The Importance of Systemic Inflammation Markers in the Survival of Patients with Complicated Colorectal Cancer, Operated in Emergency

Georgiana Bianca Constantin¹, Dorel Firescu^{2,3}, Dragoș Voicu², Bogdan Ștefănescu^{2,3}, Raul Mihailov¹, Cristina Șerban^{2,3}, Eugenia Panaitescu¹, Rodica Birlă^{1,4}, Silviu Constantinoiu^{1,4}

¹Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

²Dunarea de Jos University, Faculty of Medicine and Pharmacy, Galati, Romania

³Clinical Emergency County Hospital Sf. Ap. Andrei, Galati, Romania

⁴General and Esophageal Surgery Department, Center of Excellence in Esophageal Surgery, Saint Mary Clinical Hospital, Bucharest, Romania

Corresponding author:

Rodica Birlă, MD
General and Esophageal Surgery
Department, Center of Excellence
in Esophageal Surgery, Sf. Maria
Clinical Hospital, Bucharest, Romania
E-mail: birlarodica@yahoo.com

Abbreviations:

NLR = Neutrophil-to-lymphocyte ratio,
PLR = platelet-to-lymphocyte ratio,
LMR = lymphocyte-to-monocyte ratio,
PNI = prognostic nutritional index,
CRP = C reactive protein,
HR = hazard ratio,
CI = confidence interval,
VEGF = vascular endothelial growth
factor,
TIL = tumor-infiltrating lymphocytes,
TLS = tertiary lymphoid structures,
TNF α = tumoral necrosis factor α ,
IL-1=interleukine-1.

Rezumat

Markerii de inflamație sistemică – factori de prognostic la pacienții cu cancer colorectal complicat, operați în urgență

Introducere: Răspunsul inflamator joacă un rol critic în carcinogeneză. Există scoruri recente bazate pe răspunsul inflamator sistemic, cum ar fi raportul neutrofile/limfocite (NLR), raportul trombocite/limfocite (PLR), raportul limfocite/monocite (LMR), despre care s-a arătat că au valoare prognostică la pacienții cu cancer. Aceste scoruri permit identificarea pacienților care vor avea un răspuns slab la tratament și o supraviețuire de scurtă durată. Scopul acestui studiu este de a evalua rolul prognostic al NLR, PLR, LMR și PNI în termeni de supraviețuire la distanță pentru bolnavii cu cancer colorectal, operați în urgență.

Material și Metode: Am inclus în studiu 391 de pacienți internați și operați pentru cancer colorectal complicat în clinica Chirurgie II a Spitalului Clinic Județean de Urgență "Sf. Ap. Andrei" din Galați, în perioada 2008-2017. Am analizat factorii paraclini de inflamație sistemică NLR, PLR, LMR și PNI. Ca factori de prognostic, au fost analizate curbele de supraviețuire.

Rezultate: La pacienții din lot, valorile crescute ale NLR, precum și ale PLR au dus la creșterea riscului de deces (HR=7,581, 95% CI=(6.358,9.039), p value=0.000000, respective HR=1.043, 95% CI=(1.039, 1.047), p value=0.000000), iar valorile crescute ale LMR și PNI au condus la scăderea acestui risc (HR=0.069, 95%

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CI=(0.054,0.090), p value=0.000000, respective HR=0.758, 95%CI=(0.730,0.788), p value=0.000000). În analiza de regresie multivariată, creșterea PLR a determinat o creștere a riscului de apariție a decesului (HR=1.024, 95% CI=(1.019,1.029), p value= 0.000000) , iar pentru LMR și pentru PNI, o reducere a riscului de deces (HR=0.353, 95% CI=(0.248,0.504), p value = 0.000000, respective HR=0.852, 95% CI=(0.822,0.883), p value = 0.000000).

Concluzii: Analiza univariată a arătat că NLR și PLR sunt factori de risc, iar LMR și PNI sunt factori de protecție în ceea ce privește supraviețuirea. Analiza multivariată a relevat că PLR este factor de risc independent, iar markerii LMR și PNI au fost factori de protecție independenți.

Cuvinte cheie: cancer colorectal, urgență, marker inflamație, supraviețuire

Abstract

Introduction: The inflammatory response plays a critical role in carcinogenesis. There are recent scores based on the systemic inflammatory response, such as neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), lymphocyte/monocyte ratio (LMR), which have been shown to have prognostic value in cancer patients. These scores allow the identification of patients who will have poor response to treatment and poor survival.

The aim of this study is to evaluate the prognostic role of NLR, PLR, LMR and PNI in terms of long-term survival in patients with colorectal cancer, operated in emergency.

Material and Methods: We included 391 patients admitted and operated for complicated colorectal cancer in the Surgery II clinic of the Clinical Emergency County Hospital "Sf. Ap. Andrei " from Galati, between 2008-2017. We analyzed the paraclinical factors of systemic inflammation NLR, PLR, MRL and PNI. As prognostic factors, survival curves were analyzed.

Results: The high values of NLR and PLR increased the risk of death (HR = 7.581, 95% CI = (6.358,9.039), p value = 0.000000, respectively HR = 1.043, 95% CI = (1.039, 1.047), p value = 0.000000), and the increased values of LMR and PNI led to the decrease of this risk (HR = 0.069, 95% CI = (0.054,0.090), p value = 0.000000, respectively HR = 0.758, 95 % CI = (0.730,0.788), p value = 0.000000). In the multivariate regression analysis, the increase of PLR resulted in an increase in the risk of death (HR = 1.024, 95% CI = (1.019,1.029), p value = 0.000000), and for the LMR and PNI, a reduction of the risk of death (HR = 0.353, 95% CI = (0.248,0.504), p value = 0.000000, respectively HR = 0.852, 95% CI = (0.822,0.883), p value = 0.000000).

Conclusions: The univariate analysis showed that NLR and PLR are risk factors, and LMR and PNI are protective factors in terms of survival. The multivariate analysis revealed that PLR is an independent risk factor, and LMR and PNI were independent protection factors.

Key words: colorectal cancer, emergency, inflammation markers, survival

Introduction

The preoperative nutritional and immunological status have a strong impact on the estimation of the survival of neoplastic patients (1). The inflammatory response plays an important role in carcinogenesis process and a number of cells involved in the

inflammation process and innate signaling molecules of the immune system are involved in tumor progression (2).

The first description of the link amid inflammation and tumorigenesis was made by Virchow in 1881 (3), and since then there has been growing evidence to support this finding.

Inflammation is now considered to be a

distinctive sign for cancer development (4). Current evidence refers to the fact that inside a tumor it exists alongside cancer cells, base structures (eg, extracellular matrix), cells that don't trigger the immune system (eg, fibrous tissue cells) and immune cells, respectively basophils, lymphocytes, eosinophils, mast cells, NK cells and dendritic cells, which interact and contribute to an extremely immunosuppressive microenvironment. Lymphocytes play an essential role in this habitat, as the gradual growth of lymphocytes inside the tumor is directly associated with anticancer activity (5-7).

On the other way, necrosis and tissue hypoxia (8) can lead to complex interactions between altered cells and the nonspecific inflammatory reaction, facilitating the evolution of the disease (9). This systemic inflammatory response involves changes in the hematopoietic and neuroendocrine system, energy and protein metabolism, and liver function. The liver cells synthesize and discharge into the systemic circulation acute phase proteins that are linked with lymphocytopenia and affected T lymphocyte response in the tumor cells, destroying cell-mediated immunity (10). To estimate the systemic inflammatory response, platelets, lymphocytes, serum levels of neutrophils, albumin and C-reactive protein, either individual or in several blendings, were used as prognostic factors for patients with different malignant solid tumors.

Until recently, the most used parameter for evaluating the SIRS in patients with cancer was the increased 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 (MLR), which have been shown to have prognostic value in cancer patients. These scores allow identification of patients who will have poor response to treatment and poor survival (11).

Given the correlation between inflammatory status and prognosis of neoplasms, more and more research is being made in order to understand how the prognosis of cancer patients can be assessed by simple blood tests (12).

Cell-mediated inflammatory response, lymphocytes, neutrophils and monocytes are increasingly recognized as having an important role in carcinogenesis.

In colorectal cancer, lymphocytes have a major task in the immune response, as systemic inflammation forcefully decreases cellular immunity, resulting in a significant cutback in CD4 + lymphocytes and an increase in CD8 + suppressive T lymphocytes (13).

Some immunocytes, including neutrophils, can produce vascular endothelial growth factor (VEGF), which, by angiogenesis, promotes tumor development (14).

In this context, the relationship between neutrophils and lymphocytes becomes very useful to analyze and most of the studies recognize its role as a prognostic marker in cancer (15). Zahorec (16) was the first author to report the link between NLR and disease severity as a prognostic factor in critically ill patients. Various studies evaluating the relationship between NLR and colorectal cancer have shown that NLR is a strong prognostic factor. For colorectal cancer patients it is assumed that NLR is a combined indicator of both inflammation and immune status.

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 contradictory, but most have shown that lymphocytes decrease in patients with advanced colon cancer (18).

PLR is the ratio of platelets to lymphocytes. The mechanisms underlying the association between PLR with elevated values and poor prognosis in colorectal cancer are not fully known. Recent studies have shown that platelets can prevent tumor cell death by natural-killer cells and that platelets can secrete angiogenic and tumor growth factors (GF), including vascular endothelial GF and platelet-derived GF, and thus promote growth, progression and tumor spread (19-21). Furthermore, thrombocytosis has been promoted to be linked with poor prognosis in colorectal cancer (22,23).

LMR is the ratio between the total number of lymphocytes and the number of monocytes. Lymphocytes are involved in cytotoxic cell death and inhibition of tumor cell proliferation and migration (24,25). Lymphopenia usually indicates the severity of the disease and can cause cancer cells to escape the immunity of tumor-infiltrating lymphocytes (TILs) (26). TILs are composed of lymphocytes that migrate into the tumor microenvironment (27). Low levels of TILs have been shown to predict poorer survival in colorectal cancer patients (28). In contrast, monocytes can promote tumor progression and metastasis (29). Several proinflammatory cytokines, produced by the monocytes, are associated with poor prognosis in cancer patients, such as TNF- α and IL-1 (30). In addition, tumor-associated macrophages, derived from circulating monocytes, play a role in suppressing immunity and promoting angiogenesis, invasion, and migration (31). Thus, the decrease in LMR could be affiliated with poor prognosis for patients diagnosed with cancer.

Hypoalbuminemia is a risk factor for the survival of patients with colon cancer (32). PNI, calculated taking into account the serum albumin level and the number of peripheral lymphocytes, reflects both the nutritional and immune status of the patient (33). PNI has recently been shown to be a predictive marker for both postoperative complications and prognosis of colorectal cancer patients (34).

The target of our study is to assess the prognostic role of NLR, PLR, LMR and PNI in terms of long-term survival in patients with colorectal cancer, operated in emergency.

Material and Methods

We included 391 patients admitted and operated for complicated colorectal cancer in the Surgery II clinic of the Clinical Emergency County Hospital "Sf. Ap. Andrei" from Galati, between 2008-2017. Patient data were collected from clinical observation reports and operating protocols. We analyzed the following paraclinical systemic inflammation factors: NLR, PLR, LMR and PNI.

Neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), platelet-to-lymphocyte ratio (PLR) and PNI nutritional prognosis index (calculated with the equation $10 \times \text{serum albumin (g/dl)} + 0.005 \times \text{total lymphocyte count (per mm}^3\text{)}$) are markers of systemic inflammation. The determination of the values of these markers was made considering the laboratory results performed at admission.

As prognostic factors, the survival curves were analyzed, following the involvement of the inflammation factors in the distance survival in the Cox univariate and multivariate regression analysis. We defined the overall survival as the period since the moment of diagnosis to the date of bereavement or until the deadline of the study (01.10.2019).

The curves for the overall survival were estimated by the Cox method, and the comparison for the statistical significance with the sig.p-value test with 95.0%CI. The analysis of the Univariate Cox proportional risk ratio (HR) was performed to identify potential prognostic factors, and that of the Cox multivariate proportional risk ratio (HR) to evaluate the independent prognostic factors. The accuracy of the prognostic factors was analyzed by evaluating the sensitivity and specificity of these markers after establishing the cut off values, using the ROC curves. Statistical study was calculated using the SPSS 23.0 program from Windows Software. Statistical conclusions were made considering a statistically significant difference $p \text{ value} < 0.05$ for all calculations performed.

Results

The univariate analysis of Cox proportional hazards reports revealed that NLR and PLR are risk factors in terms of survival ($HR = 7.581$, 95% CI = (6.358,9.039), $p_{\text{value}} = 0.000000$, respectively $HR = 1.043$, 95% CI = (1.039, 1.047), $p \text{ value} = 0.000000$), and LMR and PNI are protective factors ($HR = 0.069$, 95% CI = (0.054, 0.090), $p \text{ value} = 0.000000$).

and respectively (HR = 0.758, 95% CI = (0.730, 0.788), p value = 0.000000) (Table 1).

The ROC curve designed for NLR in discriminating death in the 391 patients involved in the study (379 deceased (96.93%) and 12 survivors (3.07%)) has the area of 0.859 with 95% CI of (0.821 to 0.892), p_value = < 0.001. The cutoff point is > 2.61, with a sensitivity of 73.61 and a specificity of 100.00. (Table 2, Fig. 1).

The average survival time in patients with NLR values below 2.61 was 39.676, 95% CI = (37.189, 42.163) and in those with values above 2.61 it was 12.504, 95% CI = (11.747, 13.261), the difference between time of survival being statistically significant (p_value = 0.000000, Log-Rank) (Table 2, Fig 2).

The area of the ROC curve designed for PLR was 0.866 with 95% CI of (0.828 to 0.898), p_value = <0.001. The cutoff point is > 139.85 with the sensitivity of 78.89 and the specificity of 100.00 (Table 2, Fig. 3).

The average survival time in patients with

Figure 1. ROC curve for NLR

PLR values below 139.85 was 41,7046, 95% CI = (39,041, 44,368) and in those with values above 139.85 it was 13,294, 95% CI = (12,466, 14,121), the difference being statistically

Table 1. Survival univariate and multivariate analysis of systemic inflammation markers

Prognostic factor	Univariate		Multivariate	
	HR(95%CI)	p_value	HR(95%CI)	p_value
NLR	7.581 (6.358, 9.039)	0.000000		
PLR	1.0431.039, 1.047)	0.000000	1.024(1.019, 1.029)	0.000000
LMR	0.069 (.054, .090)	0.000000	0.353(0.248, 0.504)	0.000000
PNI	0.758 (0.730,0.788)	0.000000	0.852 (0.822, 0.883)	0.000000

Table 2. Survival analysis of systemic inflammation markers with cutoff value

Prognostic factor	Deaths	Sensitivity	Specificity	Mean –Estimate HR(95% CI)	Univariate Log-Rank	p_value
NLR		73.61	100.00			0.000000
≤2.61	94/104			39.676	(37.189,42.163)	
>2.61	285/286			12.504	(11.747, 13.261)	
PLR		78.89	100.00			0.000000
≤139.85	79/90			41.704	(39.041, 44.368)	
>139.85	300/301			13.294	(12.466, 14.121)	
LMR		66.75	100.00			0.000000
≤2.28	250/250			11.128	(10.512, 11.744)	
>2.28	129/141			35.231	(32.886, 37.576)	
PNI		60.69	100.00			0.000000
≤ 39.5	221/221			10.647	(10.038, 11.256)	
>39.5	158/170			31.741	(29.449, 34.033)

Figure 2. Survival curves for NLR with cutoff value

Figure 3. ROC curve for PLR

significant ($p_value = 0.000000$, Log-Rank) (Table 2, Fig. 4).

The area of the ROC curve designed for LMR was 0.837 with 95% CI of (0.797 to 0.872), $p_value = <0.001$. The cutoff point is <2.28 , with a sensitivity of 66.75 and a specificity of 100.00 (Table 2, Fig. 5).

The average survival time in patients with LMR values below 2.28 was 119,128, 95% CI = (10,512, 11,744) and in those with values above 2.28 it was 35231, 95% CI = (32,886, 37,576), the difference being statistically significant ($p_value = 0.000000$, Log-Rank) (Table 2, Fig. 6).

The area of the ROC curve designed for

Figure 4. Survival curves for PLR with cutoff value

Figure 5. ROC curve for LMR

Figure 6. Survival curves for LMR with cutoff value

PNI was 0.787, with 95% CI = (0.743 to 0.827), $p_{\text{value}} = <0.001$. The cutoff point is ≤ 39.5 , with the sensitivity of 60.69 and the specificity of 100.00 (Table 2, Fig. 7).

The average survival time in patients with PNI values below 39.5 was 10,647, 95% CI = (10,038, 11,256) and in those with values below 39.5 it was 31,741, 95% CI = (29,449, 34,033), the difference being statistically significant ($p_{\text{value}} = 0.000000$, Log-Rank) (Table 2, Fig. 8).

Of the potential factors selected in the univariate analysis, in the multivariate analysis, regarding PLR, its increase leads to an increased risk of death (HR = 1.024, 95% CI = (1.019, 1.029), $p_{\text{value}} = 0.000000$), this being a factor of independent risk, and for LMR and PNI, their increase leads to a lower risk of death (HR = 0.353, 95% CI = (0.248, 0.504), $p_{\text{value}} = 0.000000$), respectively (HR = 0.852, 95% CI = (0.822, 0.883), $p_{\text{value}} = 0.000000$) (Table 2), so they are independent protection factors.

Discussions

In the last years, numerous studies have been made that have demonstrated the connection between systemic inflammatory response and malignancies and, moreover, there is increasing evidence that inflammatory markers may 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. Evaluation of this response using markers of systemic inflammation allows the identification of patients at high risk (11).

Regarding the SIR in patients with complicated colorectal cancer, our study showed that:

- inflammatory markers NLR and PLR with increased values are risk factors, while increased values of LMR and PNI are protective factors for survival, as the univariate analysis has shown;
- PLR with high value was an independent risk factor in the multivariate analysis and LMR and PNI were independent protection factors.

All the markers analyzed in this study are calculated with formulas that involve the total number of lymphocytes. The anti-tumor immune response is orchestrated by cytotoxic T lymphocytes, which have the capacity to inhibit tumor growth (35). Small lymphoid groups, which contain both T lymphocytes and B lymphocytes, called tertiary lymphoid structures (TLS), have been detected in tumors and associated with a strong lymphocyte response and a good prognosis (36).

NLR has been suggested to reflect the balance between pro-tumor inflammation and anti-tumor immune function (37). An

Figure 7. ROC curve for PNI

Figure 8. Survival curves for PNI with cutoff value

increased NLR may be the outcome of one of the following: increase in neutrophils, or a decrease in lymphocytes or both. In the tumor microenvironment, an increased number of neutrophils favors tumor expansion, while a decrease in lymphocyte number indicates inefficient local tumor limitation. Thus, an elevated microenvironmental NLR may indicate tumor expansion, representing an factor of adverse prognosis. Because serum NLR is an easily measurable, reproducible and cheap marker, it may have a major clinical effect in practice in the future (38).

We have shown that the increased preoperative value of NLR was a risk factor for remote survival, as other authors have also found (39-41). In a single study conducted in 2018 at the University of Leeds in the UK, the authors reported that high NLR values were associated with a high risk of death in univariate but not multivariate analysis (42).

Many studies have reported the prognostic value of inflammatory markers NLR (43,44), LMR (18,45), PNI (46), PCR (47), but a consensus on the prognostic value of PLR has not been reached.

Ozawa et al. (48), Kwon et al. (49) and Liu H et al. (50) showed that PLR with high 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 that they analyzed (patients with non-metastatic colorectal cancer at different stages and patients with liver metastases) (51,52). Emir et al. (53) found statistical significance in the association between PLR with increased value and 5-year survival in single- and multivariate analyzes performed on 140 patients with resectable colorectal cancer.

In our study, we showed that PLR with high values was an independent risk factor in the multivariate analysis, unlike other authors, who reported that PLR is a risk factor, but not independent (54).

In the publications, there is a growing enthusiasm in finding the verge value of markers of systemic inflammation over which the probability of death increases

significantly (55-58).

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

In a recent meta-analysis, which included 23 studies (11762 patients), it is shown that increased NLR and PLR values are risk factors for colorectal cancer patients. The cutoff values for NLR and PLR were 3 and 150 respectively (59). Other authors have calculated the cutoff value of 4.7 for NLR (60) or even 5 (61,62).

The cutoff values for PLR as a prognostic factor differ a lot in the literature. In some studies, the reported value was 130 (63), and in other studies included in a meta-analysis, the cutoff value for PLR was 150 (64), different from the one we calculated in our study.

The value of the ratio of lymphocytes to monocytes is also a biomarker of the host's immune response. Recent evidence suggests that the preoperative value of LMR may be prognostic in colorectal cancer (65).

In a retrospective study involving 3281 patients treated in the Northern Sydney Local Health District, it was found that increased LMR was associated with better survival. The authors concluded that LMR is an independent predictor for survival period in patients diagnosed with colorectal tumors with curative resections and appears to be superior to pre-existing biomarkers (18). A meta-analysis that included the results of 15 retrospective observational studies, including 11783 patients, indicates that a high LMR value was a significant predictive factor for better survival (66), which we also found in our study.

In some other published works, the evaluation of the prediction strength of the LMR in metastatic tumors revealed similar results, but in the multivariate analysis it did not prove to be an independent prognostic factor (67).

The cutoff value for LMR varies widely in different studies, from 2.14 (68) to 3.78 (69). Some authors calculated the cutoff value for LMR very close to that of our study (2,28,70,71).

The literature data regarding the prognostic value of the PNI index seem to be the most consistent. In several studies it has been shown that PNI with high preoperative values is a protective factor in univariate analyzes and an independent protection factor in colorectal cancer patients in multivariate analyzes (72).

A retrospective study that included 1321 colorectal cancer patients showed that patients with low preoperative PNI were associated with more aggressive tumors, advanced stages of the disease, with lymph node metastases and 5-year survival poorer than patients with high PNI values. In this study, PNI was also an independent prognostic factor. The authors concluded that the preoperative PNI is a simple and useful marker for predicting the outcomes of colorectal cancer patients, including with respect to long-term survival, so it should be included in the routine preoperative analyzes of these patients (1).

The cutoff value for PNI varies quite a bit in the studies analyzed: 44.5 (73), 45 (1), values generally higher than those calculated by us (39.5). We appreciate that we can put this fact on account of the more pronounced hypoalbuminemia and lymphocytopenia in patients operated in emergency for complicated tumors.

In the last years, many studies have been published regarding the prognostic value of different markers of systemic inflammation for colorectal cancer patients, but very few have included patients operated in emergency. We consider that in this situation, the analysis of these markers could be even more useful, given the fact that we are talking about immunocompromised, neoplastic patients, who have a precarious biological condition, with operations made in bad local conditions (unprepared colon) or in conditions of generalized peritonitis, with septic shock.

Future prospective studies will be needed to verify the significance of these prognostic markers in clinical practice. The analysis of 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.

Conclusions

Prognostic scores based on inflammation, such as NLR, PLR, LMR and PNI, results of the SIR, have been associated with survival in patients with colorectal tumors.

In the univariate analysis, we found that the high values of NLR and PLR are risk factors, and the high values of LMR and PNI are protective factors for the survival of patients with colorectal tumors, operated in emergency.

The increased value of PLR is an independent risk factor for patients in the group, while the increased values of LMR and PNI are protective independent survival factors.

Conflicts of Interests

The authors declare no conflicts of interests.

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