

# Inflammation biomarkers as predictors of nodal metastases in colorectal cancer

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## Abstract

**Aim:** The role of chronic inflammation in the genesis and promotion of cancer has been established lately by various researchers. The neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and CRP-to-albumin ratio, and their diagnostic and prognostic significance, are currently under review. The current paper presents a preliminary study on the Greek population of patients suffering from Colorectal Cancer (CRC) to test the correlation between the inflammation markers and the possibility of nodal metastases.

**Materials and methods:** Retrospective study of all patients treated surgically for CRC in our Surgical Department during the period 2018-2021. We categorized patients as elective and complicated cases, urgently leading to the operating room. We calculated the pre-operative neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and CAR (CRP/albumin ratio) of the two groups. The primary endpoint of this study was the evaluation of the prognostic significance of NLR, PLR, and CAR as markers predictive of nodal metastases. Secondary endpoints were the set of cut-off values for each of these markers in the elective and emergency groups.

**Results:** Overall, 131 patients were included in the study, 89 of whom were treated electively. For all the biomarkers, statistically significant differences were detected between the elective and the emergency surgery groups. The only marker that was found to have prognostic significance on the nodal status was the CAR value, with a cut-off value calculated at 4.7 [sensitivity (61.82%) and specificity (66.67%)].

**Conclusion:** The inflammation markers previously proved to be related to CRC differ between patients treated electively and urgently. Better categorization of patient populations should be used to get more accurate results. CAR seems to be able to predict nodal metastases preoperatively. Further large-scale studies are needed to validate our results.

## Keywords

CAR, colorectal cancer, CRP-to-albumin ratio, emergency surgery, NLR, nodal metastases, PLR

## Introduction

Chronic inflammation has been proposed to provide the perfect environment for malignancies to rise and grow.

The role of the neutrophil-to-lymphocyte ratio (NLR) and CRP-to-albumin ratio (CAR) as predictive and prognostic factors for patients with colorectal cancer is increasingly being acknowledged. Previous studies have reported the

prognostic significance of NLR in colorectal cancer, as well as in other types of malignancies.<sup>[1]</sup> Among others, hepatocellular carcinoma, melanoma, and gynecological cancers have been shown to demonstrate a higher risk of poor prognosis when the pretreatment NLR values were high.<sup>[2]</sup>

Researchers have already implied that neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and C-reactive-protein-to-albumin ratio (CAR) are different among different populations, especially between various ethnicities and races, probably due to the different epigenetic factors to which the individuals are exposed.<sup>[3]</sup> However, no study on the Greek population suggests a possible cut-off value.

Furthermore, it has already been proven that NLR and CAR are markers affected by the organism's generalized inflammatory response. For example, patients diagnosed with cardiovascular disease, pneumonia, or bacteremia for other reasons are reported in the literature to demonstrate high NLR and CAR values, and these increased inflammation markers were associated with poorer prognosis.<sup>[4]</sup> This data suggests that patients presenting with a complicated disease, such as perforation or bowel obstruction, demonstrate higher values than those diagnosed with a routine control.

## Aim

This study aimed primarily to test the prognostic significance of the inflammation biomarkers on the nodal status of patients treated for CRC. Also, we thought it would be useful to provide preliminary data on Greek patients' NLR, PLR, and CAR values and highlight the difference in these ratios between patient groups, who were treated either urgently or scheduled for their disease, so that the basis for further research would be set.

## Materials and methods

Data on patients treated for colorectal surgery on a scheduled (Group 1) or an emergency (Group 2) basis during the period 2018-2021 were collected from CBC count forms. Blood samples were gathered either on the day before surgery for the elective group or on the same day before the beginning of surgery for the emergency operation group. The NLR, PLR, and CAR values were calculated for the two groups separately and then compared to each other via the non-parametric Mann-Whitney test. The quantitative results are reported as medians and ranges.

A logistic regression model was applied to identify the independent prognostic factors for nodal metastasis. ROC analysis was implemented to define the diagnostic accuracy of these indices. Statistical analysis was conducted using SPSS v 26.0, while Gpower 3.1 was used to conduct post hoc power analysis, and the significance was set at 0.05 in all cases. The critical appraisal was conducted by two independent researchers.

All data were analyzed anonymously. However, all patients signed a written consent form at their admission, allowing the researchers to use their medical records for research purposes. The hospital's ethics committee has also given its written consent for the conduct of the current study.

The primary endpoint of this study was to test the use of NLR, PLR, and CAR as markers predictive of nodal metastases in CRC patients. Secondary outcomes were the calculation of cut-off values for each of the two groups, elective and emergency operations.

## Results

Overall, 131 patients were included in the study; all have undergone surgery during the period 2018-2021. Fifty-six were women, and 75 were men. The mean age for the emergency surgery group was 71.7 years (range 52-90 years), while for the scheduled surgery group it was 72.9 years (range 45-90 years). Patient demographics are described in **Table 1**. Forty-two (32%) patients were treated urgently due to complications. The most common complications that led to surgery were bowel obstruction (21/42, 50%) and bleeding/hematochezia (7/42, 16.66%) (**Table 2**).

Most tumors treated were in the sigmoid colon in both the elective and the emergency groups [27 (30.34%) and 17 (40.48%), respectively]. The TNM stage varied mainly, including T3 tumors with variable nodal metastasis. Tumor characteristics may be reviewed in **Table 3**.

Because the marker for which there is the most data in the literature is NLR, the power analysis performed was based on the hypothesis that preoperative NLR could predict the nodal status of our patients. The results of the power analysis showed that a sample of 113 participants was needed to detect statistically significant differences between the two groups based on NLR values.

In **Table 4**, the information regarding the inflammation markers tested in the elective and the emergency surgery groups is presented. For all three parameters, there were statistically significant differences, indicating that patients treated urgently due to a complication demonstrated higher levels of inflammation markers. More specifically, the median NLR of the elective group was 3.08 in contrast to 5.93 for the emergency (Mann-Whitney U test 2879.5;  $p < 0.001$ ). In addition, the CAR value for the elective group

**Table 1.** Patients' demographics

	Group 1 (elective surgery)	Group 2 (emergency surgery)
Men	57	18
Women	32	24
Total number of patients	89	42
Age, mean (range)	72.9 (45-90)	71.7 (52-90)

**Table 2.** Symptoms that led to surgery

	Group 1 (N=89)	Group 2 (N=42)
Bowel ischemia	-	1 (2.4%)
Diarrhea	12 (13.5%)	1 (2.4%)
Bleeding/hematochezia	22 (24.7%)	7 (16.7%)
Loss of appetite	-	1 (2.4%)
Abdominal pain	3 (3.4%)	2 (4.8%)
Anemia	12 (13.5%)	2 (4.8%)
Bowel obstruction	-	21 (50%)
Bowel perforation	-	4 (9.6%)
Abdominal abscess	-	3 (7.2%)
Asymptomatic	13 (14.6%)	-
Constipation	15 (16.9%)	-
Weight loss	3 (3.4%)	-
Melena	2 (2.25%)	-
Fatigue	2 (2.25%)	-
Palpable mass	2 (2.25%)	-
Found in follow-up for other cancer (breast, bladder)	3 (3.4%)	-

was 1.86 (median) vs. 10 for the emergency surgery group (Mann-Whitney U test 2670.5;  $p < 0.001$ ).

Regarding the primary endpoint, first, the three markers were evaluated for patients either having nodal metastases in the pathologist's report or not. There was a significant difference only between the CAR values of patients having a positive nodal status (median 7.31 vs. 2.44 for the node-negative group,  $p < 0.007$ ). The rest of the biomarkers did not demonstrate a significant result (Table 5). The CAR prognostic significance of nodal metastases was confirmed after the logistic regression analysis, as demonstrated in Table 6, while the rest of the variables failed to prove a significant effect.

The ROC curve presented in Fig. 1 shows the discriminating ability of CAR regarding the nodal metastases' status in a pooled population of all patients, treated either urgently or electively. The only marker that was found to be significant was the CAR value, with a cut-off value of 4.7 demonstrating the best sensitivity (61.82%) and specificity

**Table 3.** Tumor characteristics

	Group 1 (N=89)	Group 2 (N=42)
<b>Tumor location</b>		
Cecum	23 (25.84%)	4 (9.52%)
Ascending colon	19 (21.34%)	7 (16.67%)
Transverse colon	7 (7.87%)	1 (2.38%)
Descending colon	4 (4.49%)	6 (14.29%)
Sigmoid	27 (30.34%)	17 (40.48%)
Rectum	9 (10.11%)	7 (16.67%)
<b>T stage</b>		
Tis	1 (1.12%)	-
T1	7 (7.87%)	2 (4.76%)
T2	18 (20.22%)	6 (14.29%)
T3	55 (61.80%)	30 (71.42%)
T4	8 (8.99%)	4 (9.52%)
<b>N stage</b>		
Nx	3 (3.37%)	1 (2.38%)
N0	52 (58.43%)	19 (45.24%)
N1	21 (23.60%)	12 (28.57%)
N2	13 (14.61%)	10 (23.81%)
<b>M stage</b>		
M0	78 (87.64%)	36 (85.71%)
M1	11 (12.36%)	6 (14.29%)

(66.67%). However, as you can see in Fig. 2, when we tested the accuracy of the markers separately for the two groups (elective vs. emergency), the prognostic significance of the CAR was more profound in the elective group. In the elective group, the cut-off value of CAR that best predicted nodal involvement was 2.28, with a sensitivity of 63.64% and specificity of 62.75% (AUC 0.63).

To conclude, a statistically significant relation between the preoperative CAR values and the nodal status of CRC patients was demonstrated, while NLR and PLR failed to predict the N status. Furthermore, the differences between the elective and urgent cases dictate that they should be considered separately as far as NLR, PLR, and CAR values in further research.

**Table 4.** NLR, PLR, and CAR values (median, range)

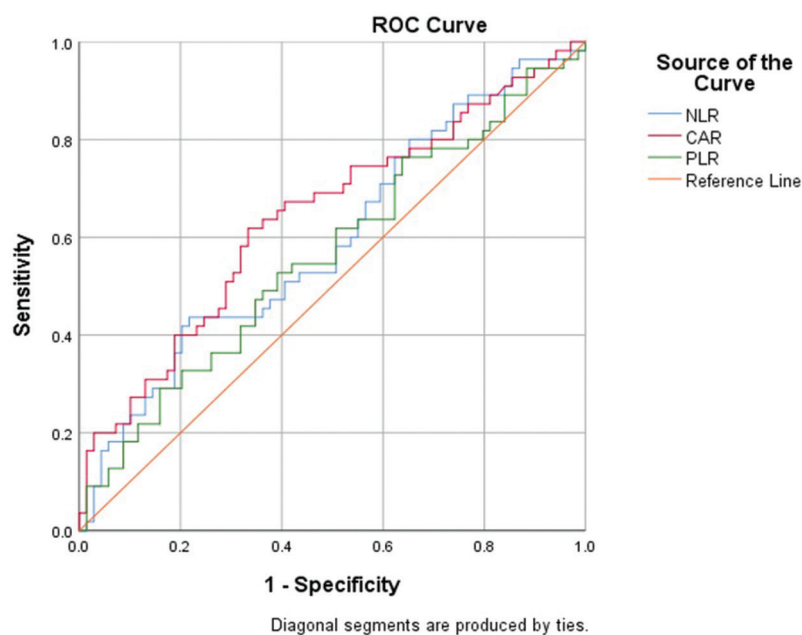
			Median	Range	Valid N	Mann-Whitney U test	Asymptotic Sig.(2-sided test)
NLR	Surgery	Elective	3.08	42.54	89	2879.500	0.000
		Emergency	5.93	34.56	42		
CAR	Surgery	Elective	1.86	98.99	87	2670.500	0.000
		Emergency	10.00	200.93	41		
PLR	Surgery	Elective	180.11	574.64	89	2512.500	0.002
		Emergency	239.96	1569.78	42		

**Table 5.** NLR, CAR and PLR relation to Nodal status

			Median	Range	Valid N		
NLR	Nodes (N)	No	3.59	42.50	72	2368.	0.059
		Yes	4.04	34.76	55		
CAR	Nodes (N)	<b>No</b>	<b>2.44</b>	<b>98.99</b>	<b>69</b>	<b>2436.5</b>	<b>0.007</b>
		<b>Yes</b>	<b>7.31</b>	<b>201.06</b>	<b>55</b>		
PLR	Nodes (N)	No	186.22	1521.35	72	2276	0.150
		Yes	211.18	879.78	55		

**Table 6.** Logistic regression analysis

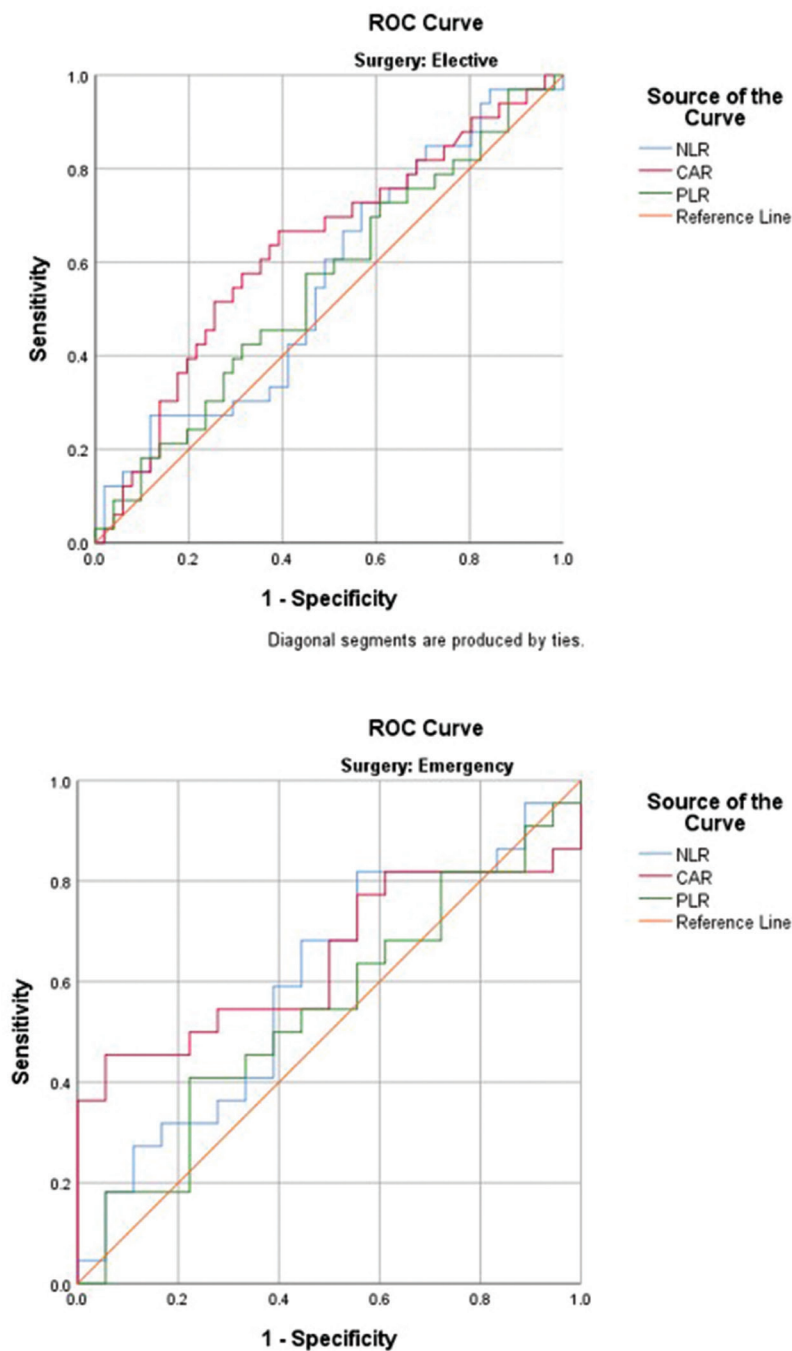
	B	S.E.	p	OR	95% CI for OR	
					Lower limit	Upper limit
CAR	<b>0.024</b>	<b>0.012</b>	<b>0.045</b>	<b>1.024</b>	<b>1.001</b>	<b>1.048</b>
Surgery type	0.278	0.437	0.524	1.321	0.561	3.107
NLR	0.020	0.037	0.595	1.020	0.948	1.097
PLR	-0.001	0.001	0.449	0.999	0.997	1.001
Constant	-0.519	0.325	0.110	0.595		



Area under the curve

Test result variable(s)	Area	Std. Error <sup>a</sup>	Asymptotic Sig. <sup>b</sup>	Asymptotic 95% CI	
				Lower bound	Upper bound
NLR	0.594	0.052	0.072	0.493	0.695
<b>CAR</b>	<b>0.642</b>	<b>0.050</b>	<b>0.007</b>	<b>0.543</b>	<b>0.741</b>
PLR	0.564	0.052	0.221	0.462	0.667

**Figure 1.** ROC curve demonstrating the sensitivity and specificity of CAR as a predictive marker of nodal metastases (elective and emergency surgery group combined).



Area under the curve						
Surgery	Test result variable(s)	Area	Std. Error <sup>b</sup>	Asymptotic Sig. <sup>c</sup>	Asymptotic 95% CI	
					Lower bound	Upper bound
Elective	NLR	0.560	0.064	0.357	0.434	0.685
	<b>CAR</b>	<b>0.630</b>	<b>0.063</b>	<b>0.046</b>	<b>0.506</b>	<b>0.753</b>
	PLR	0.551	0.065	0.428	0.425	0.678
Emergency	NLR	0.596	0.092	0.302	0.416	0.776
	<b>CAR</b>	<b>0.646</b>	<b>0.089</b>	<b>0.115</b>	<b>0.472</b>	<b>0.821</b>
	PLR	0.540	0.093	0.664	0.359	0.722

**Figure 2.** ROC curves demonstrating the sensitivity and specificity of CAR as a predictive marker of nodal metastases, separating the elective and the emergency surgery groups.

We will continue to monitor the patients and hope to present results after a five-year follow-up period regarding their Overall Survival (OS), Disease-Free Survival (DFS), and Recurrence Rate (RR), establishing also the prognostic significance of these inflammation markers in CRC progression and treatment. Further investigations should take place to validate the results of the current study.

## Discussion

Years of research on genetic and epigenetic motives have addressed several factors contributing to cancer progression.<sup>[5]</sup> The initiation of cancer, caused by a mutation in an oncogenic or a tumor-suppressor gene, is followed by a sequence of events: suppression of immune response, infinite cell proliferation, angiogenesis, cancer cells' infiltration of normal tissues, genomic changes, mutations, and avoidance of cell death. All these steps constitute cancer's promotion, resulting in its progression.<sup>[6]</sup>

Chronic inflammation has been implicated in creating a cancerous dynamic microenvironment, which facilitates malignant outgrowth and helps populations of evolving neoplastic cells to spread in a metastatic manner. More specifically, three different inflammation mechanisms have been proposed to promote cancer creation.

Firstly, leukocytes and other phagocytic cells generate reactive oxygen and nitrogen species, which cause DNA damage in various proliferation stages. These reactive products are normally produced to fight an infectious factor and mediate the inflammation process, but unfortunately, they form peroxynitrite, a mutagenic agent. Secondly, some infectious agents, such as viruses, directly alter their hosts' genomes by inserting their genetic material, which can include already active oncogenes. Finally, leukocyte adhesion molecules turn these cells into transporters of tumor cells to the endothelium of distant organs, promoting cancer cell migration and metastasis.<sup>[7]</sup>

The neutrophil-to-lymphocyte ratio has been proposed as a prognostic factor of different types of cancer, among others, colon cancer<sup>[8]</sup>, breast cancer<sup>[9]</sup>, gastric cancer<sup>[10]</sup>, and melanoma<sup>[11]</sup>. Different NLR cut-offs have been proposed by the authors regarding colon cancer, ranging from 2.5 to 3.4.<sup>[12,13]</sup> The bigger the ratio, the poorer the prognosis of the cancer and the higher the chances of lymph node metastasis. Researchers also note that NLR cut-off may differ from nation to nation, with Asians having, in general, lower ratios than Caucasians, and those in turn lower than the Black race.<sup>[14]</sup>

It is also interesting that patient factors such as age, BMI, and everyday habits (e.g., smoking and alcohol consumption) have been studied as possible contributors to the NLR value; however, age was shown to have a statistically significant relation to it, with older patients demonstrating higher NLRs.<sup>[15]</sup>

In a recent clinical study by Mazaki et al.<sup>[16]</sup>, an NLR value higher than 3 was associated with a poorer OS and DFS

(87.1% and 77.7%, respectively), when compared to the low NLR group (OS 91.5% and DFS 83.7%) after case matching. The researchers also attempted to relate NLR with cancer's sides, noting that an increased value was associated with worse OS and DFS in patients with left-sided colon cancer, but not in those with right-sided cancer. In 2012, Mallapa et al. presented a series of 297 patients treated surgically for CRC, who were followed up for 3.35 (0.1–8) years. 59 (19.8%) patients had recurrent CRC, and after multivariate analysis, the high NLR (HR 1.81, 95% CI 1.07–3.07,  $p=0.028$ ) was proved to be a significant and independent risk factor predictive of recurrence.<sup>[17]</sup>

As the role of inflammation in the genesis and progression of cancer was established, researchers started looking for other simple inflammatory markers that could be useful in cancer prognosis. Therefore, the PLR (platelet to lymphocyte ratio) was introduced. Platelets have numerous functions that facilitate tumor growth and metastasis. When activated, they damage the endothelium, promoting tumor cell invasion and metastasis, and at the same time, they have a prothrombotic function, causing a decrease in blood flow, affecting in this way the organism's immune response. Apart from the above, platelets excrete growth factors, including platelet-derived growth factors and vascular endothelial growth factors, which play a crucial role in cancer progression.<sup>[18]</sup> PLR cut-off has fluctuated throughout different studies from 176 to 246, although it has constantly been proven to be linked with worse OS, DFS, and RFS.<sup>[19-21]</sup>

Lastly, this study focused on the CAR (C-reactive protein to albumin ratio) to provide some primitive data to find a cut-off value. Researchers have also shown that CAR is an independent prognostic factor for CRC patients, with a meta-analysis that included 6 studies with 1942 CRC patients revealing that CAR levels higher than the median of 0.091 (range: 0.038–0.22) were associated with lower survival (HR: 2.09, 95% CI: 1.78–2.45,  $p=0.001$ ).<sup>[22]</sup> In a most recent study conducted by Zheng et al.<sup>[23]</sup>, the researchers demonstrated that higher CAR values accurately predicted the progression-free survival in CRC patients with liver metastases (C-index 0.69).

As far as the writers of this article are aware, there is no study comparing the NLR, PLR, and CAR among patients presented with a CRC complication and those treated on an elective basis. This distinction would be the basis of further researchers' attempts to calculate a cutoff for the Greek population for these values.

In our study, patients who demonstrated some complications of cancer demonstrated statistically significantly higher NLR and CAR values than those undergoing elective surgery. The reason for that seems logical, as the acute inflammatory response triggered by a complication of CRC would without a doubt be depicted in a rise of all (or most) of the inflammation markers. This was the primary reason for categorizing patients into urgent and elective cases in order to avoid bias in calculating a cut-off value for each variable. Emergency surgery cases were included in the study, despite this setback, as the authors of the current pa-

per believe that the prediction of nodal metastases is even more important in the urgent setting, when no thorough preoperative staging is feasible.

The results of the current study are not aligned with the literature reports of higher NLR values in patients having lymph node metastases<sup>[24]</sup> but demonstrated a significant prognostic value of the CAR in all patients regardless of their operation time. This would be of great significance for clinicians to make decisions on the extent of lymphadenectomy, especially in the emergency setting. Also, a current trend is evolving in colorectal cancer, that of preceding neoadjuvant chemotherapy for almost all colorectal cancers that show nodal metastases, even some of the right colon.<sup>[25]</sup> As the present-day most reliable preoperative prognostic factor of nodal involvement remains the CT scan<sup>[26]</sup>, which always underestimates the extent of the disease, finding a new prognostic biomarker with higher accuracy would be critical for the decision-making process.

Furthermore, the prognostic significance of CAR is yet to be determined, as there is insufficient data in the literature to evaluate whether the CAR value can predict local or distant recurrence of CRC. Its role might be even bigger for patients with oligometastatic liver disease, as the preliminary data suggest that patients with higher CAR values have poorer outcomes in terms of overall and progression-free survival.<sup>[27]</sup> This fact indicates that patients with CRC and oligometastatic liver disease might need to undergo more aggressive surgical procedures or be under closer monitoring.

In the literature, there are some references to other types of cancers, such as gastric cancer<sup>[27]</sup>, about higher CAR values and how these are associated with a worse stage at diagnosis and more advanced nodal metastasis status. Researchers also mention that higher CAR values are combined with poorer recurrence-free survivals, implying that maybe this ratio is increased in tumors of more aggressive biological behavior.

The exact mechanism that explains the role of elevated CRP or low albumin in the progression of cancer is not well established. However, researchers showed that chronic inflammation leads to an increase in IL-1, IL-6, and TNF $\alpha$ , all of which contribute to the inhibition of the albumin gene expression.<sup>[28]</sup> Therefore, someone might expect that in the cancerous state, as chronic inflammation is triggered, the patient might experience hypoalbuminemia and hence, a higher CAR value. What is certain is that patients with higher CAR values are more susceptible to cachexia and poorer survival due to their frailty. Another meta-analysis conducted by Cui et al.<sup>[29]</sup> showed that CAR was significantly associated with poor OS (HR=1.95, 95% CI 1.71-2.22) and DFS/PFS (HR=1.82, 95% CI 1.61-2.07) in patients with solid tumors. Cui commented that CAR was proven to be superior as a prognostic factor in malignancies than the NLR or PLR. They also highlighted the importance of CAR in both the preoperative and the postoperative periods.

As far as the prediction of nodal metastasis in CRC, there

are some factors established in the literature, such as male sex, increased age, and right-sided colon cancers.<sup>[30,31]</sup> Lei et al.<sup>[32]</sup> created a prediction score of lymph node metastasis based on various clinicopathological characteristics, among others, the site of the primary tumor and its size, the tumor differentiation with specific comments on different clusters, the perineural invasion, and tumor budding. This score's accuracy peaked at 86%, with a sensitivity of 81% and a specificity of 87%. However, it contained various information, some of which was only acquired from the pathologists' report, hence reducing its significance in preoperative planning and decision-making. We have not come across a study indicating that CAR could predict the nodal status, as indicated by our results.

The current study showed a significant relationship between the CAR and the positive nodal status. This relationship was established for elective surgeries but was found to be much weaker for the emergency surgery group. This may be the case because of the small number of patients in the emergency surgery group, indicating two facts. First, the significant outcome of the first ROC curve (which contains pooled data from the two groups) is mainly dictated by the elective group. Secondly, if we had more patients in the emergency group, the cut-off value for CAR would probably be a little different, as more emergency values would interfere with the analysis.

This study has some limitations, such as the relatively small sample and the lack of preoperative radiographic exams that would potentially reinforce the significance of CAR as a predictor of nodal metastases. Moreover, the tumor site and the tumor stage were not incorporated into the logistic regression. However, most patients suffered from sigmoid colon cancers and were reported as T3 in the pathologists' report.

Future studies could focus on the CAR as a predictive marker of nodal metastasis. This way, the power analysis would probably lead to slightly different results regarding the study's population. Furthermore, larger-scale studies could be conducted based on our preliminary findings regarding biomarker cut-off values. Right-sided colon cancer patients and patients with metastatic liver disease would be of greater interest due to the reasons discussed above.

## Conclusions

NLR, PLR, and CAR values differ in patients treated urgently for complicated colorectal cancer from those treated on an elective basis. This difference should be considered when researchers try to measure a potential cut-off of these ratios in the future. Furthermore, CAR seems to provide valuable information on the nodal status of such patients, probably representing a next-generation biomarker of nodal involvement prognosis. Larger-scale studies should take place to confirm our results and investigate NLR and PLR relations to overall survival and disease-free survival based on the cutoffs calculated in the present study.

## Authors contributions

Conceptualization: I.K.; study design: I.K. and G.A.; data collection: I.G. and K.P.; results interpretation: G.A. and K.P.; original draft: I.K.; revision of draft: A.R.; project supervision: A.R.

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