Ministério da Saúde

COORDENAÇÃO DE ENSINO

Programa de Residência Multiprofissional em Oncologia

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Nutritional status and neutrophil-lymphocyte ratio as predictors survival in colorectal cancer patients

Rio de Janeiro

2019

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Trabalho de Conclusão de Curso apresentado ao Instituto Nacional de Câncer José Alencar Gomes da Silva como requisito parcial para a conclusão do Programa de Residência Multiprofissional em Oncologia

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Data: 12/02/2019

Rio de Janeiro

2019

Estado nutricional e relação de neutrófilos-linfócitos como preditores de sobrevida em pacientes com câncer colorretal

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RESUMO

INTRODUÇÃO: Inflamação e o estado nutricional têm ligação intrínseca em doenças neoplásicas. A relação de neutrófilos-linfócitos (RNL) e o estado nutricional podem fornecer um valor prognóstico independente no câncer colorretal (CCR). Assim, nosso objetivo foi avaliar a influência da associação da classificação do estado nutricional e indicadores prognósticos sobre a sobrevida global (SG) de pacientes com CCR. **MÉTODOS**: Uma análise retrospectiva foi realizada em pacientes com CCR no Instituto Nacional do Câncer. As principais variáveis independentes avaliadas foram índice de massa corporal (IMC), perda de peso (PP) e RNL. Foi considerado um acompanhamento em 5 anos. Curvas de Kaplan-Meier foram conduzidas para análises de sobrevida. Regressão logística e modelo multivariado de Cox também foram utilizadas. **RESULTADOS**: Um total de 148 pacientes foram incluídos no estudo. O estado nutricional mais prevalente foi sobrepeso / obesidade (43,2%) e o PP grave teve uma maior frequência (27,0%). Sessenta e sete indivíduos (45,3%) apresentaram RNL $\geqslant$3. O RNL $\geqslant$ 3 apresentou uma taxa de risco de morte de 2,75 (IC 95%, 1,30-5,82). Além disso, PP grave teve uma associação significativa com RNL $\geqslant$3 (p <0,040). A análise das

curvas de sobrevida mostrou que o NLR ⩾3 (p <0,001) e o PP grave (p <0,009) foram significativamente associados à menor SG. No entanto, em pacientes obesos / com sobrepeso foi observada maior sobrevida (p <0,002). Curiosamente, os pacientes sem PP não apresentaram diferença estatística entre RNL ⩾3 e RNL <3 na curva de Kaplan-Meier (p> 0,215). **CONCLUSÃO**: As avaliações de NLR e PP podem ser indicadores prognósticos promissores em pacientes com CCR. Novos estudos são necessários para investigar a associação da ferramenta PP como um fator complementar ao prognóstico indicado pela NLR.

Palavras-chave: neoplasia de colorretal, indicador prognóstico, estado nutricional, taxa de sobrevida.

Nutritional status and neutrophil-lymphocyte ratio as predictors survival in patients with colorectal cancer

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ABSTRACT

BACKGROUND: Inflammation and nutritional status have intrinsic binding in neoplastic diseases. Neutrophil-lymphocyte ratio (NLR) and nutritional status may provide an independent prognostic value in colorectal cancer (CRC). Thus, our objective was to evaluate the influence of the association of nutritional status classification and prognostic indicators on the overall survival (OS) of CRC patients. **METHODS**: A retrospective analysis was conducted in patients with CRC in the Brazilian National Cancer Institute. The main independent variables evaluated were body mass index (BMI), weight loss (WL) and NLR. It was considered OS in 5 years old. Kaplan-Meier curves were conducted for survival analyses. Logistic regression and Cox multivariate model also were used. **RESULTS**: A total of 148 patients were included in the study. The most prevalent nutritional status was overweight/obesity (43.2%) and severe WL had an important frequency (27.0%). Sixty-seven subjects (45.3%) had NLR ≥3. The NLR ≥3 presented a hazard ratio of death of 2.75 (95% CI, 1.30–5.82). Additionally, severe WL had a significant association with NLR ≥3 ($p<0.040$). Survival curves analysis showed that NLR ≥3 ($p<0.001$) and severe WL ($p<0.009$) were

significantly associated with lower OS. However, in obese/overweight patients was observed higher survival rates ($p<0.002$). Interestingly, patients without WL did not present statistical difference between NLR ≥3 and NLR < 3 in OS analysis ($p>0.215$). **CONCLUSION**: NLR and WL assessments can be promising prognostic indicators in CRC patients. Further studies are necessary to investigate the association of the WL tool as a complementary factor to prognosis indicated by NLR.

Keywords: colorectal neoplasms, prognosis, nutritional status, survival rate.

SUMÁRIO

1. Introduction

Colorectal cancer (CRC) is the third most common cancer and fourth leading cause of cancer-related death worldwide. The incidence and mortality rates have been declining due to historical changes in risk factors, screening tests and improvements in treatment[5]. Nonetheless, 18–22% patients are still diagnosed with distant metastasis and have the lowest 5-year survival rate (approximately 14%) compared with those who were diagnosed with localized and regional disease[6].

As such, efforts to identify modifiable behaviors and prognostic factors associated with CRC survival are of and public health[7, 8] importance. The adequate management of CRC requires a deep knowledge of the fundamental role played by the molecular factors involved in the pathogenesis of this condition, helping to identify biomarkers that can estimate the prognosis[9-11]. The prognostic value of many biomarkers has been investigated and some studies have reported that cancer progression and prognosis are determined not only by tumor characteristics but also by nutritional and immunological status[12, 13].

In the last decade, there has been new evidence that cancer-related inflammation plays an important role in tumor progression and metastasis through inhibition of apoptosis, promotion of angiogenesis and DNA damage[14-16]. Systemic inflammatory markers such as serum C-reactive protein, neutrophil lymphocyte ratio (NLR) have shown potential prognostic value in several human cancers, such as lung, CRC, ovarian and endometrial, independent of the disease stage[17-20].

The NLR have been suggested as simple and reliable markers of systemic inflammation, easy to identify in cancer patients from a complete blood count. In the tumor microenvironment, an increased concentration of neutrophils may promote the growth of some types of tumors, while a decreased concentration of lymphocytes may be indicative of ineffective local tumor control[21]. Thus, increased NLR may indicate tumor progression,

representing a poor prognosis of CRC. However, it remains unknown whether elevation of such markers is a cause or consequence of cancer progression[22].

In addition, cancer treatment can affect the ability to feed or absorb nutrients properly, and may lead to weight loss (WL) during treatment[23]. Few studies have evaluated weight change and body mass index (BMI) with regard to CRC survival, and have suggested that post-diagnosis WL may be associated with lower survival[24-29]. Besides that, alterations caused by cancer lead to changes in protein-energy metabolism, exacerbated pro-inflammatory state and immune depression[30, 31]. This may reflect on outcomes such as deterioration of nutritional status, which may lead to malnutrition, decrease of quality of life, increased length of hospital stay and hospital costs[23].

However, few studies have investigated the association between inflammatory markers and nutritional status using standardized assessment tools[32], showing that this correlation may aggravate the patient's condition, worsening suvival[33.] Thus, the use of prognostic indicators that assess the relationship between nutritional status, inflammatory and hematological parameters could help the prediction of unfavorable outcome in cancer patients[32, 34, 35].

Consequently, the present study aims to evaluate the influence of the association of nutritional status classification and prognostic indicators on the overall survival (OS) of CRC patients.

2. Methods

This retrospective observational cohort study was carried out with subjects diagnosed with CRC from the age of 20 years of both sexes, with diagnosis confirmed by the histopathological analysis, enrolled at the Brazilian National Cancer Institute José Alencar Gomes da Silva (INCA) between January 2008 and December 2012, for a 5-year follow-up.

Exclusion criteria

Patients were excluded under the following conditions: diagnosed with other types of cancer; active hematological, inflammatory or autoimmune infectious disease; patients receiving hormone therapy; with decompensated respiratory disease; heart failure or acute myocardial infarction for less than six months; in use of immunomodulatory drugs (eg. corticosteroids, cyclosporine). Patients who did not have the available biochemical tests and those who did not follow the oncological treatment were also excluded.

Population

The medical records of the patients included in the study were retrospectively analyzed. We collected the data: age; sex; alcoholism; smoking; tumor site, histological type; level of differentiation; staging; presence of metastasis; treatment start date; body weight; stature; BMI; percentage of WL; concentrations of lymphocytes, neutrophils and occurrence of death.

OS was defined as the time in years from the date of histopathological diagnosis of the disease until the date of death. The segment for the study was accomplished during 5 years from the diagnosis date. For deaths not related to CRC, the date for the end of segment considered as the date of death.

BMI was calculated from weight (in kilograms), height (in meters) and expressed in kg/m^2. We categorized this parameter according to the criteria of the World Health Organization[36]. The significance of WL was classified as proposed by Blackburn *et al.*[37], which considers period and percentage of reduction of body weight.

Serum lymphocyte and neutrophil concentrations were used to calculate NLR. This variable was dichotomized according to scientific literature[22]. The NLR ≥ 3.0 was classified as "high" and "low" for NLR <3.0.

All of these factors were measured prior to treatment and patient information ware turn into anonymous prior to analysis. The study was approved by the ethics committee of the institution (CAAE: 80835617.0.0000.5274).

Statistical Analysis

Kolmogorov-Smirnov test was performed to assess distribution of variables. Categorical variables were expressed as absolute or relative frequencies and continuous variables, such as mean and standard deviation or median, minimum and maximum range, as appropriate. In order to verify the possible associations between the NLR and the clinical factors and life habits of the patients, we used contingency tables and the Pearson Chi-square test ($\chi 2$). Multiple logistic regression model was performed to assess the associations adjusted by factors whose p-value was <0.250 in the bivariate analysis[38], generating odds ratios (OR) and their respective 95% confidence intervals (CI).

Kaplan-Meier (KM) curves were used to evaluate the OS of patients up to 5 years of follow-up. To verify the possible OS differences between the variable categories, the log rank test was used. The KM curves were also used to evaluate the proportionality between the factors. In addition, a multivariate survival analysis using a Cox proportional hazard model was performed to identify the most important subset of independent variables associated with prognostic factors, generating hazard ratios (HR) and their respective 95% CI.

Statistical analysis was processed using the Statistical Package for Social Sciences (SPSS) 22.0. A p value <0.05 was considered statistically significant, with 95% CI.

3. Results

Data from 148 patients were included in the study. The mean age was 62 (±12.8) years, with predominance of males (52.0%) and disease in stage III and IV (71.6%). The most prevalent nutritional status was overweight/obesity (43.2%) and, according to the WL, it was

a severe loss (27.0%) among the patients. Sixty-seven subjects (45.3%) had NLR ≥3. Others patient characteristics are shown in Table 1.

The proportions of nutritional status, evaluated using BMI, showed differences according to age (p= 0.003). Individuals aged <62 years had a higher prevalence of overweight/obesity (54.5%), while in the others (≥62 years), the highest frequency was eutrophy (37.8%). On the other hand, disease staging had no relation with BMI and WL. There were no statistically significant differences in the proportion of patients with NLR ≥3 according to age or disease staging (**Table 2**).

Within a median follow up of 5 yers, 24 patients developed distant metastases namely: liver (n = 11), lung (n = 2), brain (n = 1), bone (n = 2), pelvic (n =1), simultaneous lung and liver (n = 5), simultaneous liver, peritoneal carcinomatosis and bone (n = 1), and disseminated peritoneal carcinomatosis (n = 1).

According to logistic regressions, severe WL had a significant association with NLR ≥3 (p<0.040) and in contrast, patients without WL (no loss) did not present significant association (OR:0.52, *p*= 0.250; 95% CI, 0.17–1.60) **(Table 3)**. In the multivariate Cox regression, only the NLR (HR:2.75, p= 0.008; 95% CI, 1.30–5.82) and metastasis (HR: 3.09 p <0.001; 95% CI, 1.58–6.01) were associated with death **(Table 4)**.

Analysis of the survival curve showed that the NLR above the cutoff point was significantly associated with the lower OS (p <0.001) (**Figure 1**). Regarding nutritional status, there was a higher survival rate for overweight/obese patients (p= 0.002) and a lower survival rate among subjects with severe WL (p= 0.009) (**Figure 2**). Surprisingly, patients without WL evaluated in Kaplan-Meier analysis, did not present statistical difference in the NLR (p>0.215). In this study, the NLR index had no predictive effect of survival in patients without WL. However, other different nutritional classifications stratified by the NLR classification did not show any significant changes in survival analysis (**Figure 3**).

4. Discussion

Due to the magnitude of the CRC problem in public health, the search for prognostic indicators related to the clinical evolution of the disease is extremely relevant. The present study demonstrated that patients with CRC with severe WL and high NLR in pre-treatment had significant lower OS. The WL tool also demonstrated association with NLR. In addition, in an independent way, patients with metastatic cancer or NLR ≥3 presented poor prognosis.

In BMI classification, we observed that overweight/obese individuals had better OS in relation to eutrophic and malnourished group. The literature describe that the relationship between mortality risk and BMI is U-shaped, with an increased risk not only of cachexia or a very low BMI, but also of obesity or a high BMI[39]. However, evidence suggesting a J-shaped association between body weight and CRC survival, where overweight individuals may have higher survival rates[40-44].

The association between overweight and better CRC prognosis has been termed the obesity paradox[45, 46]. There are divergent opinions about such a paradox. The first hypothesis is that certain obesity-associated CRC subtypes might be less aggressive than others. Second, certain molecular CRC subtypes might be differentially associated with prognosis, dependent on BMI[44]. The third proposition derives from the fact that BMI is a crude measure of body weight, and does not capture differences in body composition (muscle vs. fat) or fat distribution (subcutaneous vs. visceral)[47]. These differences also vary according to sex. Women generally present proportionately more body fat and men more central adiposity[48]. Finally, overweight and/or obesity might function as protective factors from malnutrition, cancer cachexia, or sarcopenia, altered immune functions, or anorexia in cancer patients, which are common consequences of cancer metabolic changes[49].

On the other hand, subjects who presented severe WL had reduced OS compared to

patients without WL or significant WL. Previous studies have demonstrated that pre and post-diagnosis body weight control is an important factor for CRC survival[24, 28, 44, 50]. A higher pretreatment WL may indicate a longer course of disease before diagnosis and less nutrient intake. Our result may suggest that patients with a significant WL before treatment could be treated with early nutritional intervention to improve body weight. However, whether it could prolong survival time remains to be further studied.

In addition, patients without WL and stratified according to NLR values did not present a significant difference in OS. So, although high NLR values are reliable and significant markers of poor survival, this understanding may be modified if patients did not present WL. Although high NLR values are reliable and significant markers of poor survival, this understanding may be modified if patients did not present WL. These findings corroborate the understanding that cancer survival is not only determined by tumor, but also by host-related factors, in particular, nutritional status and systemic inflammation[51,52]. Therefore, these findings confirm the importance of avoiding WL among CRC patients, even among those who are overweight or obese[43].

The inflammatory response to cancer can cause anorexia, loss of body weight, changes in body composition, and decline in physical function [53]. According to our results, only WL was associated with NLR. However, A study with patients with low weight (BMI <20 kg/m²) treated by laparoscopic surgery demonstrated a significant and inverse relationship between BMI and preoperative NLR[50]. The literature is scarce to associate WL and inflammation in patients with cancer. In a study with different types of cancer, 25.3% of the gastrointestinal tract, it was observed that the parameter of inflammation evaluation, CRP> 10 mg/dL, was associated with 79.2% individuals with weight loss[54].

Revision studies have described that high pretreatment NLR values predicts poor prognosis in patients with CRC. These results are consistent for both individuals with

localized disease and those with liver metastases, being a convenient and low cost prognostic marker[22].

The indices derived from the comprehensive blood tests are a reflection of the inflammation status generated both at the local level and systemically. It has been reported that tumour-infiltrating lymphocytes and neutrophils correlated with peripheral blood lymphocytes and neutrophils[55]. Previous studies have shown that NLR may be an independent prognostic marker to predict long-term outcomes in stages II and III[56], III and IV[57] and metastatic[58]. In our study, we demonstrated that NLR have predictive values for OS in patients with CRC. High NLR was an independent factor affecting OS in patients with CRC.

However, our results have certain limitations. This study was retrospectively performed in a single center. Therefore, we could not avoid selection bias when collecting information on patients with CRC. However, we attempted to minimize any bias by repeatedly reviewing the medical records. Second, a relatively small sample size for the size of the results.

There is currently a growing interest in these markers and the possible prognostic implications. However, there is a shortage in studies linking nutritional status to NLR, and this relationship needs to be addressed in future research with larger populations.

5. Conclusion

The present study concluded that in patients with CRC, NLR ≥3 and severe WL in pretreatment had significant poor OS. Although the underlying mechanisms were not fully investigated, impairment of antitumor immunity might occur in WL patients and is associated with higher NLR. Therefore, our findings suggest that patients who have high NLR and

severe WL should be more carefully managed when establishing a treatment strategy. These tools are easy to measure and inexpensive and may even have potential increase in prognostic indices. Such findings may be useful in improving decisions about therapeutic protocols, quality of life, and the prospects for survival in patients with CRC.

Acknowledgements

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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TABLE 1. Clinical characteristics of the patients with colorectal cancer in the city of Rio de Janeiro, Brazil (N= 148).

Variables		N	%
Age (years)[a]		62.1	12.8
Sex	Female	71	48.0
	Male	77	52.0
Alcohol consumption	Yes	51	34.5
	No	97	65.5
Smoking	Yes	25	16.9
	No	123	83.1
Tumor location	Sigmoid	48	32.4
	Rectum	46	31.0
	Colon	45	30.4
	Others[c]	9	6.2
Histological type	Adenocarcinoma	144	97.3
	Carcinoma	4	2.7
Level of differentiation	Well differentiated	4	2.7
	Moderately differentiated	128	86.5
	Poorly differentiated	11	7.4
	Undifferentiated mucinous	1	0.7
	UM	4	2.7
Staging	I and II	13	8.8
	III and IV	106	71.6
	UN	29	19.6
Presence of metastasis	Yes	35	23.6
	No	113	76.4
BMI classification	Undernourished/Low weight	28	18.9
	Eutrophy	56	37.9
	Overweight/Obesity	64	43.2
WL classification	No loss	22	14.9
	Significant loss	33	22.3
	Severe loss	40	27.0
	UN	53	35.8
Lymphocytes (x 10^{-6}) [b]		1817	(399-8080)
Neutrophils (x 10^{-6}) [b]		5024	(900-91667)
NLR ≥3	Yes	67	45.3
	No	81	54.7

Note: BMI= body mass index; N= number of observations; NLR= neutrophil-to-lymphocyte ratio; UN= uninformed; WL= weight loss; %= frequency.
[a]Mean/standart deviation; [b]Median/minimum and maximum.

TABLE 2. Classification of body mass index, significance of weight loss and neutrophil-to-lymphocyte ratio according to clinical characteristics of the patients with colorectal cancer.

Variables		BMI classification						p value**	WL classification						p value**	NLR ≥3				p value**
		Undernourished/ Low weight		Eutrophy		Overweight/ Obesity			No loss		Significant loss		Severe loss			Yes		No		
		N	%	N	%	N	%		N	%	N	%	N	%		N	%	N	%	
Staging[a]	I and II	-	-	4	30.8	9	69.2	0.083	4	57.1	2	28.6	1	14.3	0.197	3	23.1	10	76.9	0.329
	III and IV	21	19.8	42	39.6	43	40.6		18	26.1	24	34.8	27	39.1		39	36.8	67	63.2	
Age (years)[b, c]	<62	5	7.6	25	37.9	36	54.5	**0.003***	7	16.7	20	47.6	15	35.7	0.058	32	48.5	34	51.5	0.481
	≥62	23	28.0	31	37.8	28	34.1		15	28.3	13	24.5	25	47.2		35	42.7	47	57.3	

Note: BMI= body mass index; N= number of observations; NLR= neutrophil-to-lymphocyte ratio; WL= weight loss; %= frequency.
[a]N= 119; [b]N= 148; [c]Age categozed according to mean.
*p value < 0,05 **P-value refers to Pearson Chi-square test.

TABLE 3. Regression models for NLR ≥ 3 according to outcomes in CRC.

Independent variables		NLR ≥ 3				
		N	OR	95% CI		*p*-value
				Lower	Upper	
Tumor location	Colon	-	1.00	-	-	-
	Rectum	36	2.38	0.93	6.06	0.070
Level of differentiation	Poorly differentiated/ Undifferentiated	-	1.00	-	-	-
	Well / Moderately differentiated	83	0.12	0.01	1.10	0.061
Metastasis	No	-	1.00	-	-	-
	Yes	24	1.24	0.44	3.52	0.685
WL	No loss	22	0.52	0.17	1.60	0.250
	Significant loss	32	0.25	0.09	0.73	0.011*
	Severe loss	38	1.00	-	-	0.040*

Note: CI= confident interval; OR= odds ratio; N= number of observations; NLR= neutrophil-to-lymphocyte ratio; WL= weight loss.
*p value < 0,05

TABLE 4. Multivariate Cox models among factors which might the overall survival in CRC.

Independent variables		N	HR	95% CI		*p*-value
				Lower	Upper	
Alcohol consumption	No	-	1.00	-	-	-
	Yes	33	1.57	0.81	3.04	0.183
Tumor location	Colom	-	1.00	-	-	-
	Rectum	36	0.71	0.37	1.39	0.320
Level of differentiation	Poorly differentiated/ Undifferentiated	-	1.00	-	-	-
	Well / Moderately differentiated	83	1.54	0.63	3.79	0.346
Metastasis	No	-	1.00	-	-	-
	Yes	24	3.09	1.58	6.01	<0.001*
WL	No loss	22	0.58	0.22	1.52	0.268
	Significant loss	32	0.92	0.41	2.04	0.835
	Severe loss	38	1.00	-	-	0.533
NLR	<3	-	1.00	-	-	-
	≥3	45	2.75	1.30	5.82	0.008*

Note: CI= confident interval; HR= hazard ratio; N= number of observations; NLR= neutrophil-to-lymphocyte ratio; WL= weight loss.
*p value < 0,05

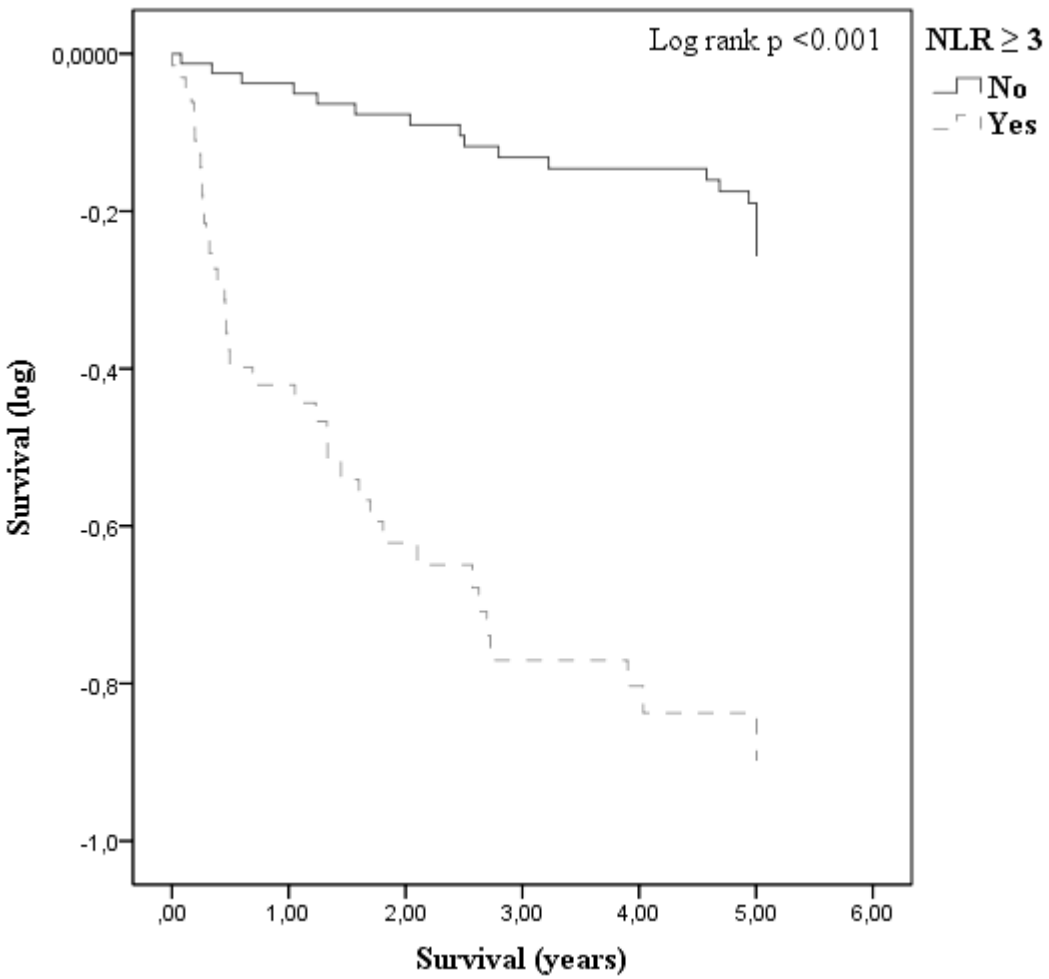

FIGURE 1. Kaplan-Meier plots quantifying the effects of NLR status on the overall survival in patients with CRC.

Note: NLR= neutrophil-to-lymphocyte ratio.

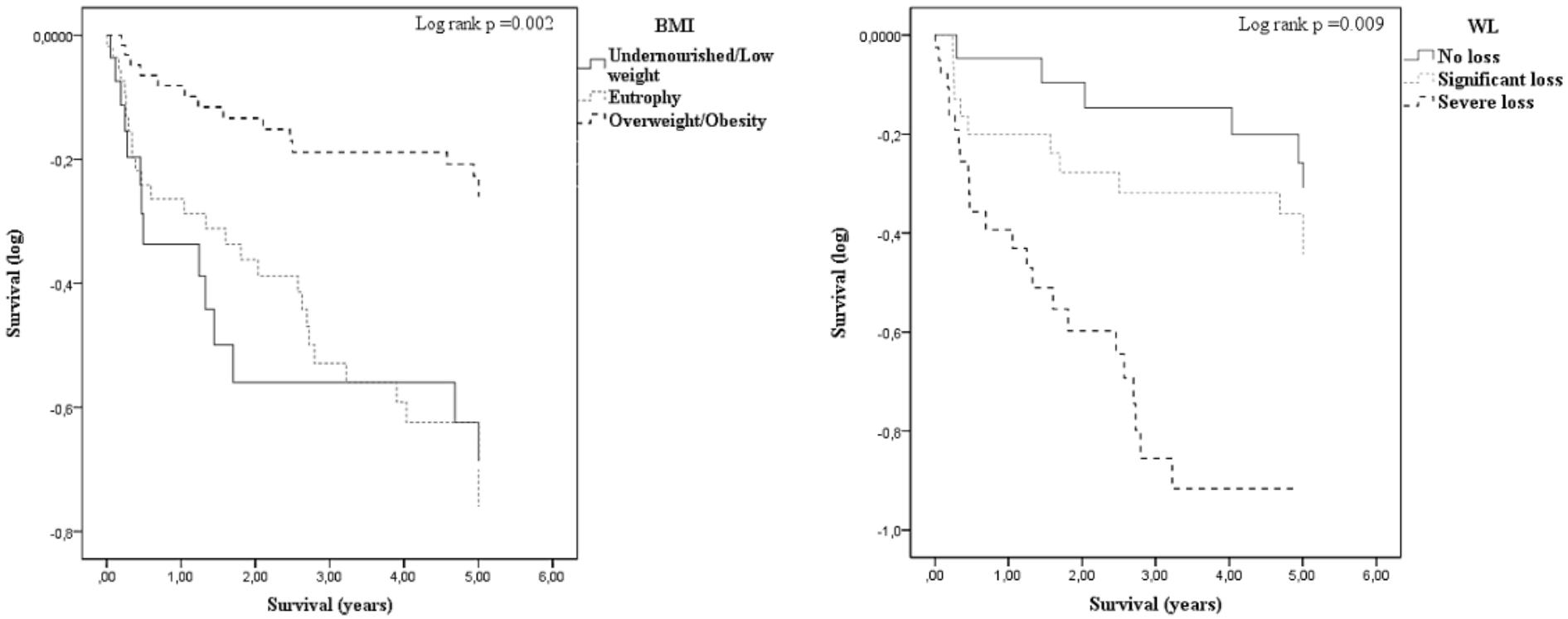

FIGURE 2. Kaplan-Meier plots quantifying the effects of BMI and WL status on the overall survival in patients with CRC.

Note: BMI= body mass index; WL= weight loss.

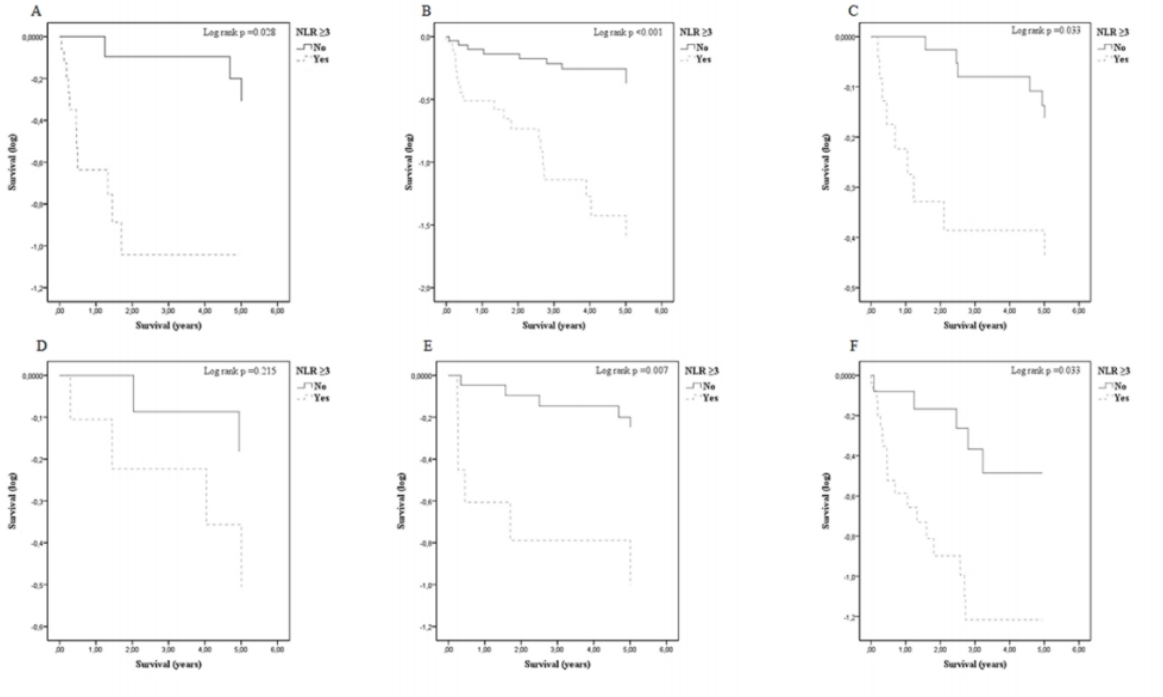

FIGURE 3. Kaplan Meier curves for overall survival according to stratification of nutritional status classification by BMI and WL in patients with CRC.

Note: BMI= body mass index; NLR= neutrophil-to-lymphocyte ratio; WL= weight loss.

[A] stratified by undernourished/low weight; [B] stratified by eutrophy; [C] stratified by overweight/obesity; [D] stratified by no loss; [E] stratified by significant loss; [F] stratified by severe loss.