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Original Article

Prognostic impact of the preoperatory neutrophil/lymphocyte index on early surgical complications of patients with colorectal cancer

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Abstract: Colorectal cancer (CRC) is found among those with greatest frequency and exponential increase worldwide, with high mortality rates, which are observed as increasing due to the postsurgical complications that come to present. Systemic inflammation participates in the development and progression of cancer; therefore, inflammatory and/or immunological response markers such as the neutrophil/lymphocyte index (NLI) can aid us in predicting the poor results of our interventions. The purpose of our study was to determine the impact of an NLI of ≥2.6 as a predictor of early postsurgical complications. By means of a prospective cohort, we analyzed 158 patients with CRC who were submitted to elective surgery with a later 30-day follow-up. We found that the preoperatory NLI of ≥2.6 obtained an odds ratio (OR) = 2.24 (95% confidence interval [CI], 1.15-4.36) as a prognostic factor of early postsurgical complications according to the Clavien-Dindo classification scale, which represents a low prognostic impact due to its predictive yield with low accuracy, which is the opposite of what other reports have previously published. The use of chemotherapy before the surgical procedure was also determined to be a risk factor for post-surgical complications.

Keywords: Neutrophils, lymphocytes, postoperatory complications, colorectal neoplasms

Introduction

Colorectal cancer (CRC) is one of the cancer types that is diagnosed with greatest frequency [1], with an exponential increase in Mexico and in the world due to the acquisition of poor dietary habits and the preservation of customs that are harmful. Greatest incidence was established between the ages of 60 and 65 years, but currently, it presents in younger persons [2]. Survival expectancy is improving, due to early detection and to better tools for treatment, where the majority of patients are submitted to surgery, and some also will receive chemo- and/or radiotherapy. However, mortality continues to be high, thus being a result of main interest. There is concern about the prognosis of these patients in terms of the identification of predictors of mortality [1] and of their clinical evolution [3].

Postoperatory complications occur in up to 50% of patients with CRC and are associated with greater morbility and mortality rates [4]. A surgical complication is defined as any negative event that occurs in a patient during their hospital stay or within 30 days after the surgery [5, 6]. These complications should be borne in mind for quality control of in any health center, in that it has been demonstrated that the gravity of a complication is correlated with a prolonged hospital stay, higher costs, and patient dissatisfaction [5].

The tumor microenvironment and, in particular, the inflammatory response, plays an important role in the development and progression to cancer and can be associated with systemic inflammation [7]. This latter results in the positive regulation of the cytokines and the inflammatory mediators, which cause a greater propensity to malignancy through the inhibition of apoptosis, the promotion of angiogenesis, and greater damage to the DNA [8].

Some studies have determined that the neutrophils and the lymphocytes play prominent roles in the inflammatory and immunological responses of tumors. Neutrophils are the principal source of the vascular endothelial growth factor (VEGF), which contributes to the angiogenesis related with the tumor. The neutrophils also suppress the cytolitic activity of the T CD8+ lymphocyte cells, which in effect delay tumor progression similarly to the manner of the natural killer cells (NKC) and regulate the activation of the T cells. This creates an immunosuppressor medium, which is beneficial for the tumorigenesis. Contrariwise, the lymphocytes induce cytotoxic cell death and suppress the proliferation migration of the tumor cells, which are important for defense against the proliferation and development of cancer [9].

The Neutrophil/Lymphocyte Index (NLI) refers to the absolute neutrophil count divided by the absolute lymphocyte count [3], Zahorec and colleagues utilized the NLI for the first time to reflect the equilibrium between neutrophils and lymphocytes and as an inflammatory marker to evaluate the systemic inflammatory response in critical patients; after this, the NLI was widely employed in diverse clinical situations [10] and has been recognized as a simple and reliable marker [11].

The incidence of a high preoperatory NLI has been significantly associated with many clinical characteristics, such as the presence of vascular tumor invasion (lesions of >5 cm), which implies the possibility of impoverishing the prognosis of the results of the surgery in patients with CRC [12]. We physicians utilize prognostic information when we speak with our patients, and the NLI can provide us with independent prognostic information [7].

The platelet/lymphocyte index (PLI) is very similar to the NLI, but instead of using neutrophils as the numerator in the equation, the platelets are utilized. A frequent high count of the latter is associated with an inflammatory process, in that the inflammatory mediators stimulate megakaryocytic proliferation. The high PLI has been related with poor results of the outcomes of many other diseases, including cancer. Thus, it also can be considered as a prognostic factor [8, 13].

Our primary objective was to determine the prognostic impact of the preoperatory NLI on the presentation of early postsurgical complications in patients with CRC submitted to elective surgery, postulating that an NLI of ≥2.6 is related with a greater risk of complications. As secondary objective, we wanted to compare the prognostic impact of the PLI with that of the NLI.

Materials and methods

All patients with a diagnosis of colorectal cancer (CRC) confirmed by histopathologic study, in any of its disease stages, without nutritional risk or a low or intermediate nutritional risk that did not require the support of total parenteral nutrition, who had or had not received chemotherapy and/or radiotherapy, and who were submitted to a major elective surgery, at the Oncology Hospital of the Mexico City-based XXI Century National Medical Center of the Mexican Institute of Social Security (IMSS), from January through June, 2021, were included. Patients with recent previous surgery, acute infection on hospital admission, acute hemorrhage prior to the surgery, without a confirmed diagnosis of CRC, or who had received steroids of immunomodulators were excluded.

Study design

We carried out a longitudinal prospective cohort study, in which the general characteristics of the participants (age, sex, and comorbilities) were collected from the direct interrogation carried out during the elaboration of the admission form of our Service. The variables selected for the study (nutritional risk index, body mass index, clinical disease stage, surgery performed, experience of the surgeon, chemotherapy, radiotherapy, and postsurgical complications) were obtained from the hospital clinical file.

The blood samples were taken during the performance of the preoperatory studies and were

Table 1. Demographic characteristics, cancer site, clinical stage, surgery performed, and type of complication of patients with CRC submitted to elective surgery, complicated vs. not complicated

Characteristic	Complicated *n* = 77	Not compliced *n* = 81	*P value*
Age (DS)	60.6 ± 13.6	59.9 ± 12.5	0.732*
Sex (%)			
Female	36 (46.8)	47 (58)	0.156**
Male	41 (53.2)	34 (42)	
Cancer site (%)			
Sigmoid colon	14 (18.2)	17 (21)	0.027***
Ascending colon	11 (14.3)	19 (23.5)	
Lower-third rectum	17 (22.1)	12 (14.8)	
Middle-third rectum	15 (19.5)	13 (16)	
Clinical stage (%)			
IV A	15 (19.5)	11 (13.6)	9.801***
III C	9 (11.7)	10 (12.3)	
III B	9 (11.7)	7 (8.6)	
Surgery performed (%)			
LAR	22 (28.6)	29 (35.8)	0.015***
HCD	9 (11.7)	13 (16)	
LAR Laparoscopic	9 (11.7)	8 (9.9)	
APR	9 (11.7)	6 (7.4)	
Complication type (%)			
Anastomotic dihiscence	10 (13)		0.000***
Itra-abdominal infection	8 (10.4)		
Surgical-wound infection	8 (10.4)		
Surgical-wound dehiscence	8 (10.4)		

SD, standard deviation; LAR, lower abdominal resection; RHC right hemicolectomy; APR, abdominoperineal resection; *Student t test; **Pearson X^2 test; *** Kruskal-Wallis test.

placed in BD Vacutainer® tubes that contain the EDTA K2 anticoagulant applied by aspersion on the walls of the tube, for complete blood and/or plasma analysis, and was processed in Sysmex XN-2000 hematic-biometry analytical equipment.

Our dependent variable was the presence of early postsurgical complications according to the Clavien-Dindo classification scale, this is where the criterion for affording the degree of the complication is determined based on the treatment that is needed to correct the complication, and the following of patients during 30 days after the surgical intervention.

Statistical analysis

The categorical variables were compared with the X^2 test or the Fisher test depending on their type, and the quantitative variables, with the Student *t* test or the Mann-Whitney *U* test. In the comparison of three or more groups, we utilized the Kruskal–Wallis test. The odds ratio (OR) was established for variables with statistical significance. We performed the analyses of the Receiver Operating Characteristic (ROC) curve with the Fagan nomogram, for the NLI and the PLI, in order to establish our cut-off point and the predictable yield of these indices. To evaluate the effect of the confounder variables in perioperatory morbility, we conducted a uni and multivariate analysis with logistic regression. We performed the statistical analysis employing SPSS Statistics version 25 statistical software (IBM Systems, Chicago, IL, USA), in addition, for paired-propensity scoring among the NLI, chemotherapy, and the presence of post-surgical complications, we used the STATA/MP version 14.0 software program. Statistical significance was established at $P < 0.05$.

Ethical approval

The study was reviewed and approved by the Ethical Committee of the Oncology Hospital of the Mexico City-based XXI Century National Medical Center (CMN.SXXI) of the IMSS with registry number CONBIOETICA 09 CEI 022 2017082, on December 31, 2020, and by the Local Health Investigation Committee of the CMN-SXXI Oncology Hospital with registry number the R-2021-3602-003, on January 19, 2021.

Results

The studied population comprised 165 participants, among whom seven withdrew from the study, due to that three of these were lost to follow-up, two because of their surgery being suspended, one due to receiving total parenteral nutrition and one because of presenting an active acute infection at the moment of their hospitalization. Of the remaining population, that is, 158 participants, 77 (48.7%) presented

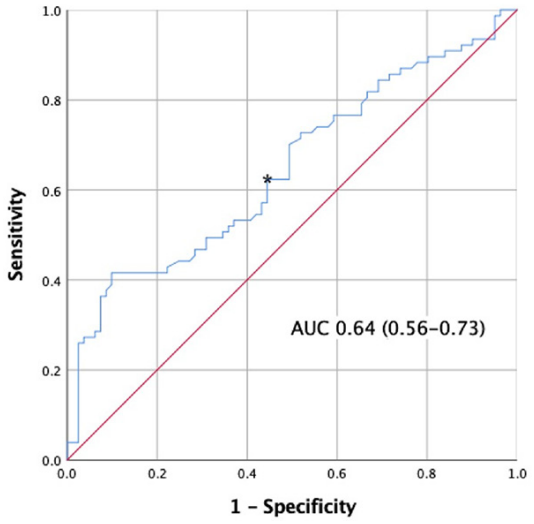

Figure 1. ROC curve for the neutrophil/lymphocyte index.

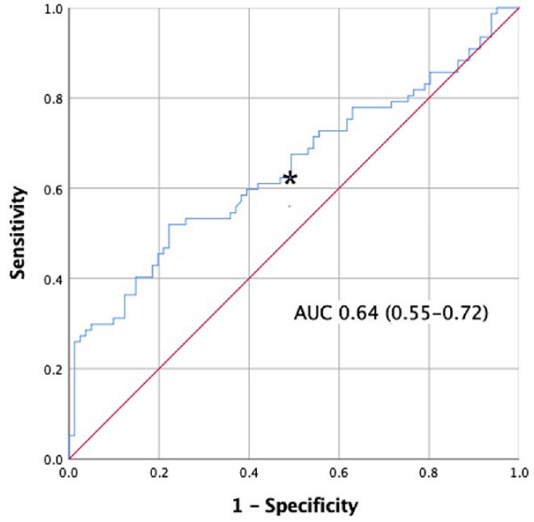

Figure 2. ROC curve for the platelet/lymphocyte index.

an early postsurgical complication, mean age for this group was 60.6 years, among whom 53.2% were males. The most frequent clinical disease stages were IV A (*n* = 26), III C (*n* = 19), and III B (*n* = 16). The most frequent CRC sites were sigmoid colon (19.6%), ascending colon (18.9%), lower-third rectum (18.9%), and middle-third rectum (17.7%). The surgeries most frequently conducted were lower abdominal resection, right hemicolectomy, and laparoscopic lower abdominal resection with 51, 22, and 17 events, respectively. The most frequent surgical complications that presented were anastomotic dehiscence (13%), intra-abdominal infection (10.4%), and surgical-wound infection (10.4%) (**Table 1**).

The ROC curve analysis of the NLI (**Figure 1**) and of the PLI (**Figure 2**) yielded an Area Under the Curve (AUC) of 0.66 and 0.64, respectively, which allows us to establish a cut-off point of 2.6 for the NLI and of 216.2 for the PLI in our population. Both indices presented a prevalence of 48.7%. The probability coefficient calculated for the Fagan nomogram (**Figure 3**) and the analyses of the predictive yield for both indices obtained low accuracy (**Table 2**).

Among the risk factors for the development of early postsurgical complications, we found in the bivariate analysis that the following three of these obtained statistical significance: the use of chemotherapy; the use of radiotherapy and the NLI ≥2.6 (**Table 3**).

We considered these three variables for the calculation of the OR for the purpose of establishing which of these continued to maintain statistical significance and to assess how much they contributed in this model, in order to be able to insert the multivariate analysis (**Table 4**).

In the multiple logistic regression model, the use of chemotherapy with an OR = 6.67 (95% CI 1.24-34.89) and the NLI ≥2.6 with an OR = 2.09 (95% CI 1.03-4.23), obtained statistical significance, explaining only 13.1% of early postsurgical complications in patients with colorectal cancer (**Table 5**).

The paired-propensity score of surgical complications with the NLI was ≥2.6 (**Figure 4**) and with the use of chemotherapy (**Figure 5**) demonstrated good equilibrium of the covariables with adequate statistical significance (**Table 6**).

Discussion

Our results show agreement in age with the presentation of colorectal cancer (CRC) of 60 years in our population, as reported in the international literature [14, 15]. In gender, we had a prevalence in women of 52.5%, higher than that referred in previous studies in which the prevalence was higher in men [14], although the latter demonstrated that this entertains a

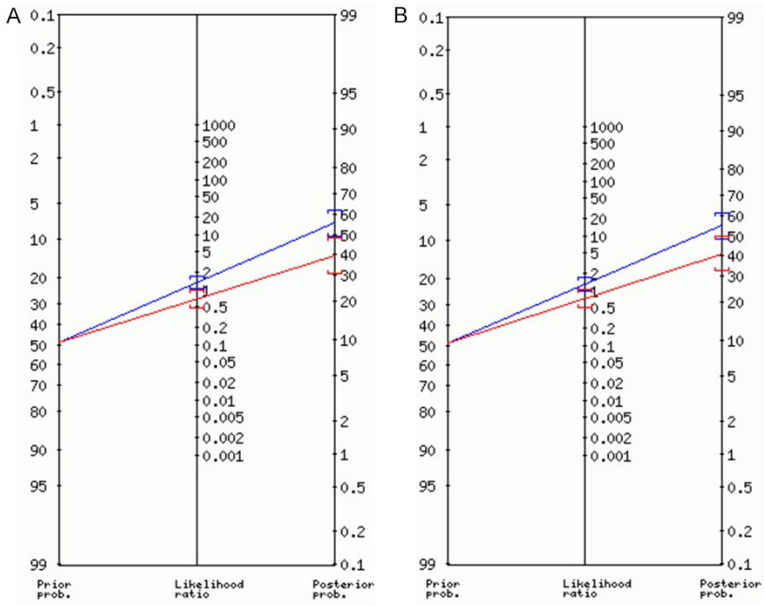

Figure 3. Fagan nomogram of the neutrophil/lymphocyte index and the platelet/lymphocyte index. A. Neutrophil/lymphocyte index nomogram; B. Platelet/lymphocyte index nomogram.

Table 2. Comparison of the predictive performance of the neutrophil/lymphocyte index and the platelet/lymphocyte index

	NLI	PLI
Prevalence (%)	48.7	48.7
Sensitivity (%)	66.2	63.6
Specificity (%)	50.6	50.6
LR (+)	1.34	1.29
LR (-)	0.67	0.72

NLI, neutrophil/lymphocyte index; PLI, platelet/lymphocyte index; LR (+), positive likelihood ratio; LR (-), negative likelihood ratio.

variation according to the socioeconomic factors of each country [16].

In the literature, it is mentioned that the most frequent site for the presentation of cancer is the proximal colon with 41%, the rectum with 28%, and the distal colon, with 22% [16]. Notwithstanding this, in our study, prevalence was higher in the rectum with 50.6%, in the distal colon with 25.3%, and in the proximal colon, with 23.4%. Therefore, the type of surgery performed changes, in that the international reference mentions right hemicolectomy as the main surgery performed with 37.7%, the left hemicolectomy with 26.2%, and the sigmoidectomy, with 15.6% [3], while we found that the lower anterior resection was the principal surgery performed with 32.3%, followed by the right hemicolectomy with 13.9%, and the laparoscopic lower abdominal resection, with 10.8%.

The NLI and the PLI obtained a high prevalence that explains why the study was conducted at a tertiary-care-level oncological concentration hospital. While both indices exhibited great similarity in their predictive yields, the PLI in the bivariate analysis did not achieve a significant Odds Ratio (OR). Thus, the PLI was discarded for the multivariate analysis. The paired-propensity scoring analysis supported the NLI and the use of chemotherapy for the presentation of post-surgical complications on showing adequate equilibrium in these covariables.

We found that the use of chemotherapy and an NLI of ≥2.6 obtained a significant OR in terms of the presentation of early postsurgical complications, although the 95% CI were quite ample, due very surely to the sample size. With respect to chemotherapy, we know that some patients can experience low blood-cell counts that can increase the possibility of infection, bleeding, or hematomas after the incisions or minor lesions with its use [17]. Thus, we can establish that this is a risk factor for postsurgical complications as well.

Our study comes to confirm that the NLI is a prognostic tool independent of other, conventional risk factors for the presentation of post-surgical complications in patients with CRC, as demonstrated by the studies of Urréjola G. et al. [3] and Xia L. et al. [18] and is also a tool that optimizes the results of an inflammatory index of prognostic prediction on CRC, in combination with other markers [19]. Notwithstanding this, we recognize that this does not represent a great prognostic impact for the detection of post-surgical complications, as other studies affirm.

In view of the latter, although the result of our work demonstrated that the NLI in itself pos-

Table 3. Risk factors vs. surgical complications

Risk factors	Complicated n = 77	Not complicated n = 81	*P* value
Comorbility (%)	47 (61)	43 (53.1)	0.313*
Clinical stage IIIA to IVC (%)	46 (59.7)	42 (51.9)	0.318*
Chemotherapy (%)	42 (54.5)	35 (45.5)	0.001*
Radiotherapy (%)	35 (45.5)	21 (25.9)	0.010*
Experience of the surgeon (%)			
≥6 years	48 (62.3)	42 (51.9)	0.183*
BMI (%)			
≥25 kg/m^2	43 (44.2)	40 (49.4)	0.416*
NRI (%)			
Slight/Moderate	29 (38.2)	36 (45)	0.386*
NLI (%)			
≥2.6	56 (72.7)	44 (54.3)	0.016*
PLI (%)			
≥216.26	49 (63.6)	40 (49.4)	0.071*

BMI, body mass index; NRI, nutritional risk index; NLI, neutrophil/lymphocyte index; PLI, platelet/lymphocyte index; *Pearson X^2 test.

sesses prognostic value, this leads us to think about the possibility of combining it with other inflammation markers that also have demonstrated a significant value [20] in terms of creating a more robust and reliable predictor model.

With respect to the platelet/lymphocyte index (PLI) and the nutritional risk index (NRI), our study did not demonstrate that these were adequate prognostic indexes for predicting postsurgical complication in patients with CRC. This result was similar to that found by Song and colleagues [21], in which the preoperatory NLI was superior to the monocyte/lymphocyte index (MLI), to the PLI, and to the NRI as a prognostic predictor. In addition, these authors propose that the NLI can serve as an additional index in the current TNM staging system in CRC. There is a scarcity of studies that relate the nutritional state with the inflammatory profile [22], thus our interest in the NRI during this work. We do wish to withhold merit from the role of the PLI as an inflammatory prognostic factor for patients with CRC, in that it is well known that the platelets can promote the carcinogenesis of various forms, such as a mechanical protection of tumor cells-in-transit in the circulation, as well as in enriching the tumor microenvironment for various bioactive pro-tumorigenic molecules transported and released from their granules [23]. Therefore, although our results did not favor it, we consider that this should be continued to be studied.

We must not forget that the NLI is a simple and reliable marker of systemic inflammation, easy to identify in patients with cancer from a complete hemogram. In the tumor microenvironment, a greater concentration of neutrophils can promote the growth of certain types of tumors, while a diminution of the concentration of lymphocytes can be indicative of inefficient local tumor control. Thus, it is that an increase in the NLI can indicate tumor progression, which represents a poor prognosis of CRC [22].

The limitations that our study presented included the prolongation of the times to perform a surgical procedure due to the Covid-19 pandemic, which delayed the admission of patients into the study. Our study strengths comprised the surgeries and its result continued in present time. This permitted us to obtain reliable results; we also were able to comply with the inclusion criteria adequately, and that the loss of patients to follow-up was very controlled, avoiding this from happening. Additionally, the investigation was conducted at a center specialized in cancer, center which contributed to our obtaining uniform information, and we did include all of the disease stages, early as well as advanced, which broadened our study's field of observation.

Conclusions

We conclude that our study demonstrated that the value ≥2.6 of the neutrophil/lymphocyte index (NFI) has low predictive power and it can be employed for the identification of patients with colorectal cancer who are vulnerable in terms of a greater risk of early postsurgical complications, with some reservation. In this regard, it aids us in considering tighter surveillance of these patients.

This represents having within our reach a prognostic tool, one that is accessible, economical,

Table 4. Odds ratio (OR) with adjustment for the (OR) risk factors for surgical complications

Variable	Complicated n = 77 n%		Non-complicated n = 81 n%		OR	IC 95%		*p***	R^{2}***
						Lower	Upper		
Chemo-therapy*	42	54.5	35	45.5	3.026	1.565	5.850	0.001	0.071
Radio-therapy*	35	45.5	21	25.9	2.381	1.219	4.650	0.010	0.042
NLI*									
≥2.6	56	72.7	44	54.3	2.242	1.153	4.362	0.016	0.030

NLI, neutrophil/lymphocyte index; *The values are presented in percentages; **Pearson X^{2} test; ***Coefficient of determination.

Table 5. Multivariate analysis by means of multiple logistic regression of prognostic factors for surgical complications in patients with colorectal cancer

Variable	Odds ratio	95% CI
Chemotherapy	6.670	1.247-34.894
Radiotherapy	0.360	0.065-1.982
LNI		
≥2.6	2.090	1.031-4.238
R^{2}* 13.1%		

LNI, neutrophil/lymphocyte index; *Coefficient of determination.

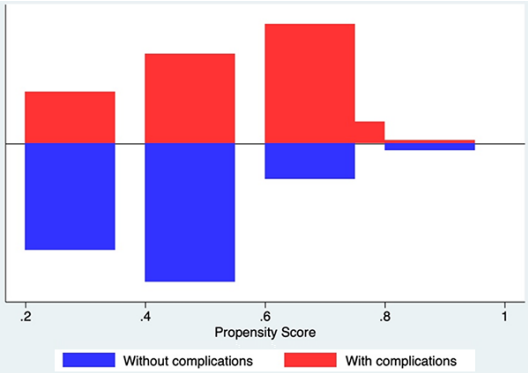

Figure 4. Paired-propensity scores in patients with a neutrophil/lymphocyte index of ≥2.6 and surgical complications. In the lower part of the blue color is demonstrated the absence of a complication. In the upper part of the red color are found those presenting a complication, demonstrating the equilibrium between a greater NLI and a greater presence of post-surgical complications.

and useful for determining the risk of complications in this group of patients and whose main benefit is that it can be put into practice during the carrying out of the routine preoperatory valuation that is conducted in a hospital setting, within the framework of safety and quality

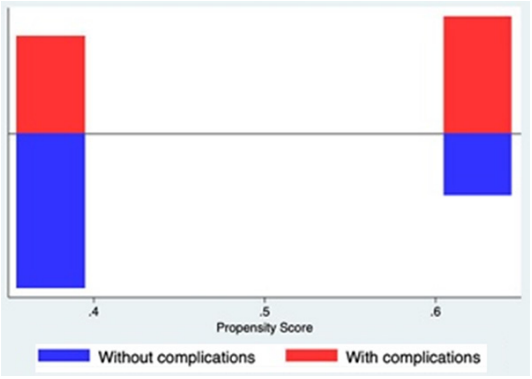

Figure 5. Paired-propensity scores in patients with the use of chemotherapy and surgical complications. In the lower part of the blue color the absence is shown of a complication. In the upper part of the red color are found those presenting a complication. In the left column are found the patients who did not use chemotherapy, while in the right column, we find those who did use chemotherapy. This demonstrates an equilibrium between the use of chemotherapy with a greater presence of post-surgical complications.

Table 6. Result of the propensity matched scoring analysis

Variable	Coefficient	*p*	95% Confidence interval
NLI ≥2.6	0.181	0.024	0.024-0.338
Chemotherapy	0.234	0.003	0.079-0.390

NLI, neutrophil/lymphocyte index.

in the care of the patient. The latter renders it necessary to support this, together with other instruments, in order to predict the surgical risk.

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Disclosure of conflict of interest

None.

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