, with statistical significance not only in univariate analysis, but also in multivariate analysis. To our knowledge, this is the first study that shows a correlation between the COP-NLR score and the OS in mCRC patients prior to the administration of first line chemotherapy. A COP-NLR score of 2 increased the likelihood of death along with other factors already established in mCRC, such as the presence of lung and peritoneal metastases, while surgery or radiofrequency ablation of metastases were associated with a decreased risk of death. Our results, along with other existing research could validate for the future inexpensive predictive markers for cancer therapy and survival.

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