Clinical Value of Hematological Biomarkers in Uterine Cervical Cancer

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Rezumat

Rolul clinic al biomarkerilor hematologici în cancerul de col uterin

Anumite combinații ale componentelor hematologice din cadrul răspunsului inflamator sistemic, în mod special raportul neutrofile/ limfocite (NLR) sau multiplicarea monocitelor cu neutrofilele (MNM) au fost demonstrate a avea o valoare prognostică într-o varietate de cancere.

Material și metode: Studiu retrospectiv ce a inclus paciente diagnosticate cu neoplasm de col uterin care au beneficiat de terapie multimodală, în care s-au urmărit corelațiile dintre factorii de prognostic și valorile NLR și MNM.

Rezultate: Valoarea NLR se corelează cu prezența ganglionilor invadați ($p=0.016$), invazia în parametre ($p=0.035$), invazia limfovaculară ($p=0.0151$) și cu mărimea tumorii ($p=0.0017$). Rezultatele arată că valoarea MNM este semnificativ mai mică pentru stadiile preoperatorii I și II ($p=0.02$). Analiza corelațională a demonstrat că există o asociere semnificativă între MNM și numărul ganglionilor invadați (0.020), invazia în parametre (0.00010), invazia limfovaculară care influențează semnificativ valoarea MNM ($p=0.0018$), mărimea tumorii peste 4 cm. În cazul pacientelor cu răspuns complet la neoadjuvanță, markerii hematologi de tipul NLR și MNM au

valori scăzute comparativ cu pacientele cu răspuns parțial sau non-responderi.

Discuții: Odată cu apariția studiilor care au pus în evidență rolul prognostic al biomarkerilor hematologici, o altă imagine se poate construi cu ajutorul acestora în patologia cervicală neoplazică.

Cuvinte cheie: cancer de col uterin, raport neutrofile/limfocite, multiplicare monocite cu neutrofile

Abstract

Certain combinations of the hematological components, specifically, neutrophils and lymphocytes, named neutrophil to lymphocyte ratio (NLR) or multiplication of neutrophil and monocyte (MNM) have been shown to have prognostic value in a variety of cancers.

Material and methods: Retrospective study which included 133 patients with uterine cervical cancer with or without neoadjuvant therapy based on prognostic factors and correlations between NLR and MNM values, markers that were analyzed as continuous variables. This study aimed to establish the critical value of hematological markers.

Results: NLR is significantly lower for preoperative stages I and II ($p = 0.0004$). There is a significant association between NLR and lymph node metastasis ($p = 0.016$), parametrial invasion ($p = 0.035$), lymphovascular space invasion ($p = 0.0151$) and tumor size ($p = 0.0017$). Correlational analysis showed that there is a significant association between MNM and lymph node metastasis ($p = 0.020$), parametrial invasion

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($p = 0.00010$), lymphovascular space invasion materially affecting the value MNM ($p = 0.0018$), tumor size more than 4 cm ($p = 0.0314$). NLR and MNM were significantly lower in patients with complete response to neoadjuvant treatment. *Discussion:* The results of this study outlines the importance of hematological panel and parameters that can be easily used at no extra cost to establish further evolution of patients to treatment.

Key words: uterine cervical cancer, neutrophil to lymphocyte ratio, multiplication of neutrophil and monocyte

Background

Cancer incidence is increasing worldwide. Although it is clear that the development of cancer has a genetic basis, recent studies have shown that the host inflammatory response plays an important role in carcinogenesis and progression of the disease (1,2). Identification of prognostic factors for tumor progression is an important part of cancer research because it allows stratification and selection of patients for an adequate treatment. It is well known that the clinical results and evolution are determined not only by the basic characteristic of the tumor, but also by the host response to neoplasia progression (3,4). Certain combinations of hematological components of the systemic inflammatory response, specifically, neutrophils and lymphocytes, named neutrophil to lymphocyte ratio (NLR) or multiplication of neutrophil and monocyte (MNM) have been shown to have prognostic value in a variety of cancers. Oncogenic transformation induce an inflammatory micro-environment that promotes tumor growth and inflammation

promotes angiogenesis and metastasis. Recently, several inflammatory markers or certain cells of the blood system were studied in relation to cancer of the uterine cervical cancer. The aim of our study was to assess the role of hematological markers in uterine cervical cancer, regard to their association with clinico-pathological features. Study looked at correlations between prognostic factors and NLR and MNM values, markers that were analyzed as continuous variables. This study also aimed to establish the critical value of hematological markers (cut-off value).

Material and Methods

Retrospective study based on prospectively collected data conducted in Ist Surgical Clinic, Regional Institute of Oncology, Iași. We included in the study 133 patients diagnosed with cervical cancer from May 2012 to November 2013 which benefited from neoadjuvant chemo-radiation therapy, and patients who were proposed for surgical treatment of first choice (Table 1). NLR (neutrophil to lymphocyte ratio) was defined as the ratio of the absolute neutrophil and absolute-lymphocyte value (normal range = 2000-8000 neutrophils / microliter; normal range = 1000-4000 lymphocytes / microliter). MNM (multiplication of neutrophil and monocyte) was calculated as: (absolute value of neutrophil x absolute value of monocytes) / 10.000 (normal monocytes = 300-1000 / microliter).

Statistic method

Data were analyzed using SPSS V.21 software. (IBM). The statistical study addressed two issues: descriptive statistics and analytical statistics. Differences between the parameters analyzed were tested using ANOVA (analysis of variance -

Table 1. Baseline patient characteristics (n=133)

	Treatment			Total
	Surgery n=65	Neoadjuvant treatment+surgery n=68	p (95%CI)	
Age‡	53.8±11.4	55.5±10.2	0.386445	54.7±10.8
≤ 48 years (%)*	18 (51.43%)	17 (48.57%)	0.72449	35 (26.32%)
> 48 years (%)	47 (47.96%)	51 (52.04%)		98 (73.68%)
FIGO stage				
Incipient (IA-IIA)	56 (82.35%)	12 (17.65%)	< <0.01‡	68 (51.13%)
Locally advanced (IIB-IVB)	9 (13.85%)	56 (86.15%)		65 (48.87%)
Hysterectomy / trachelectomy				
Trachelectomy	1 (25)	3 (75%)	0.00051‡	4 (3.01%)
Hysterectomy type A	20 (80%)	5 (20%)		25 (18.8%)
Hysterectomy type B	39 (48.15%)	42 (51.85%)		81 (60.9%)
Hysterectomy type C	4 (18.18%)	18 (81.82%)		22 (16.54%)
Hysterectomy type D	1 (100%)	0 (0%)		1 (0.75%)

‡ Continuous variables were shown as mean ± standard deviation or median (min-max)

* Categorical variables were shown as number (%)

‡p<0.05 indicates statistical significance

Table 2. Comparative analysis of hematological markers according to clinico- pathological factors

	NLR			MNM		
	mean $\pm$ SD	Min	Max	mean $\pm$ SD	Min	Max
FIGO stage		p=0.0004*		p=0.02*		
IA	3.3 $\pm$ 2.5	0.7	10.7	170.4 $\pm$ 82.9	57.2	358.4
IB	3.4 $\pm$ 2.1	0.9	10.3	228.8 $\pm$ 224.2	40.0	845.5
IIA	4.7 $\pm$ 2.8	1.3	9.2	249.0 $\pm$ 66.5	57.6	307.8
IIB	5.5 $\pm$ 4.5	1.3	20.6	258.5 $\pm$ 225	22.4	921.2
IIIA	7.4 $\pm$ 7.3	2.3	12.6	321.8 $\pm$ 207.5	175.0	468.5
IIIB	7.6 $\pm$ 1.7	1.2	9.2	359.9 $\pm$ 105.7	47.9	384.1
IVA	8.3 $\pm$ 7.9	3.5	24.7	346.8 $\pm$ 306.9	62.5	874.2
IVB	9.1	9.1	9.1	402.6	402.6	402.6
Lymph node metastasis	r=0.3084	p=0.016*	r=0.42009	p=0.020*		
Parametrial invasion	p=0.035*		p=0.0001*			
absent	4.18 $\pm$ 2.9	0.70	20.57	196.8 $\pm$ 145.9	22.4	845.5
present	5.70 $\pm$ 5.56	0.85	24.66	366.6 $\pm$ 255.2	40.0	921.2
Lympho-vascular space invasion (LVSI)	p=0.0151*		p=0.0018*			
absent	4.22 $\pm$ 2.9	0.70	20.57	191.0 $\pm$ 124.7	568.4	98.2
present	5.21 $\pm$ 4.9	0.85	24.66	332.1 $\pm$ 259.5	921.2	144.7
Tumor size	p=0.0017*		p=0.031*			
<4 cm	3.45 $\pm$ 2.36	0.70	10.78	185.3 $\pm$ 130.6	45.1	799.7
>4cm	5.32 $\pm$ 4.32	0.85	24.66	274.6 $\pm$ 218.4	22.4	921.2

* p<0.05 indicates statistical significance

Analysis Of Variance) used only for normal distribution of frequency. Otherwise it was used with good results non-parametric Kruskal-Wallis test, based on analysis of ranks "assigned". Chi-square test was applied to nonparametric analysis. Yates correction was applied when the frequency of the event was less than 5. The level of significance (significance level, p-value) was considered 0.05 (5%), which is sufficiently accurate, the probability (confidence level - confidence intervals) of 95% showing that the decision is fair.

Results

NLR value is significantly lower for stages I and II FIGO and higher in locally advanced stages ($H_{Kruskal-Wallis} = 26.5$, $p = 0.0004$). Correlational analysis showed that there is a significant association between NLR and lymph node metastasis ($r = 0.308$, $p = 0.016$, 95% CI). For patients with parametrial invasion, NLR was significantly higher ($H_{Kruskal-Wallis} = 4.3$, $p = 0.035$). NLR value was significantly influenced by lymphovascular space invasion ($F = 9.079$, $p = 0.0151$). For patients with tumors larger than 4 cm, the average NLR (5.32 ± 4.32 DS) was significantly higher ($H_{Kruskal-Wallis} = 9.83$, $p = 0.0017$) compared to NLR value to patients with tumors less than 4 cm (2.36 DS ± 3.45) (Table 2).

Results of multiple regression analysis showed that preoperative status ($\beta_{standardized} = 0.515$, $p < 0.01$) and parametrial invasion ($\beta_{standardized} = 0.378$, $p = 0.031$) significantly correlated with NLR values, standardized beta coefficient having significant value. Thus we can consider values NLR significant predictors for preoperative stage and parametrial invasion (Table 3).

MNM

MNM counts are significantly lower in preoperative

stages I and II ($F = 22.48$, $p = 0.02$) and increase significantly in stages IVA and IVB. Correlational analysis showed that in the study group there is a significant association between MNM and the lymph node metastasis ($r = 0.42$, $p = 0.02$, 95% CI). MNM counts showed significant changes according to the degree of parametrial invasion ($p = 0.0001$, 95% CI). In patients with lymphovascular space invasion, mean MNM was significantly higher ($p = 0.0018$) than in patients without lymphovascular space invasion. The analysis results demonstrate that significantly higher MNM counts ($H_{Kruskal-Wallis} = 4.63$, $p = 0.031$, 95% CI) are recorded in tumors larger than 4 cm compared to tumors less than 4 cm in size, mean MNM 274.6 ± 218.4 DS and 185.3 ± 130.6 DS, respectively (Table 2).

Multivariate analysis (MNM)

Multivariate analysis demonstrated that parametrial invasion ($\beta_{standardized} = 0.469$, $p = 0.007$) and lymphovascular invasion ($\beta_{standardized} = 0.39$, $p = 0.041$) significantly correlated with MNM value, the standardized beta coefficient having a significant value. This result indicated that MNM value has a great predictive power for parametrial and lymphovascular space invasion (Table 4).

The analysis demonstrated that in patients with complete response to neoadjuvant therapy the hematological markers NLR and MNM had low values compared to partially responding patients or patients classified as non-responders. NLR value was significantly lower (4.57 ± 1.97 DS) in patients with complete response compared to non-responders (8.86 ± 5.33 DS). MNM value was lower in patients with complete response (153.14 ± 117.85 DS) compared with patients classified as non-responders (245.84 ± 184.93 DS) (Table 5).

Table 3. Multiple regression analysis - NLR
Coefficients^a

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B		Collinearity Statistics	
	B	Std. Error				Lower Bound	Upper Bound	Tolerance	VIF
1 (constant)	2.690	1.432		1.878	.063	-.144	5.524		
Lymph node metastasis	.268	.193	.125	1.386	.168	-.114	.650	.832	1.202
FIGO stage	.556	.201	.274	2.759	.007*	.157	.955	.693	1.443
Parametrial invasion	.872	.947	.100	.921	.359	-1.003	2.747	.579	1.726
LVSI	.274	.814	.035	.337	.736	-1.336	1.885	.648	1.542
Tumor size	.368	.789	.048	.466	.642	-1.195	1.930	.629	1.591
2 (constant)	2.340	.901		2.598	.010	.557	4.122		
Lymph node metastasis	.279	.190	.131	1.471	.144	-.096	.654	.851	1.175
FIGO stage	.554	.199	.272	2.780	.006*	.160	.947	.700	1.428
Parametrial invasion	1.030	.824	.118	1.251	.213	-.600	2.661	.756	1.324
Tumor size	.379	.783	.050	.484	.629	-1.170	1.929	.630	1.587
3 (constant)	2.072	.654		3.169	.002	.778	3.365		
Lymph node metastasis	.276	.188	.129	1.468	.144	-.096	.648	.855	1.169
FIGO stage	.611	.167	.301	3.664	.000*	.281	.941	.986	1.014
Parametrial invasion	1.145	.766	.131	1.495	.137	-.370	2.659	.865	1.157
4 (constant)	2.047	.656		3.119	.002	.749	3.346		
FIGO stage	.639	.166	.515	7.844	.000*	.310	.968	1.000	1.000
Parametrial invasion	1.558	.715	.378	4.179	.031*	.144	2.973	1.000	1.000

* p<0.05 indicates statistical significance

Table 4. Multiple regression analysis - MNM
Coefficients^a

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B		Collinearity Statistics	
	B	Std. Error				Lower Bound	Upper Bound	Tolerance	VIF
1 (Constant)	133.54	45.739		2.920	.004	43.041	224.058		
FIGO stage	1.79	8.431	.017	.213	.832	-14.889	18.479	.974	1.027
Parametrial invasion	110.28	45.090	.247	2.446	.016*	21.057	199.507	.629	1.589
LVSI	74.44	40.281	.183	1.848	.067	-5.263	154.156	.651	1.537
Lymph node metastasis	4.270	9.574	.039	.446	.656	-14.675	23.215	.832	1.201
2 (constant)	140.09	33.741		4.152	.000	73.332	206.857		
Parametrial invasion	110.25	44.921	.247	2.454	.015	21.372	199.142	.629	1.589
LVSI	73.81	40.021	.182	1.844	.067	-5.376	153.003	.654	1.529
Lymph node metastasis	4.53	9.456	.042	.480	.632	-14.172	23.247	.847	1.181
3 (constant)	140.02	33.640		4.163	.000	73.470	206.584		
Parametrial invasion	115.20	43.592	.258	2.643	.009	28.958	201.451	.664	1.506
LVSI	76.52	39.503	.189	1.937	.055	-1.634	154.680	.667	1.498
4 (constant)	182.87	18.891		9.681	.000	145.503	220.250		
Parametrial invasion	120.25	43.694	.469	2.752	.007*	33.812	206.698	.668	1.497
LVSI	78.114	39.695	.392	1.968	.041*	10.318	86.646	.668	1.497

* p<0.05 indicates statistical significance

Table 5. Hematological markers vs. response to neoadjuvant treatment

Hematological markers	Response to neoadjuvant treatment (n=68)			p (95%CI)
	Compleat response (mean±DS)	Partial response (mean±DS)	Non-responders (mean±DS)	
NLR	4.57±1.97	4.95±3.86	8.86±5.33	0.000001
MNM	153.14±117.85	195.43±122.20	245.84±184.93	0.008369

Role of hematological markers – predictive factors in cervical cancer

The results indicated an AUC value = 0.6898 ($p = 0.0001686$, 95% CI: 0.59-0.78 $\rightarrow$ AUC), which demonstrates that NLR has a good discriminatory power for the early or locally advanced stages (Table 6). The calculated NLR cut-off value for the prediction of preoperative stage was 2.7, with a corresponding sensitivity of 83.08% and specificity of 55.2%, and a NLR cut-off value over 1.95 was associated with a high likelihood of tumors larger than 4 cm (Table 7).

It has been demonstrated that a MNM cut-off value over 191 is associated with an increased risk of positive nodes ($Se = 76.67\%$, $Sp = 62.14\%$) (Table 8). As to parametrial invasion,

the results showed an AUC value = 0.72 ($p < 0.0001$, 95% CI: AUC $\rightarrow$ 0.62-0.83), which demonstrates a good discriminatory power of MNM values (Table 9), a MNM cut-off value higher than 145 being associated with significantly increased likelihood of parametrial invasion ($Se = 87.5\%$, $Sp = 47.19\%$). A MNM cut-off value over 139 is associated with an increased risk of lymphovascular space invasion (AUC = 0.66 ($p = 0.0018$, 95% CI: AUC $\rightarrow$ 0.56–0.76), which demonstrates a good discriminatory power of MNM values for lymphovascular space invasion. MNM values also have a significant predictive power of tumor size (AUC=0.6098, $p=0.03140$, 95%CI: AUC $\rightarrow$ 0.51–0.70), the calculated MNM values above the cutoff threshold of 204 indicating a high probability of a tumor larger than 4 cm (Table 8).

Table 6. Estimated parameters in ROC curve analysis

Test Result Variable(s)NLR	Area Under the Curve				
	Area Under the Curve (AUC)	Std. Error	Asymptotic Sig. ^b (p)	Asymptotic 95% Confidence Interval Lower Bound	Upper Bound
FIGO stage	0.6898	0.04664	0.0001686	0.5984	0.7812
Lymph node invasion	0.5251	0.05879	0.6765	0.4098	0.6403
Parametrial invasion	0.4392	0.06158	0.699	0.3185	0.5599
LVSI	0.4593	0.05599	0.554	0.3495	0.5690
Tumor size	0.6432	0.05051	0.004992	0.5442	0.7422

b. Null hypothesis: true area = 0.5

Table 7. Optimal values

OPTIMAL VALUES NLR	FIGO stage	LN metastasis	Parametrial invasion	LVSI	Tumor size
Cutoff	2.7090	1.7310	1.6120	1.507	1.9530
Se - Sensibility	83.08%	93.33%	90.63%	93.18%	93.59%
Sp - Specificity	55.22%	19.42%	13.86%	12.36%	36.36%

Table 8. Estimated parameters in ROC curve analysis

Test Result Variable(s) MNM	Area Under the Curve				
	Area Under the Curve (AUC)	Std. Error	Asymptotic Sig. ^b (p)	Asymptotic 95% Confidence Interval Lower Bound	Upper Bound
FIGO stage	0.4554	0.05113	0.625	0.3552	0.5556
Lymph node invasion	0.6579	0.05952	0.008611	0.5413	0.7746
Parametrial invasion	0.7288	0.05177	< 0.0001	0.6273	0.8303
LVSI	0.6666	0.05083	0.001807	0.5670	0.7662
Tumor size	0.6098	0.04863	0.03140	0.5145	0.7051

b. Null hypothesis: true area = 0.5

Table 9. Optimal values

OPTIMAL VALUES MNM	FIGO stage	LN metastasis	Parametrial invasion	LVSI	Tumor size
Cutoff	327	191.5	144.7	138.8000	204.2
Se - Sensibility	26.15%	76.67%	87.5%	79.55%	52.56%
Sp - Specificity	83.82%	62.14%	50.5%	47.19%	72.73%

Discussions

Prognostic factors such as tumor size, positive lymph nodes, lymphovascular space invasion, and histological type are routinely used to predict the outcome of patients with cervical cancer. These parameters are generally useful, although sometimes are not sufficient to predict optimally the individual prognosis. Therefore, the identification of the biological mechanisms which contribute to tumor progression and, moreover, of some prognostic factors able to assess the individual risk is essential (5).

Several studies investigated the relationship between NLR and survival and response to chemotherapy in cancer patients. A study by Lee et al. on a sample of 1061 patients diagnosed with stage IB-IV cervical cancer reported that a higher NLR value (cut-off ≥ 1.9) was recorded in younger patients with more advanced-stage disease. Univariate analysis revealed that age, NLR value, clinical stage and histologic type have prognostic significance for survival. The authors concluded that pretreatment NLR can be an effective and low-cost biomarker useful to stratify patients with cervical cancer at high risk of recurrence and death (6). The results of the present study are in agreement with the data reported by Mizunuma, namely that NLR value is lower in patients with a good response to radiotherapy or concurrent radiochemotherapy (7). In a study that included vulvar cancer patients, Ertas et al. reported that the mean neutrophil, lymphocyte, and platelet counts were higher in the group of patients with positive lymph nodes compared to node-negative patients ($p < 0.001$, $p = 0.001$). The authors concluded that in vulvar cancer NLR and PLR are directly associated with positive lymph node status and that they can be used in a simple, effective way and are easy to calculate (8). Chiang et al. showed that high NLR in patients with colorectal cancer is associated with a tumor size greater than 5 cm and a more advanced stage (9). The results of the present study show that NLR value is significantly lower in the preoperative stages I and II ($p = 0.0004$). According to the data in the literature, the correlational analysis of the study group revealed a significant association between NLR and the presence of positive nodes. NLR is significantly correlated with parametrial invasion, lymphovascular space invasion and the presence of tumors larger than 4 cm.

The relationship between NLR and clinical-pathological characteristics was studied in hepatocellular carcinoma and the results showed that high values of this hematologic biomarker (cut-off > 2.31) were significantly correlated with tumor size (mean > 5 cm, $p < .001$), clinical TNM stage ($p < .001$) and distant metastasis ($p = .005$) (10). Another study analyzing this biomarker in relation to clinical-pathological parameters was conducted by Viersat et al. in a group of patients with urothelial carcinoma of the bladder. The results show that patients with $NLR \geq 2.7$ are older ($p = 0.0001$) and male ($p = 0.009$), and have higher neutrophil count ($p < 0.0001$) and lower lymphocyte count ($p < 0.0001$). Histopathologically, this group of patients have larger tumors (3.7 vs. 2.6, $p < 0.0001$), higher N stage ($p = 0.002$) and a higher number of positive lymph nodes ($p = 0.001$) (11). In a study by Kim et al. the leukocyte

count, including the monocyte and neutrophil counts, was significantly higher in patients with endometrial cancer as compared to a group of patients without this disease. Moreover, neutrophil count, MNM and CA125 were higher in advanced stages ($p = 0.033$, 0.016 , and 0.041 , respectively). The authors concluded that the combined use of MNM and CA125 has a significantly higher diagnostic accuracy (12). In cervical cancer, monocyte count was positively correlated with tumor stage ($p = 0.020$), and neutrophil count with lymphovascular space invasion and tumor size ($p = 0.043$) (13).

Only few studies assessed MNM in relation to clinical or histopathological factors. That is the reason why in this study we aimed at observing what happens with MNM values in certain situations. The results show that MNM value is significantly lower in preoperative stages I and II ($p = 0.02$) and significantly higher in stages IVA and IVB, pertinent finding given that, as mentioned above, neutrophil and monocyte counts increase with tumor stage. Correlational analysis demonstrated a significant association between MNM and the number of positive nodes ($p = 0.020$), parametrial invasion ($p = 0.00010$), lymphovascular space invasion which significantly influences the MNM value, and tumor size more than 4 cm ($p = 0.0314$).

Although the above mentioned results suggest that the hematologic markers correlate with certain clinical-pathological characteristics, I sought to identify from what value of these markers the presence of negative prognostic factors can be considered in patients with cervical cancer. The calculated NLR cutoff for the prediction of preoperative stage was 2.7, and for tumor size 1.95. Higher values reflect a significantly increased likelihood of a locally advanced stage and a tumor larger than 4 cm. As to the MNM hematologic marker, the study results show that the calculated cutoff values can predict the presence of positive nodes ($p = 0.008$), parametrial invasion ($p < 0.0001$), lymphovascular space invasion ($p = 0.001$) and tumor more than 4 cm in size ($p = 0.03$). The calculated MNM cutoff value cannot predict an early or locally advanced stage ($p = 0.6$).

Conclusions

Various prognostic factors are known to predict the outcome of patients with cervical cancer, e.g. tumor stage, histopathological type, lymph node status, parametrial invasion, but all this information is gathered after surgery. With the advent of studies that have highlighted the prognostic role of hematological biomarkers, another image can be constructed with their aid in this neoplastic disease. The results of this study outline the importance of hematologic findings and of the parameters that can be easily used at no extra cost to establish further course on treatment.

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Conflict of interest

Authors have no conflict of interest to declare.

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