Prognostic Value of Inflammation-based Prognostic Scores in Patients with Colorectal Cancer

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Abstract

Background Anatomopathological staging is the primary method to determine the prognosis of patients with colorectal carcinoma (CRC). However, new tools have been developed that can complement it, such as the analysis of the elevation of systemic inflammatory markers.

Objective To evaluate the impact of the elevation of scores based on inflammatory markers (the neutrophil-to-lymphocyte ratio [NLR], the Glasgow Prognostic Score [GPS], and isolated C-reactive protein [CRP]) in the prognosis of patients diagnosed with CRC and submitted to potentially curative surgery in Hospital de Braga, Portugal, between January 1st, 2005, and December 31st, 2010.

Methods A retrospective analysis of the data of **426 patients** was performed, with a collection of several clinico-pathological variables, as well as the levels of lymphocytes, neutrophils, albumin and CRP, in the pre- and postoperative periods, to apply the different scores to the sample.

Results From the analysis of the survival curves, we concluded that patients with **increased NLR** in the **pre- and postoperative periods** present a **lower cancer-related survival** than patients with normal NLR (preoperative period: 93.7 versus 122 months; $p < 0.001$; postoperative period: 112 versus 131 months; $p = 0.002$). Patients with **increased NLR in the pre- and postoperative periods** also had a **lower disease-free survival** (preoperative period: 88.0 versus 122 months; $p < 0.001$; postoperative period: 111 versus 132 months; $p = 0.002$). In addition, **increased pre- and postoperative NLR** was associated with a **higher risk of death due to CRC** (preoperatively: hazard ratio [HR] = 2.25; $p < 0.001$; postoperatively: HR = 2.18; $p = 0.003$). However, the

Keywords
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- scores of systemic inflammatory markers
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- GPS
- CRP

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multivariate analysis shows that **only postoperative NLR** (ajusted HR =2.66; p = 0.002) **does so independently of the remaining variables.**

Conclusion Regarding the scores applied to the sample, the NLR was the one that most consistently related to the prognosis of the patients. However, it would be useful to develop a prospective study that could confirm this relationship.

Introduction

Recently, the impact of elevated systemic inflammatory markers such as the Glasgow Prognostic Score (GPS), the neutrophil-to-lymphocyte ratio (NLR) or isolated C-Reactive Protein (CRP) on the prognosis of different oncological diseases, namely in colorectal carcinoma (CRC) has been studied and recognized.[1–7]

The GPS consists of the combination of CRP values and serum albumin, and its increase may reflect a systemic inflammatory response state associated with the neoplastic process. Hypoalbuminemia can also be related to cachexia present in advanced stages of the disease.[8,9]

The increase in the NLR has been associated with a worse prognosis not only in several oncological diseases, but also in cases of cardiovascular diseases. The rationale that supports this association is also based on the fact that a greater systemic inflammatory response, often subclinical, may be related to a worse prognosis.[10]

Given these assumptions, it is extremely important to understand the relationship between these scales and the prognosis of patients operated due to CRC in order to be able to more quickly and easily establish the prognosis of patients and guide them in a more personalized and effective manner.

Materials and Methods

The present is an observational, retrospective and descriptive study.

The study population consisted of all patients with a diagnosis of CRC who underwent surgical treatment between January 1st, 2005, and December 31st, 2010. A non-probabilistic convenience sample was developed, applying several inclusion and exclusion criteria to the target population. Inclusion criteria: patients with postoperative histological diagnosis of colorectal adenocarcinoma, who underwent surgical resection at Hospital de Braga between January 1st, 2005, and December 31st, 2010. Exclusion criteria: patients undergoing surgical resection with palliative intent; patients undergoing urgent surgical resection; patients in whom it was not possible to assess the value of inflammatory parameters; patients with no result of histological staging; and patients who died in the postoperative period (30 days or less after surgery).

For each patient, we collected data on: gender; age at the date of surgery; personal history of neoplasia; family history of CRC; duration of the symptoms; tumor location; macroscopic aspect of the tumor; preoperative levels of carcinoembryonic antigen (CEA); tumor dimension; histological type; tumor staging; levels of lymphocytes, neutrophils, albumin and pre- and postoperative CRP; date of death; and date of onset of local recurrence and distant progression of the disease.

Cancer-related survival was defined as the period in months from the date of the first surgery to the date of cancer-related death.

Disease-free time was defined as the period from the first surgery until the diagnosis of local recurrence or distant progression of the disease.

As the present is a retrospective study, it was not possible to guarantee that the analyses had been carried out at the same pre- and postoperative periods. In order to minimize the impact of this situation, the data was collected at a interval-time within a maximum period of 15 days before and 3 days after surgery.

The statistical analysis was performed using the Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, IBM Corp., Armonk, NY, US) software, version 22.

For all tests performed, statistically significant results were defined as $p < 0.05$.

Initially, a descriptive analysis of the many variables collected was carried out, in order to characterize the sample under study. Then, three scales were chosen to characterize the systemic proinflammatory state of the patients: the NLR, the GPS, and elevation of isolated CRP. Each of the scales was applied to patients in the pre- and postoperative periods.

With regard to the NLR, which is the ratio between the absolute levels of neutrophils and lymphocytes, values above 5 eere considered high, according to a study by Urrejola et al.[11]

The GPS, which results from the combination of the CRP and albumin levels, was categorized into 3 groups (0, 1 and 2), depending on whether they had 0 altered values, only 1 or 2 respectively, as can be seen in ►**Table 1**. For the calculation of this scale, CRP levels higher than 1 mg/dl and albumin lower than 3.5 g/dl were defined as altered, since these were the reference values of the laboratory responsible for the analytical evaluation of all patients.

Table 1 Categorization of the different groups on the Glasgow Prognostic Score (GPS)

GPS = 0	CRP ≤ 1 mg/dl and albumin ≥ 3.5 g/dl
GPS = 1	CRP > 1 mg/dl or albumin < 3.5 g/dl
GPS = 2	CRP > 1 mg/dl and albumin < 3.5 g/dl

Abbreviation: CRP, C-reactive protein.

Finally, levels of isolated CRP was defined as increased when higher than 1 mg/dl, for the same reason mentioned for the calculation of the GPS.

In order to determine the correlation between the different scales and the clinico-pathological characteristics of the patients, crosstabs were performed, and the interdependence of the variables was analyzed using the Fisher exact test whenever the number of cells with a value lower than 5 was greater than 20% of the total cells, and the Pearson Chi-squared (χ^2) test when it was lower than 20%. As a measure of effect size, the Phi coefficient (Φ) was used for 2×2 tables, as well as the Cramer V for larger tables. For both coefficients, small, medium or large effects were considered for values close to 0.1, 0.3 and 0.5 respectively. For the variables that showed a statistically significant correlation, adjusted standardized residuals were evaluated, and residuals with an absolute value greater than 1.96 were considered as statistically significant, in order to determine the contribution of each cell to the significance of the test and thus determine the direction of the association.

In order to determine the impact of the elevation of the different scales on the outcome of the patients, an attempt was made to compare the time from surgery to the occurrence of two events: death by CRC or recurrence of the disease. For this purpose, Kaplan-Meier survival curves were made, in order to check if there were differences between the groups with increased and normal inflammatory parameters in relation to the survival time and disease-free time. The comparison between the survival curves of the different groups was performed using the log-rank test.

Finally, a univariate analysis of the impact of all variables under study on the patients' survival time was performed, followed by a multivariate analysis using only those that, in the univariate analysis, significantly influenced the survival time. For this evaluation, the Cox proportional-hazards model was used.

The present study was carried out in accordance with the principles of the Declaration of Helsinki, the Convention on Human Rights and Biomedicine, the guidelines of the Council for International Organizations of Medical Sciences, and the Guide to Good Clinical Practice, and was approved by the Ethics Subcommittee on the Life and Health Sciences of Universidade do Minho (SECVS-063/2017) and by the Health Ethics Committee of Hospital de Braga (HB-70/2017).

Results

After applying the exclusion criteria, a sample of 426 patients was obtained.

The clinico-pathological characteristics and the distribution of the sample in relation to the different scales are described in ►**Tables 2** and **3** respectively.

Of the studied patients, 32.8% died due to CRC. The remaining 67.2% are either still alive, or died of other causes, or were lost to follow-up. The average cancer-related survival of the patients was of about 117 months.

The cancer-related survival curve obtained by the Kaplan-Meier method is shown in ►**Figure 1**.

Table 2 Clinico-pathological characteristics of the sample

	n (%)
Gender	
Male	260 (61.0)
Female	166 (39.0)
Age (years)	
< 45	16 (3.8)
> 45	410 (96.2)
Previous neoplasia	
Present	56 (13.1)
Absent	370 (86.9)
Family history of colorectal canrcinoma	
Present	3 (7.7)
Absent	359 (83.3)
Unknown	34 (8.0)
Time with symptoms (months)	
< 6	287 (67.4)
> 6	59 (13.8)
Asymptomatic	80 (18.8)
Location	
Right colon	99 (31.7)
Left colon	213 (68.3)
Rectum	114 (26.8)
Macroscopic appearance	
Polypoid	222 (52.1)
Ulcerated	106 (24.9)
Infiltrative	34 (8.0)
Exophytic	29 (6.8)
Indeterminate	35 (8.2)
Carcinoembryonic antigen (ng/ml)	
≤ 10	307 (72.1)
> 10	52 (12.2)
Indeterminate	67 (15.7)
Tumor size (cm)	
≤ 4.5	255 (59.9)
> 4.5	154 (36.1)
Indeterminate	17 (4.0)
Histological type	
Adenocarcinoma	379 (89.0)
Mucinous adenocarcinoma	44 (10.3)
Signet-ring cell adenocarcinoma	3 (0.7)
Stage	
I	79 (18.5)
II	187 (43.9)
III	160 (37.6)

Of the studied patients, 23.2% had local or distant recurrence of the disease. The average disease-free time was of about 114 months.

Table 3 Distribution of patients in relation to the scales of systemic inflammatory markers

	Preoperative period	Postoperative period
Neutrophil-to-lymphocyte ratio		
Normal (≤ 5)	282	104
Increased (> 5)	75	276
Indeterminate	69	46
Glasgow Prognostic Score		
0	5	0
1	56	14
2	6	56
C-reactive protein		
Normal (≤ 1mg/dl)	9	1
Increased (> 1mg/dl)	90	177
Indeterminate	327	248

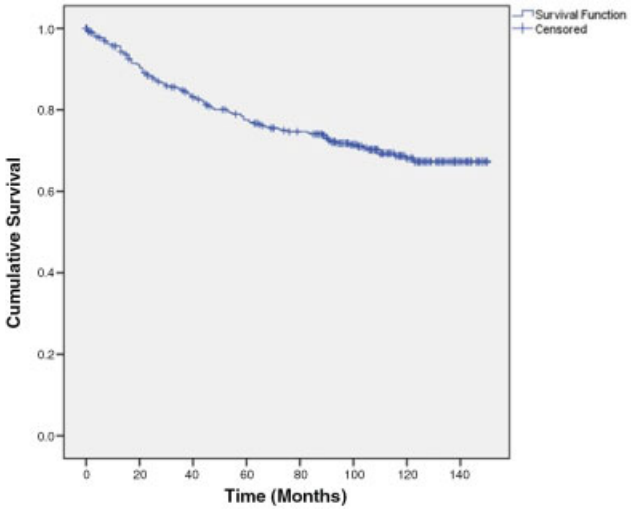

Fig. 1 Kaplan-Meier curve for CRC survival.

The survival curve related to disease-free time obtained by the Kaplan-Meier method is shown in ►**Figure 2**.

Interdependence Analysis

The assessment of the interdependence of the different clinical variables under study and the scales under analysis is outlined in ►**Tables 4**, **5**, **6**.

The evaluation of the crosstab tables regarding the various scores used revealed the existence of a correlation between increased preoperative NLR and the tumor location in the colon/rectum ($\chi^{2(1)} = 6.251$; $p = 0.012$; Φ = -0.132). The value of Φ shows that it is a weak association. The analysis of standardized adjusted residuals confirms that colon injury is associated with increased preoperative NLR, as can be seen in ►**Table 4**.

The preoperative NLR also showed a correlation with CEA values ($\chi^{2(1)} = 7.041$; $p = 0.008$; $\Phi = -0.152$) and more advanced

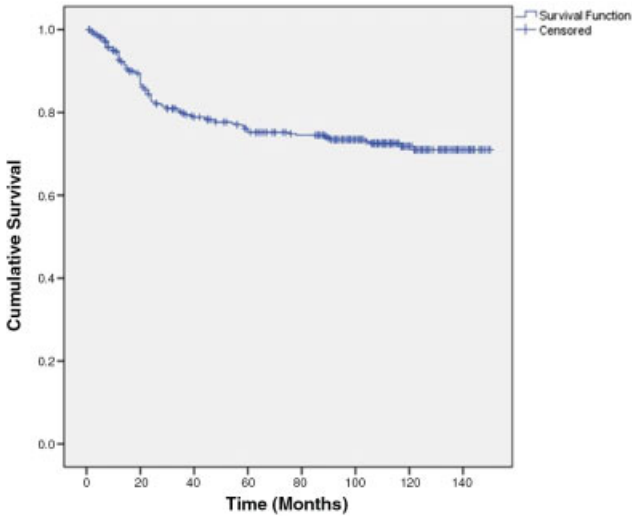

Fig. 2 Kaplan-Meier curve for the disease-free survival of patients.

stages of the disease ($\chi^{2(2)} = 8.823$; $p = 0.012$; Cramer V [V] = 0.157). Both situations reflect a weak correlation. The analysis of the standardized adjusted residuals shows that increased NLR is positively related to an increase in the CEA value, and to more advanced stages of the disease, as can be seen in ►**Table 4**.

Regarding the postoperative NLR, its increase is related to the patient's gender ($\chi^{2(1)} = 4.579$; $p = 0.032$; Φ = -0.110), and, in this case, it was higher NLR in male patients. There is also a correlation with the increase in CEA ($\chi^{2(1)} = 5.576$; $p = 0.018$; Φ = -0.132), with higher values of NLR associated with higher values of CEA. Again, in both cases it is a weak association, as can be seen in ►**Table 4**.

The preoperative GPS was associated with the stage of the disease (Fisher exact test; $p = 0.017$), with a lower GPS associated with less advanced stages of the disease, as can be seen in ►**Table 5**.

The postoperative GPS, on the other hand, was associated with family history (Fisher exact test; $p = 0.010$), with a higher GPS with the presence of family history. There was also a correlation between the elevation of the preoperative GPS and the occurrence of symptoms prior to diagnosis ($\chi^{2(1)} = 11.430$; $p < 0.001$; $\Phi = 0.404$), as can be seen in ►**Table 5**.

The increase in preoperative CRP, in turn, was associated with the location of the tumor in the colon (Fisher exact test; $p = 0.019$) and with its larger dimension (Fisher exact test; $p = 0.026$), as can be seen in ►**Table 6**.

Cancer-Related Survival Assessment

In order to assess the time of cancer-related survival in relation to the various scales under study, Kaplan-Meier curves were made for each group, and these were compared using the log-rank test.

Patients with increased NLR in the preoperative period had a significantly lower survival than patients with normal NLR (average survival of 122 months and 93.7 months respectively; $p < 0.001$), as shown in ►**Figure 3A** and ►**Table 7**.

Table 4 Analysis of interdependence between pre- and postoperative NLR and several clinico-pathological variables

	Preoperative NLR			Postoperative NLR		
	≤ 5	> 5	Statistics	≤ 5	> 5	Statistics
Gender						
Male	176	49	$\chi^2 = 0.217$ $\Phi = -0.25$ $p = 0.641$	57	184	$\chi^2 = 4.579$ $\Phi = -0.110$ $p = \mathbf{0.032}$
Female	106	26		47	282	
Age (years)						
≤ 45	10	2	$p \leq 0.99$	6	9	$\chi^2 = 1.253$ $\Phi = 0.057$ $p = 0.263$
> 45	272	73		98	267	
Previous tumor						
Yes	66	9	$\chi^2 = 0.317$ $\Phi = -0.30$ $p = 0.573$	9	42	$\chi^2 = 2.801$ $\Phi = 0.086$ $p = 0.094$
No	241	41		95	234	
Family history						
Yes	26	4	$p = 0.473$	6	25	$\chi^2 = 0.993$ $\Phi = 0.053$ $p = 0.319$
No	239	61		88	230	
Presentation						
Asymptomatic	60	10	$\chi^2 = 2.371$ $\Phi = 0.082$ $p = 0.124$	21	52	$\chi^2 = 0.089$ $\Phi = 0.015$ $p = 0.766$
Symptomatic	222	65		83	224	
Time with symptoms						
$<$ 6 months	182	56	$\chi^2 = 0.618$ $\Phi = -0.046$ $p = 0.432$	71	185	$\chi^2 = 0.381$ $\Phi = 0.035$ $p = 0.537$
$>$ 6 months	40	9		12	39	
Location						
Colon	196	86	$\chi^2 = 6.251$ $\Phi = -0.132$ $p = \mathbf{0.012}$	76	199	$\chi^2 = 0.036$ $\Phi = 0.010$ $p = 0.850$
Rectum	63	12		28	77	
Macroscopic appearance						
Polypoid	154	33	$\chi^2 = 1.677$ $V = 0.071$ $p = 0.624$	54	147	$\chi^2 = 0.585$ $V = 0.041$ $p = 0.900$
Ulcerated	74	15		27	68	
Infiltrative	22	8		10	21	
Exophytic	21	4		6	19	
Carcinoembryonic antigen (ng/ml)						
≤ 10	220	27	$\chi^2 = 7.041$ $\Phi = 0.152$ $p = \mathbf{0.008}$	88	191	$\chi^2 = 5.576$ $\Phi = 0.132$ $p = \mathbf{0.018}$
> 10	44	14		6	37	
Tumor size (cm)						
≤ 4.5	170	102	$\chi^2 = 1.356$ $\Phi = 0.063$ $p = 0.244$	66	162	$\chi^2 = 1.752$ $\Phi = 0.069$ $p = 0.186$

(*Continued*)

Table 4 (*Continued*)

	Preoperative NLR			Postoperative NLR		
	≤ 5	> 5	Statistics	≤ 5	> 5	Statistics
> 4.5	39	32		31	106	
Histological type						
Adenocarcinoma	250	65	$p = 0.818$	97	239	$p = 0.157$
Mucinous adenocarcinoma	30	9		7	34	
Signet-ring cell adenocarcinoma	2	1		0	3	
Stage						
I	63	8	$\chi^2 = 8.823$ V = 0.157 $p = \mathbf{0.012}$	17	59	$\chi^2 = 2.717$ V = 0.085 $p = 0.257$
II	120	28		41	119	
III	99	39		46	98	

Abbreviations: NLR, Neutrophil-to-lymphocyte ratio; V, Cramer V; Φ, Phi coefficient; χ^2, Chi-squared.

Also, patients with increased NLR in the postoperative period had a lower survival than patients with normal NLR (average survival of 132 months and 112 months respectively; p = 0.002), as shown in ►**Figure 3B** and ►**Table 7**.

The application of the GPS did not show significant differences between patients who scored 0, 1 or 2 on the scale, both in the pre- and postoperative periods (p = 0.092 and 0.254 respectively), as shown in ►**Figures 4A** and **4B**.

The value of the isolated CRP was only used in the preoperative period, since, in the postoperative period, only one patient had values within normal limits. However, the increase in preoperative CRP showed a statistically significant decrease in patient survival (p = 0.038), which is illustrated in ►**Figure 5**.

Evaluation of Disease-Free Time

Similarly, the time from surgery to the occurrence of local and distant recurrences of the disease was also evaluated, using the comparison of the Kaplan-Meier curves of the patients according to the different scales.

The evaluation and comparison of the curves showed significant differences in disease-free time in patients with increased NLR in the preoperative period compared to patients with normal NLR (88.0 months and 123 months respectively; p < 0.001), as shown in ►**Figure 6A** and ►**Table 8**. In the postoperative period, these differences were also noticeable (132 months if normal NLR, and 111 months if increased NLR; p = 0.002), as shown in ►**Figure 6B** and ►**Table 8**.

The application of the GPS did not show significant differences at any time with regard to the time until recurrence (p = 0.083 and 0.538 respectively), as shown in ►**Figures 7A** and **7B**.

In this case, it was only possible to evaluate the CRP in the preoperative period, which showed a tendency towards significance between the two groups (p = 0.059), as shown in ►**Figure 8**.

Uni- and Multivariate Analysis of the Impact on Cancer-Related Survival

In order to determine the impact of each variable on the cancer-related survival of the patients, a univariate analysis was performed according to the Cox regression model. Then, using the variables that showed statistical significance in the univariate analysis, a multivariate analysis was carried out in order to determine which variables influenced the survival time independently of the others, as shown in ►**Table 9**.

An observation of the univariate analysis in ►**Table 9** enables us to conclude that the risk of death from CRC among patients with levels of CEA greater than 10 ng/ml is 2.21 times higher than that of patients with normal CEA levels (unadjusted hazard ratio [HR] = 2.21; p = 0.002). In addition, the risk of dying due to CRC among patients in stage II is 3.02 times higher than that of patients in stage I (unadjusted HR = 3.02; p = 0.007). In turn, stage-III patients have a 6.06-fold higher risk (unadjusted HR = 6.06; p < 0.001). The univariate analysis of the impact of inflammatory markers on CRC-related survival confirms what had already been verified in the analysis of survival curves. The increase in the NLR in the preoperative period is associated with a 2.25-fold increased risk of death from CRC (unadjusted HR = 2.25; p < 0.001). In the postoperative period, the increase in this scale implies an increase of 2.18 in the risk (unadjusted HR = 2.18; p = 0.003).

The increase in the GPS in the pre- and postoperative periods was not associated with a statistically significant increase in the risk of death from CRC, as did the CRP score in the preoperative period.

The multivariate analysis enables the identification of the variables that influence the survival time related to CRC independently from the other variables. By observing the multivariate analysis in ►**Table 9**, we can conclude that patients in stages II (adjusted HR = 3.37; p = 0.013) and III (adjusted HR = 6.71; p < 0.001) present a risk of 3.37 times and 6.71 times higher of death from CRC respectively. Also, the increased postoperative NLR independently increases the risk of death from CRC by 2.66 times (adjusted HR = 2.66 and p = 0.002).

Table 5 Analysis of interdependence between pre- and postoperative GPS and several clinico-pathological variables

	Preoperative GPS			Postoperative GPS		
	0	1/2	Statistics	1	2	Statistics
Gender						
Male	4	49	$p \leq 0.99$	9	37	$\chi^2 = 0.016$ $\Phi = -0.015$ $p = 0.900$
Female	1	13		5	19	
Age (years)						
≤ 45	0	2	$p < 0.99$	0	1	$p \leq 0.99$
> 45	5	60		14	55	
Previous tumor						
Yes	1	4	$p = 0.330$	1	3	$p \leq 0.99$
No	4	58		13	53	
Family history						
Yes	2	6	$p = 0.110$	5	4	$p = \mathbf{0.010}$
No	3	54		8	51	
Presentation						
Asymptomatic	1	17	$p \leq 0.99$	7	6	$\chi^2 = 11.430$ $\Phi = 0.404$ $p < \mathbf{0.001}$
Symptomatic	4	45		7	50	
Time with symptoms						
$<$ 6 months	3	33	$p \leq 0.99$	6	41	$p \leq 0.99$
$>$ 6 months	1	12		1	9	
Location						
Colon	2	50	$p = 0.070$	11	39	$p = 0.742$
Rectum	3	12		3	17	
Macroscopic appearance						
Polypoid	2	35	$p = 0.369$	10	25	$p = 0.315$
Ulcerated	3	15		2	18	
Infiltrative	0	5		0	4	
Exophytic	0	5		1	6	
Carcinoembryonic antigen (ng/ml)						
≤ 10	4	53	$p \leq 0.99$	11	41	$p \leq 0.99$
> 10	0	6		2	6	
Tumor size (cm)						
≤ 4.5	5	36	$p = 0.148$	9	31	$p = 0.592$
> 4.5	0	25		5	24	
Histological type						
Adenocarcinoma	4	54	$p = 0.526$	14	46	$p = 0.194$
Mucinous adenocarcinoma	1	8		0	10	
Signet-ring cells adenocarcinoma	–	–		–	–	
Stage						
I	3	7	$p = \mathbf{0.017}$	4	7	$\chi^2 = 2.187$ $\Phi = 0.177$ $p = 0.335$
II	2	30		5	25	
III	0	25		5	24	

Abbreviations: GPS, Glasgow Prognostic Score; Φ, Phi coefficient; χ^2, Chi-squared.

Table 6 Analysis of the interdependence between preoperative C-reactive protein and several clinico-pathological variables

	Preoperative C-reactive protein		
	≤ 1	> 1	Statistics
Gender			
Male	7	65	$p \leq 0.99$
Female	2	25	
Age (years)			
≤ 45	0	4	$p \leq 0.99$
> 45	9	86	
Previous tumor			
Yes	1	10	$p \leq 0.99$
No	8	80	
Family history			
Yes	1	8	$p = 0.568$
No	7	78	
Presentation			
Asymptomatic	2	20	$p \leq 0.99$
Symptomatic	7	70	
Time with symptoms (months)			
< 6	6	56	$p \leq 0.99$
> 6	1	14	
Location			
Colon	4	74	$p = \mathbf{0.019}$
Rectum	5	16	
Macroscopic appearance			
Polypoid	4	48	$p = 0.087$
Ulcerated	2	22	
Infiltrative	3	6	
Exophytic	0	6	
Carcinoembryonic antigen (ng/ml)			
≤ 10	7	70	$p \leq 0.99$
> 10	0	8	
Tumor size			
≤ 4.5 cm	9	55	$p = \mathbf{0.026}$
> 4.5 cm	0	33	
Histological type			
Adenocarcinoma	8	79	$p \leq 0.99$
Mucinous adenocarcinoma	1	11	
Signet-ring cell adenocarcinoma	Not available	Not available	
Stage			
I	3	12	$p = 0.234$
II	4	41	
III	2	37	

Note: The value of the isolated CRP was only used in the preoperative period, since, in the postoperative period, only 1 patient had normal values.

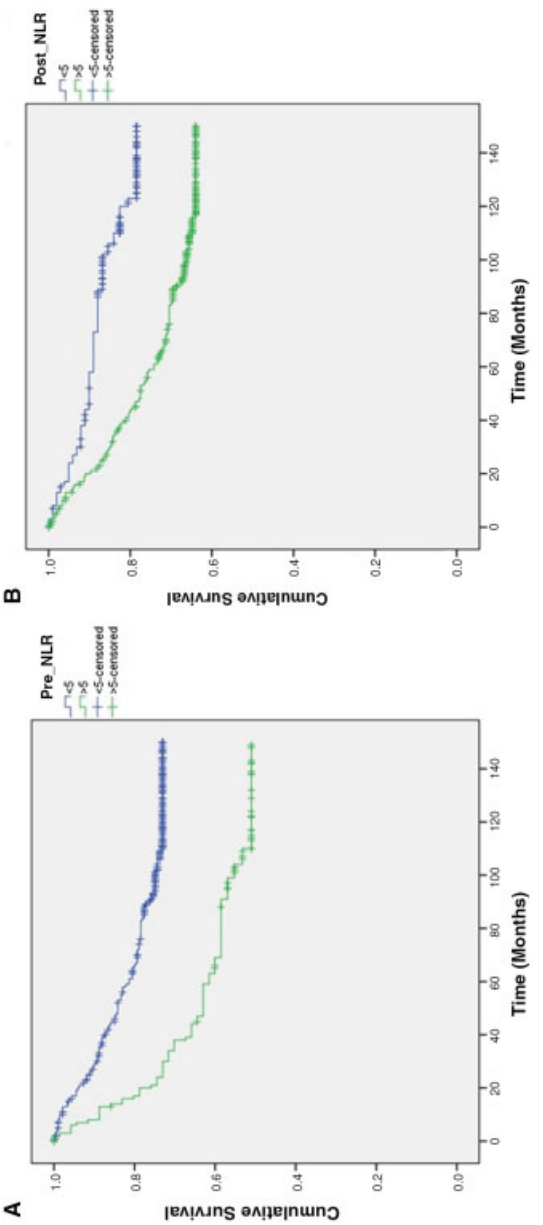

Fig. 3 Kaplan-Meier curves for survival according to the NLR in the preoperative (A) and postoperative (B) periods.

The levels of CEA and the value of the preoperative NLR do not significantly increase the risk of death from CRC independently of the other variables.

Table 7 Average cancer-related survival time according to NLR in the preoperative and postoperative periods

	Average			
	Estimate	Standard error	95% confidence interval	
			Inferior limit	Superior limit
Preoperative NLR				
< 5	122.248	3.009	116.350	128.145
> 5	93.675	7.332	79.305	108.045
Global	116.401	2.900	110.717	122.086
Postoperative NLR				
< 5	131.792	4.100	123.757	139.827
> 5	112.022	3.408	105.343	118.701
Global	117.488	2.751	112.096	122.880

Abbreviation: NLR, Neutrophil-to-lymphocyte ratio.

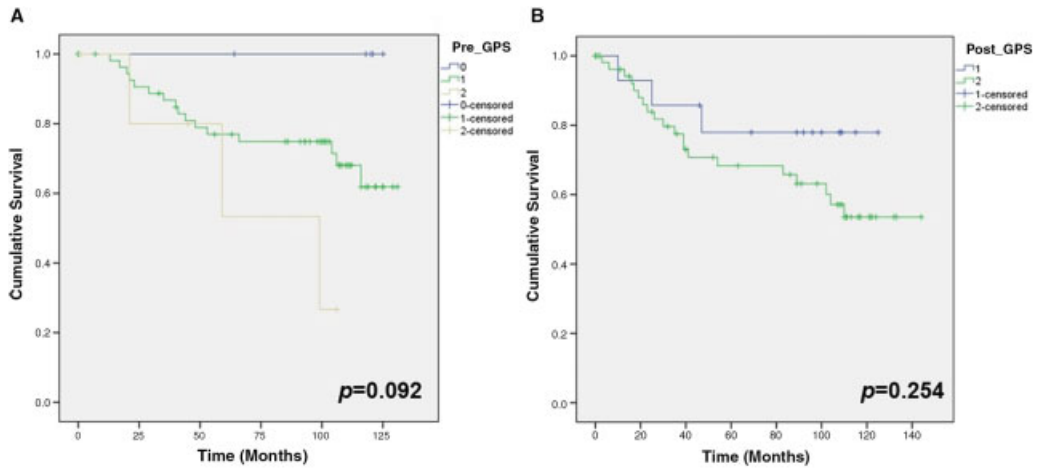

Fig. 4 Kaplan-Meier curves for survival according to the GPS in the preoperative (A) and postoperative (B) periods.

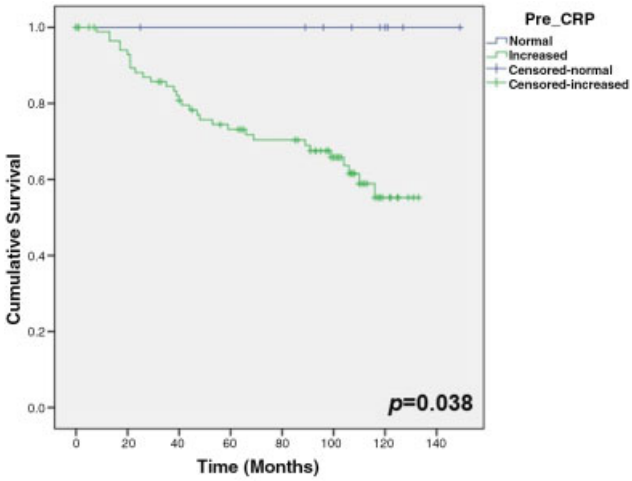

Fig. 5 Kaplan-Meier curve for survival according to CRP levels.

Discussion

Currently, staging is the main determinant of the prognosis of patients with CRC.[1,12] Recently, the impact of the elevation of systemic inflammatory markers has gained increasing interest. Scales such as the GPS, the NLR and isolated CRP have been shown to influence the prognosis of various cancers, including CRC.[2–7,11,13]

The study sample, composed of 426 patients, showed a predominance of male individuals, which is in agreement with what is described in the literature.[14] Moreover, the median age at diagnosis, 71.5 years, with 96.2% of the diagnoses occuring after the age of 45 years, is in accordance with the bibliographic data, which place age as one of the main non-modifiable risk factors for the development of CRC.[1,13,15] Regarding the location of the tumor, there was a predominance of tumors located in the left colon (50.0%), which is also in accordance with what is described in the literature.[16–18]

Regarding the impact of the elevation of the different inflammatory markers on survival, we found that patients with increased NLR in the preoperative period ($p < 0.001$) had a significantly lower survival rate than patients with normal NLR. The same was true for patients with increased NLR in the postoperative period ($p = 0.002$).

In addition, the increase in the preoperative levels of isolated CRP was associated with a significant decrease in patient survival ($p = 0.038$).

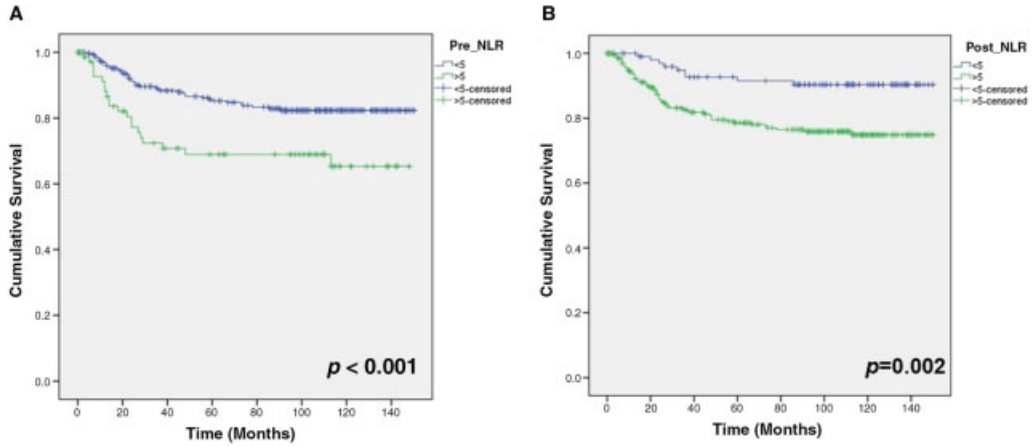

Fig. 6 Kaplan-Meier curves for disease-free survival according to the NLR in the preoperative (**A**) and postoperative (**B**) periods.

Table 8 Average disease-free time according to NLR in the preoperative and postoperative periods

	Average			
	Estimate	Standard error	95% confidence Interval	
			Inferior limit	Superior limit
Preoperative NLR				
< 5	122.710	3.201	116.436	128.984
> 5	88.004	7.685	72.942	103.065
Global	115.657	3.105	109.572	121.742
Postoperative NLR				
< 5	132.010	4.377	123.430	140.590
> 5	110.784	3.720	103.493	118.075
Global	116.977	2.973	111.150	122.805

Abbreviation: NLR, Neutrophil-to-lymphocyte ratio.

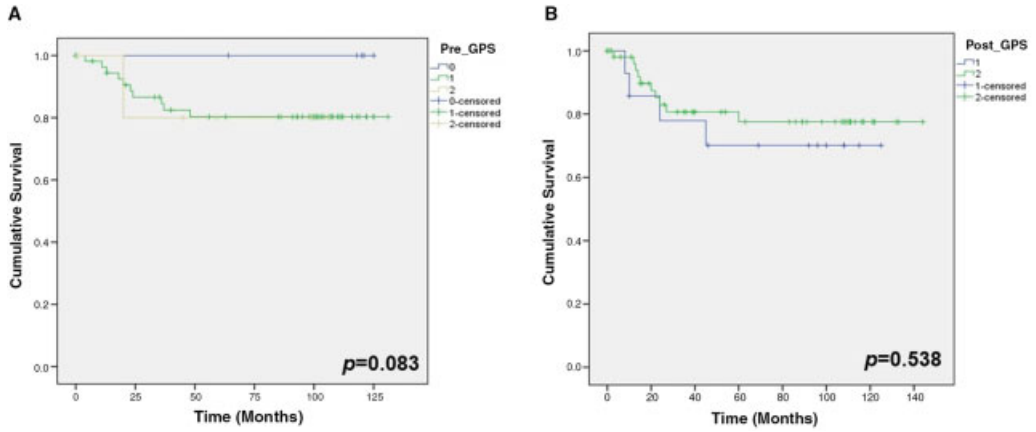

Fig. 7 Kaplan-Meier curves for disease-free survival according to the GPS in the preoperative (**A**) and postoperative (**B**) periods.

Regarding the GPS, no significant differences in survival were detected either in the preoperative period ($p = 0.092$) or in the postoperative period ($p = 0.254$).

With regard to the local and distant recurrences of the disease, significant differences were detected in the disease-free time in patients with increased NLR in the preoperative period compared to patients with normal NLR ($p < 0.001$). This was also observed in the postoperative period ($p = 0.002$). However, neither the application of the GPS (preoperatively: $p = 0.083$; postoperatively: $p = 0.538$), nor the isolated CRP ($p = 0.059$ in the preoperative period) showed significant differences in relation to recurrence.

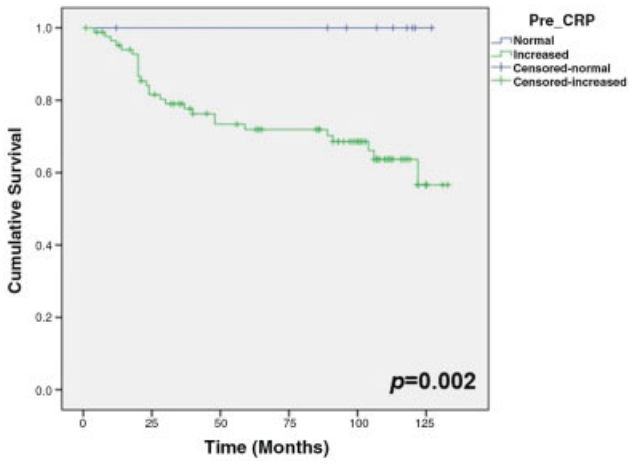

Fig. 8 Kaplan-Meier curve for disease-free survival according to CRP levels in the preoperative period.

The univariate analysis of the data showed that the increase in the levels of CEA (unadjusted HR = 2.21; p = 0.002), more advanced stages of the disease (stage II: unadjusted HR = 3.02; p = 0.007; stage III: unadjusted HR = 6.06; p < 0.001), and an elevation of the NLR in the preoperative and postoperative periods (unadjusted HR = 2.25; p <0.001; unadjusted HR = 2.18; p = 0.003 respectively) are associated with a higher risk of death due to CRC.

The multivariate analysis, in turn, showed that, of these variables, only the advanced stage (stage II: adjusted HR = 3.37; p = 0.013; stage III: adjusted HR = 6.71; p <0.001) and the postoperative NLR (adjusted HR = 2.66; p = 0.002), increase the risk independently of the remaining variables.

The fact that the preoperative NLR did not show significant results in the multivariate analysis may be due to the existence of a correlation (p = 0.012) between increased preoperative NLR and more advanced stages of the disease, which is not the case for postoperative NLR, as can be confirmed in ►**Table 4**.

Table 9 Univariate and multivariate analyses of the impact of different variables on the time of cancer-related survival of patients, according to the Cox regression model

	Univariate analysis			Multivariate analysis		
	Unadjusted hazard ratio	95% confidence interval	p-value	Adjusted hazard ratio	95% confidence interval	p-value
Gender (female)	1.012	0.689–1.486	0.953	–	–	–
Age (> 45 years)	1.534	0.487–4.830	0.465	–	–	–
Previous tumor (yes)	0.937	0.535–1.640	0.818	–	–	–
Family history (yes)	0.507	0.222–1.158	0.107	–	–	–
Presentation (symptomatic)	1.220	0.752–1.978	0.421	–	–	–
Time with symptoms (> 6 months)	0.757	0.412–1.388	0.368	–	–	–
Location (Rectum)	1.047	0.695–1.578	0.826	–	–	–
Macroscopic appearance				–	–	–
Polypoid	0.877	0.376–2.044	0.761			
Ulcerated	1.070	0.445–2.572	0.880			
Infiltrative	1.527	0.580–4.019	0.391			
Carcinoembryonic antigen (> 10)	2.206	1.334–3.647	**0.002**	1.707	0.986–2.954	0.056
Tumor size (>4.5 cm)	1.116	0.757–1.645	0.580	–	–	–
Histological type (mucinous)	1.374	0.770–2.452	0.283	–	–	–
Stage						
II	3.018	1.357–6.710	**0.007**	3.367	1.299–8.729	**0.013**
III	6.064	2.774–13.257	< **0.001**	6.706	2.630–17.102	< **0.001**
Preoperative NLR (> 5)	2.252	1.484–3.418	< **0.001**	1.509	0.902–2.523	0.117
Postoperative NLR (>5)	2.178	1.310–3.621	**0.003**	2.656	1.412–4.998	**0.002**
Preoperative GPS (1 or 2)	2.47	0.042–8.028	0.352	–	–	–
Postoperative GPS (2)	2.000	0.593–6.474	0.264	–	–	–
Preoperative CRP (> 1 mg/dl)	2.481	0.217–2.841	0.184	–	–	–

Abbreviations: GPS, Glasgow Prognostic Score; CRP, C-reative protein; NLR, Neutrophil-to-lymphocyte ratio.

Thus, we can conclude that, in the study sample, the NLR would be the scale whose results most consistently influenced the patients' prognosis, regarding cancer-related survival and the time to relapse of the disease. However, only the postoperative NLR of the scales under analysis influences the prognosis independently of the remaining variables.

This conclusion can be supported by the understanding of the pathophysiological mechanisms in which these immune cells are involved, since the increase in the number of neutrophils has been associated with tumor progression, by the creation of cytokines that induce tumor growth, as well as by the creation of an proangiogenic environment, favorable to vascularization and tumor invasion.[19–21] In contrast, lymphocytes play a primarily antitumor role, and their increase reflects the activation of the patient's immune system.[22–25]

The first study to demonstrate a direct relationship between elevated inflammatory markers and decreased survival in patients with CRC was carried out in 2007 by McMillan et al.,[26] who showed that an increase in the preoperative GPS was associated with a shorter survival.

In 2012, Sugimoto et al.[3] also demonstrated that an increased GPS was related to decreased survival, as did Guthrie et al.,[27] who, in 2013, obtained similar results. The latter study even concluded that the GPS was a scale superior to the NLR in assessing the impact on survival.

There are several studies demonstrating the association between patients and an increase in the preoperative inflammatory parameters; however, few are related to the postoperative period. Nevertheless, in 2015, Shibutani et al.[28] concluded that an elevated NLR both in the preoperative and postoperative periods correlated with a decrease in patient survival.

More recently, Rosi et al.[29] demonstrated that the GPS and the NLR are superior to other markers in assessing the survival of patients with CRC.

Much less frequent are the studies relating the increase in inflammatory parameters with the recurrence of the disease. However, in 2017, Balde et al.[30] demonstrated that an increase in the preoperative NLR is a strong predictor of shorter survival time without recurrence.

The present study has some limitations. The fact that this is a retrospective study makes it difficult to collect the data, and to ensure the homogeneity of the records. In addition, some patients were lost to follow-up. Regarding the comparison of the scales, there was less data available for the GPS and CRP than for the NLR, which may help to justify the fact that the former two did not show significant results.

Conclusion

Inflammatory markers have been increasingly associated with the prognosis of different neoplasias, namely CRC. The present study demonstrated an association between pre- and postoperative NLR and the survival and recurrence of patients with CRC. In addition, it showed that the postoperative NLR influences CRC mortality independently of the remaining variables.

These markers are routinely requested in the preoperative exams of patients, so they are accessible and do not represent an additional cost; therefore, their implementation in clinical practice is simple and will enable an assessment of additional surgical risk as well as the prognosis of the patient.

Conflict of Interests

The authors have no conflict of interests to declare.

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