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ORIGINAL ARTICLE

The Systemic Inflammation Marker NLR as a Prognostic Factor in Complicated Colorectal Cancer

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SUMMARY

The aim of this study is to evaluate the importance of the systemic inflammation marker NLR in the long-term survival of patients with complicated colorectal cancer, operated in emergency.

ABSTRACT

Many recent scores based on the inflammatory response, such as Neutrophil Lymphocyte Ratio (NLR), Platelet Lymphocyte Ratio (PLR), Lymphocyte Monocyte Ratio (LMR) have been demonstrated to have a prognostic value in cancer patients. The ratio between neutrophils and lymphocytes is a very useful tool, most studies admitting its role as a prognostic marker in cancer.

We made a retrospective study on 391 patients hospitalized and operated in emergency for complicated colorectal cancer in the Surgery II clinic of the "St. Ap. Andrei" from Galati, Romania, between 2008-2017. We demonstrated that the increased preoperative value of NLR was a negative prognostic factor for long-term survival in patients with complicated colorectal cancer (HR = 7.581, 95% CI = (6.358,9.039) (p = 0.000000)). The cut-off point is > 2.61, with sensitivity of 73.61 and specificity of 100.00. The mean survival time in patients with NLR < = 2.61 was 39,676, 95% CI = (37,189, 42,163) and in those with NLR > 2.61 it was 12,504, 95% CI = (11,747, 13,261), the difference between the survival time of patients with values above the cutoff and below the cutoff being statistically significant (p = 0.000000, Log-Rank).

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Introduction

The preoperative nutritional and immunological status have a strong impact in estimating the survival of neoplastic patients [1]. The inflammatory response has a critical role in carcinogenesis and a number of inflammatory cells and innate immune signaling molecules are involved in the progression of tumors [2].

The first description of the association between inflammation and tumorigenesis was made by Virchow in 1881 [3]. After that, more and more evidence supported this finding.

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The inflammation is now considered to be a hallmark of cancer development [4]. Current evidence suggests that within a tumor tissue there are, alongside cancer cells, host structures (such as extracellular matrix), non-immune cells (like fibrous tissue cells) and immune cells, namely eosinophils, basophils, mast cells, lymphocytes, natural-killer cells and dendritic cells [5-7] that interact and contribute to a highly immunosuppressive microenvironment. The lymphocytes have a major role in this microenvironment, as the progressive increase of tumor infiltrating lymphocytes is directly correlated with antitumor activity.

From another perspective, tissue hypoxia and necrosis [8] can cause complex interactions between tumors and the nonspecific inflammatory response of the host, favoring the evolution of the disease [9]. This systemic inflammatory response involves changes in the neuroendocrine and hematopoietic system, protein and energy metabolism and liver function. The hepatocytes synthesize and release into the systemic circulation acute phase proteins that are associated with lymphocytopenia and an impaired T lymphocyte response in the tumor, compromising the cell-mediated immunity [10].

To estimate the systemic inflammatory response, serum levels of neutrophils, lymphocytes, platelets, C-reactive protein and albumin, alone or in multiple combinations, have been used as prognostic factors for patients with solid malignant tumors.

Since recently, the most used parameter to evaluate the systemic inflammatory response in patients with neoplasias was the elevated level of CRP. However, there are recent scores based on the inflammatory response, such as Neutrophil Lymphocyte Ratio (NLR), Platelet Lymphocyte Ratio (PLR), Lymphocyte Monocyte Ratio (LMR), which have prognostic value in cancer patients. These scores are able to identify the patients who will have a poor response to treatment and a short survival [11].

Considering the correlation between the inflammatory status and the prognosis of neoplasms, more and more research is being done in order to understand how the prognosis of cancer patients can be assessed by simple blood tests [12].

The cell-mediated inflammatory response, lymphocytes, neutrophils and monocytes are increasingly recognized as having a very important role in carcinogenesis.

In colorectal cancer, the lymphocytes have a major role in the immune response, as systemic inflammation significantly decreases cellular immunity, resulting in an important decrease in CD4+ lymphocytes and an increase in CD8+ suppressor T lymphocytes [13].

Some immunocytes, including neutrophils, can secrete Vascular Endothelial Growth Factor (VEGF), which, through angiogenesis, favors the tumor development [14].

In this context, the ratio between neutrophils and lymphocytes becomes a very useful tool, most studies recognizing its role as a prognostic marker in cancer [15]. Zahorec R [16] was the first author to report the relationship between NLR and the disease's severity as a prognostic factor in critically ill patients. Some studies evaluating the relationship between NLR and colorectal cancer have shown that NLR is a strong prognostic factor. For colorectal cancer patients, NLR is assumed to be a combined indicator of both inflammation and immune status.

The lymphocytes play a vital role in cytotoxic cell death and cytokine production, which in turn prevent the proliferation and metastasis of malignant cells [17]. Studies on lymphocytes are conflicting, but most have shown that lymphocytes decrease in patients with advanced colon cancer [18].

Specific objective

Evaluation of the importance of the systemic inflammation marker NLR in the long-term survival of patients with complicated colorectal cancer, operated in emergency.

Patients and methods

We included in the study 391 patients hospitalized and operated in emergency for complicated colorectal cancer in the Surgery II clinic of the "St. Ap. Andrei" from Galati, between 2008-2017.

The preoperative diagnosis established in most cases was the intestinal obstruction (77.03 %). The other complications were: intestinal perforation and haemorrhage.

There were practiced 4 types of surgeries: external derivations (41.5%), Hartmann procedure (31.1%), internal derivations (20.9%) and resections with anastomosis (6.7%).

Patient data were collected from observation sheets and operative protocols.

We analyzed the paraclinical factor of systemic inflammation NLR, with the data collected from the results of the laboratory tests performed at admission.

The inclusion criteria were: adult patients with colorectal cancer, admitted and operated in emergency, with complete data in the observation sheets.

The excluding criteria: non-malignant tumors, patients with colorectal cancer electively operated.

As prognostic factors, survival curves were analyzed, tracking the involvement of inflammatory factors in long-term survival in univariate and multivariate Cox regression analysis.

Statistical analysis

For the survival analysis, the overall survival was defined as the time from the time of diagnosis to the date of death or to the end of the study (01.10.2019).

Curves for overall survival were estimated by the Cox method and comparison for statistical significance with the sig.p-value test with 95.0% CI. Univariate Cox proportional Hazard Ratio (HR) analysis was performed to identify potential prognostic factors, and multivariate Cox proportional Hazard Ratio (HR) analysis was performed to assess independent prognostic factors. The accuracy of the prognostic factors was analyzed by evaluating the sensitivity and specificity of these markers after establishing cut-off values, using ROC curves. In this study, we used the approach based on the value of the area under the ROC curve, thus defining the optimal value of the cut-off point as the value whose sensitivity and specificity are closest to the value of the area under the ROC curve and the absolute value of the difference between sensitivity and specificity values are minimal.

Statistical analysis was performed using the SPSS 17 system within Windows Software.

Statistical conclusions were calculated using $p < 0.05$ as the statistically significant difference threshold for all calculations performed.

Results

Univariate analysis to assess risk/protective factors for long-term survival in patients with colorectal cancer undergoing emergency surgery

Comparing the survival in patients who showed increased NLR values with those who had reduced NLR values, we calculated the risk of death in the presence of increased NLR values -HR = 7.581, 95% CI = (6.358,9.039) (p = 0.000000) (Table 1, figure 1)- the presence of increased NLR values is a risk factor.

The ROC curve was made for NLR in the discrimination of death in the 391 patients involved in the study, of which 379 died (96.93%) and 12 survived (3.07%). The area of the ROC curve was 0.859 with 95% CI of (0.821, 0.892), p = < 0.001. The cut-off point is >2.61, with sensitivity of 73.61 and specificity of 100.00 (Table 2, figure 2).

Among the 105 patients with NLR threshold value < 2.61, 94 died by 01.10.2019 and 11 (10.5%) survived until the end of the study.

Of the 286 patients with NLR threshold value > 2.61, 285 did not survive and 1 (0.3%) was alive at the end of the study.

The mean survival time in patients with NLR < = 2.61 was 39,676, 95% CI = (37,189, 42,163) and in those with NLR > 2.61 it was 12,504, 95% CI = (11,747, 13,261), the difference between the survival time of patients with values above the cutoff and below the cutoff being statistically significant (p = 0.000000, Log-Rank) (Table 3, figure 3).

Comparison of ROC curves for NLR, PLR, LMR and PNI.

Comparing the 4 ROC curves, two by two, a significant difference is obtained between PLR ~ PNI (p = 0.0001), PNI ~ LMR (p = 0.0060), PNI ~ NLR (p < 0.0001) (Table 4, figure 4).

Multivariate Cox analysis to assess whether markers of systemic inflammation are independent prognostic factors.

Table 1: Corelation of the NLR with the survival.

Variables in the Equation								
	B	SE	Wald	df	Sig. (*p* - value)	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
NLR	2.026	.090	509.279	1	**0.000000**	7.581	6.358	9.039

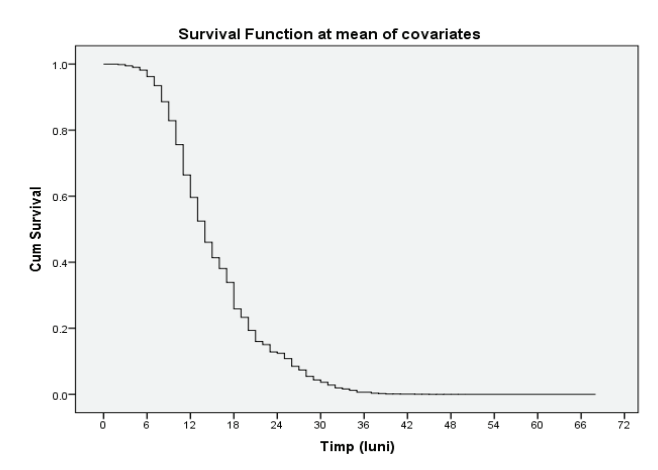

Figure 1 The survival Cox curve depending on NLR.

Table 2: Analysis of the ROC curve for the predictive capacity of the variable NLR.	
Variable	NLR
Classification variable	Deces01
Sample size	391
Positive group [a]	379(96.93%)
Negative group [b]	12(3.07%)
[a]Deces01 = 1	
[b]Deces01 = 0	
Disease prevalence (%)	unknown
Area under the ROC curve (AUC)	
Area under the ROC curve (AUC)	0.859
Standard Error[a]	0.0306
95% Confidence interval[b]	0.821 to 0.892
z statistic	11.744
Significance level P (Area=0.5)	< 0.0001
[a] DeLong et al., 1988	
[b] Binomial exact	
Youden index	
Youden index J	0.7361
Associated criterion	> 2.61
Sensitivity	73.61
Specificity	100.00
Survival analysis by NLR threshold value	

Case Processing Summary

NLR_prag	Total N	N of Events	Censored	
			N	Percent
< 2.61	105	94	11	10.5%
> 2.61	286	285	1	.3%
Overall	391	379	12	3.1%

Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	249.140	1	0.000000
Breslow (Generalized Wilcoxon)	184.490	1	0.000000

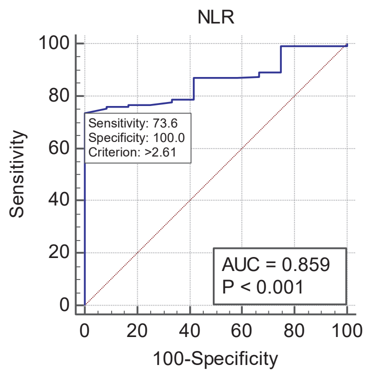

Figure 2 The ROC curve for NLR.

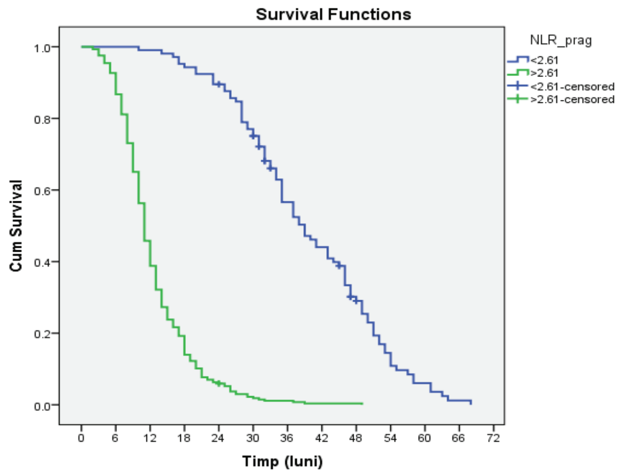

Figure 3 The survival curves for NLR with a threshold value.

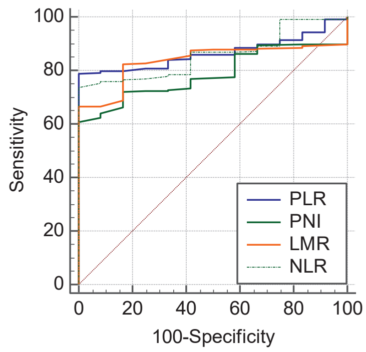

Figure 4 Comparative representation of ROC curves for NLR, PLR, LMR and PNI.

Comparing survival in patients with elevated NLR values with those with low NLR values but with the same values for PLR, LMR and PNI, the risk of death in the presence of elevated NLR values was calculated - but no significance was obtained statistic within the proposed model.

Table 3: Estimation of the survival media and median depending on the NLR threshold value.

NLR_prag	Mean[a]				Median			
	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
< 2.61	39.676	1.269	37.189	42.163	39.000	2.398	34.299	43.701
> 2.61	12.504	.386	11.747	13.261	11.000	.337	10.339	11.661
Overall	19.815	.754	18.338	21.293	14.000	.616	12.792	15.208

Discussion

Lately, a lot of studies have been done that have showed the association between the systemic inflammatory response and the malignant tumors and even more, there are more and more data that reveal that inflammatory markers can influence the prognosis of neoplastic patients.

The chronic systemic inflammatory response is involved in the nutritional and functional decline of cancer patients with the natural course of the disease. The evaluation of this response using the markers of systemic inflammation allows the identification of patients at high risk [11].

Regarding the systemic inflammatory response in patients with complicated colorectal cancer, our study showed that: the inflammatory marker NLR with increased values is a risk factor.

The index analyzed in this study is calculated with a formula involving the total number of lymphocytes. The anti-tumor immune response is orchestrated by

Table 4: Comparative analysis of ROC curves for NLR, PLR, LMR and PNI.

Variable 1	PLR
Variable 2	PNI
Variable 3	LMR
Variable 4	NLR
Classification variable	Deces01
Sample size	391
Positive group [a]	379(96.93%)
Negative group [b]	12(3.07%)

[a]Deces01 = 1
[b]Deces01 = 0

Variable	AUC	SE[a]	95% CI[b]
PLR	0.866	0.0234	0.828 to 0.898
PNI	0.787	0.0341	0.743 to 0.827
LMR	0.837	0.0282	0.797 to 0.872
NLR	0.859	0.0306	0.821 to 0.892

[a] DeLong et al., 1988
[b] Binomial exact

Pairwise comparison of ROC curves	
PLR ~ PNI	
Difference between areas	0.0789
Standard Error[a]	0.0200
95% Confidence Interval	0.0398 to 0.118
z statistic	3.956
Significance level	P = 0.0001
PLR ~ LMR	
Difference between areas	0.0288
Standard Error[a]	0.0215
95% Confidence Interval	-0.0133 to 0.0709
z statistic	1.342
Significance level	P = 0.1795
PLR ~ NLR	
Difference between areas	0.00682
Standard Error[a]	0.0143
95% Confidence Interval	-0.0211 to 0.0348
z statistic	0.478
Significance level	P = 0.6325
PNI ~ LMR	
Difference between areas	0.0501
Standard Error[a]	0.0182
95% Confidence Interval	0.0144 to 0.0859
z statistic	2.750
Significance level	P = 0.0060
PNI ~ NLR	
Difference between areas	0.0721
Standard Error[a]	0.0144
95% Confidence Interval	0.0439 to 0.100
z statistic	5.001
Significance level	P < 0.0001
LMR ~ NLR	
Difference between areas	0.0220
Standard Error[a]	0.0215
95% Confidence Interval	-0.0202 to 0.0641
z statistic	1.022
Significance level	P = 0.3066

Variables in the equation								
	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
NLR	**-.072**	**.188**	**.147**	**1**	**0.701601**	**.930**	**.643**	**1.346**
PLR	.024	.003	53.076	1	**0.000000**	1.025	1.018	1.031
LMR	-1.064	.192	30.860	1	**0.000000**	.345	.237	.502
PNI	-.162	.019	73.241	1	**0.000000**	.851	.820	.883

cytotoxic T lymphocytes, which have the ability to inhibit tumor growth [19]. Small lymphoid clusters, containing both T and B lymphocytes, called Tertiary Lymphoid Structures (TLS), have been detected in tumors and associated with a strong lymphocytic response and good prognosis [20].

NLR has been proposed to reflect the balance between pro-tumor inflammation and anti-tumor immune function [21].

An elevated NLR can be the result of either an increase in neutrophils, a decrease in lymphocytes, or both. In the tumor microenvironment, an increased concentration of neutrophils promotes tumor growth, while a decreased concentration of lymphocytes indicates ineffective local tumor control. Thus, an increased microenvironmental NLR may indicate tumor progression, representing a marker of unfavorable prognosis. Because serum NLR is an easy-to-measure, reproducible and cost-effective marker, it may have a great clinical impact in the future [22].

We showed that the increased preoperative value of NLR was a negative prognostic factor for long-term survival, as found by other authors [23-26]. In a single study conducted in 2018 at the University of Leeds in the UK, the authors reported that elevated NLR values were associated with a high risk of death in univariate but not multivariate analysis [27].

Many studies have reported the prognostic value of the inflammatory markers NLR [28,29], LMR [30,31], PNI [32], PCR [33], but no consensus has been reached regarding the prognostic value of PLR. Ozawa T, et al. [34], Kwon HC, et al. [35] and Liu H, et al. [36] showed that PLR with increased values is a risk factor in colorectal cancer, a fact that we also found in our study, while other authors did not find statistical significance in this association in any of the groups they analyze (patients with non-metastatic colorectal cancer in different stages and patients with liver metastases) [37,38]. Emir S, et al. [39] found statistical significance in the association between increased PLR and 5-year survival in uni- and multivariate analyzes performed on 140 patients with resectable colorectal cancer.

In our study, we showed that elevated PLR was an independent risk factor in multivariate analysis, unlike other authors, who reported that NLR and PLR were risk factors, but only NLR was an independent risk factor [40].

In the literature, there is a growing interest in finding the threshold value of markers of systemic inflammation above which the probability of death increases significantly [41-45].

The cutoff values for NLR and PLR in our study were 2.61 and 139.85, respectively, values close to those reported in other studies.

In a recent meta-analysis, which included 23 studies (11762 patients), it is shown that increased values of NLR and PLR are risk factors for patients with colorectal cancer. The cutoff values for NLR and PLR were 3 and 150, respectively [46]. Other authors calculated the cutoff value 4.7 for NLR [47] or even 5 [48,49].

Lately, there were published a lot of studies about the prognostic value of different markers of systemic inflammation for patients with colorectal cancer, but very few have included emergency operated patients. We believe that in this situation, the analysis of these markers could be even more useful, given the neoplasia, the immunodepressed patients, who have a poor biological condition, who are operated on an unprepared, distended colon or in conditions of generalized peritonitis, with septic shock.

Future prospective studies are required in order to verify the significance of these prognostic indices in clinical practice. Analyzing markers of systemic inflammation is convenient, simple and cost-effective. Their routine evaluation could be useful in assessing the prognosis of patients with colorectal cancer operated in emergency.

Conclusion

The NLR inflammation-based prognostic score, a result of the systemic inflammatory response, was associated with the patients' survival.

In the univariate analysis, we found that the increased values of NLR are risk factors for the survival of patients with colorectal cancer, operated in emergency.

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