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Pretreatment albumin and leukocytes levels maybe useful as markers of postoperative complications in colorectal patients cancer: a retrospective cohort study

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ABSTRACT

Purpose: The aim of the study was to investigate whether the use of nutritional status assessment tools and markers of systemic inflammation are capable of predicting postoperative complications for surgical patients with colorectal cancer. **Methods**: A retrospective cohort study was performed with 673 surgical colorectal cancer patients registered in an oncology reference center from January 2008 to December 2013. Data on sociodemographic, clinical and tumor characteristics, nutritional status, T stage, lymph node involvement, blood count cells, and occurrence of postoperative complications were collected. Neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR) and lymphocyte to monocyte ratio (LMR) were calculated. Univariate and multivariate analysis logistic regression was performed using a 95% confidence interval. Statistical significance was defined as p-value <0.05. All analyses were performed using SPSS 22.0. **Results:** Elevated leukocyte levels (≥9410 unit/µl; OR:2.76, 95% CI:1.22-6.27, p=0.015) and low values of albumin (≤3.7g/dl; OR:2.35, 95% CI:1.05-5.24, p=0.037) were independent factors to increase the risk for postoperative complications. Body mass index (BMI), Patient-generated subjective global assessment (PG-SGA) and Weight loss tool did not present statistically significant difference. **Conclusion:** Elevated leukocyte levels and low values of albumin increased independently the risk for postoperative complications. Such data could be useful in the definition of clinical protocols.

Keywords: Colorectal Neoplasm, Inflammation, Nutritional Status, Postoperative Complication

Introduction

Colorectal cancer (CRC) is the third most common cancer in men and the second in women [1], representing ten percent of all new cancer cases in the world [2]. Globally, it is one of the cancers whose incidence has increased [1] and affects mainly developed countries with wide distribution of all cases in these regions [3].

Surgery is the first line of treatment for colorectal cancer and, depending on the stage of the tumor, patients can still undergo chemotherapy or radiation therapy [4-7]. However, cancer patients may present clinical features that alter the treatment outcome. Some of these characteristics can facilitate the development of postoperative complications, which can cause delay in adjuvant treatments and, in the most severe cases, lead to death [8,9].

Inflammation in cancer may also be responsible for the metabolic change that can trigger malnutrition. This deterioration in nutritional status has been seen in patients with colorectal cancer [10,11]. Changes in molecular pathways linked to energy metabolism, increase caloric expenditure and directly impacting body reserves of lipids, glucose and proteins. This caloric imbalance promotes important changes in nutritional status and may have consequences on antineoplasic treatment [12-15], as the emergence of postoperative complications and survival prognosis [15-17].

In this context, studies have demonstrated the prognostic ability of nutritional status and inflammatory markers to predict the worst prognosis in several types of cancer, including CRC [18-22].

Systemic inflammation increases the values of leukocytes, lymphocytes and monocytes and decrease albumin levels in peripheral blood. Neutrophil to lymphocyteratio (NLR) and lymphocyte to monocyte ratio (LMR) can act as a measure of the degree of tumor inflammation. Likewise, platelets release cytokines and chemokines that exacerbate the inflammatory process in the tumor microenvironment, making platelet to lymphocyte ratio (PLR) another possible measure of inflammation and prognosis [23-25].

Thereby, the aim of the study was to investigate whether the nutritional status assessment tools and markers of systemic inflammation are capable of predicting possible occurrences of postoperative complications in colorectal cancer patients.

Methods

Population

We performed a retrospective cohort study with primary colorectal cancer patients who had the diagnosis validated by histopathological analysis. The researchers included all patients older than twenty years, of both sexes and with surgery procedure as a first treatment at a Brazilian oncology reference center. On the other hand, we excluded: patients with hematological, inflammatory, autoimmune or decompensated respiratory disease or hormonal / immunomodulatory therapy; with myocardial infarction or heart failure within six months prior to collection; patients who did not perform routine biochemical tests and nutritional diagnosis up to fifteen days before surgery and those who missed follow-up at the institution (Figure 1). We collected data from patients enrolled in the reference center from January 2008 to December 2013.

Data collection

Data collection was carried out by consulting electronic and physical records. This collection was carried out in two moments: on the date of the histopathological diagnosis and in the postoperative period, considering the thirty days after the surgery, according to Dindo et al [26] (Table 1).

The following data were collected:

•Socio-demographic and lifestyle data: age, sex, alcohol consumption, smoking and clinical comorbities;

•Tumor characteristics data: date of diagnosis, tumor site subdivided into right and left abdominal quadrant according to Nawa et al [27], histological type, level of differentiation, staging, lymph node involvement and tissue invasion;

•Nutritional status data: body weight, height, weight loss according to Blackburn et al [28] and Patient-Generated Subjective Global Assessment according to Gonzalez et al [29];

Body mass index (BMI) was calculated based on the measured of weight (in kilograms) and height (in meters) and expressed in Kg/m^2. This parameter was categorized according to World Health Organization [30].

•Blood level: lymphocytes, neutrophils, monocytes, leukocytes, platelets, albumin and glucose. All exams were collected of routine preoperative tests. Serum levels of lymphocyte, neutrophil, platelets and monocytes were used to calculate the NLR, PLR and LMR.

Data on postoperative complications were considered present or absent. Any complication contained in any of the five classifications of Clavien-Dindo [26] was considered positive (Table 1).

This study was approved by the ethics committee of the institution under the protocol CAAE: 80835617.0.0000.527. All patients had their identities preserved. We assessed the quality of this study according to the STROBE Statement [31].

Statistical Analysis

A descriptive analysis was performed to describe the sample profile. Clinical variables were categorized according to terciles of their distribution and the variables of age and BMI were classified according to the literature. With the purpose to verify possible associations between postoperative complications and related factors, Pearson's chi-square test was used.

Multivariate analysis was performed using a logistic regression model including the variables with p values <0.25 in the univariate analysis [32]. In order to avoid collinearity, to quantify the effect of each prognostic factor, these were considered in each multivariate model without the presence of the other. Data were reported as the odds ratio (OR) and 95% confidence interval (CI).

Statistical significance was defined as p-value <0.05, with 95% CI. All analyses were performed using SPSS 22.0.

Results

Patient demographics and clinical characteristics

A total of 695 patient’s medical records were identified. The final data of 673 patients were obtained and analyzed in this study according to the exclusion criteria as shown in Figure 1.

The sample consisted of 330 males (49%) and 343 females (51%). Their ages ranged from 29 to 85 years with the median of 64 years. Most of the population denied alcohol consumption (58.8%) and smoking (56.6%).

Regarding the degree of tumor differentiation, 87.9% of the population studied was moderately differentiated, 8.8% poorly differentiated and 3.3% well differentiated. Most patients (91.8%) had advanced staging (TIII/TIV). The percentage of patients with significant and severe weight loss totaled 45.5 and 18.9%, respectively (Table 2).

Relationship between postoperative complications according Clavien-Dindo and colorectal cancer clinicopathological parameters

Fisher's exact test indicated a significant relationship between postoperative complications and sex, age, PG-SGA, NLR, leukocytes and albumin. Other baseline characteristics of the population related to postoperative complications are shown in Table 2.

In univariate analysis, our results demonstrated that patients with advanced age, males, PG-SGA C, leukocytes and albumin were significantly related with postoperative complications. However, when adjusted in the multivariate model, only the elevation of the leukocyte levels (OR: 2.76, 95% CI:1.22-6.27, p=0.015) and low albumin values (OR: 2.25, 95% CI:1.05-5.24, p=0.037) significantly increased independently the chance of postoperative complications (Table 3).

Discussion

Colorectal cancer patients undergoing surgical treatment require special attention and specific care. Therefore, the identification of prognostic markers of postoperative complications, are necessary to help the therapeutic decision.

Here, we observe that some factors contribute to the occurrence of postoperative complications. Elevated leukocyte levels (≥9410 unit/µl) and low albumin levels (≤3.7g/dl) were highlighted as independent factors for the occurrence of these complications.

Current studies have also shown the relation between preoperative albumin values and the occurrence of surgical complications [33, 34]. Albumin levels are markers of inflammatory and nutritional status, and may also influence wound healing

processes because it interferes with oncotic pressure homeostasis [33, 35, 36]. Haskins et al [37] showed that patients with CRC with hypoalbuminemia (<3.5g/dl) had a higher risk of sepsis, prolonged paralytic ileus, increased hospitalization time, and greater risk of death.

Additionally, this protein has been indicated in the current literature as a predictor of clinical outcomes [37,38]. This relation may be due to the response to catabolism, oxidative stress and infections that may be associated to cancer. Novello et al [39] concluded that preoperative albumin values ≥3.4 were also associated with a protective effect on postoperative mortality in CRC patient.

A study with rectal cancer patients showed that the reduction in albumin levels was independently related with high degrees of postoperative morbidity [40]. Furthemore, a database of the US population of 30,376 individuals with CRC demonstrated that hypoalbuminemia was related to deep vein thrombosis, pulmonary embolism, surgical site infection, pneumonia, septic shock and also high postoperative mortality [41].

In turn, elevated leukocyte levels may be involved in postoperative complications. These cells have the function of protecting the body from foreign substances through phagocytosis, production of cytotoxic enzymes and also antibodies [42]. However, leukocytosis maybe considered a nonspecific marker for systemic inflammatory status [43]. The systemic inflammation exacerbated may trigger vascular injury and eventual organ dysfunction [44]. Thus, high levels of preoperative leukocytes may be directly linked to the increased risk of postoperative complications [43].

Moghadamyeghaneh et al [43] evaluate the correlation between white blood cell values and surgical complications of 59,760 patients with CRC, and demonstrated that preoperative asymptomatic leukocytosis is associated with increased risks of ventilator dependence, unplanned intubation, surgical site infection and mortality in colorectal cancer patients undergoing surgery. These authors still found a prevalence of preoperative asymptomatic leukocytosis in 5.6% of patients with CRC, which resulted in a significant increase in the risk of morbidity and mortality.

On the other hand, the nutritional status markers did not present a significant increase in the risk of complications in our cohort. BMI and Weight Loss tool did not show an increase in risk for the occurrence of surgical complications. Nevertheless, PG-SGA tool demonstrated influence on postoperative complications in univariate analysis

($p<0.001$). Meantime, when adjusted for multivariate analyzes, PG-SGA was not considered an independent risk factor for operative complications ($p=0.250$).

In contrast to our findings, Maurício et al [17] find that the incidence of postoperative complications was different according to grades of BMI classification. In addition, this study demonstrated that malnutrition classified by PG-SGA was associated with a 2.08 increased risk in postoperative complications in the colorectal cancer patients. In spite of our study not showing significant results with the PG-SGA, this tool has been considered a good method for nutritional assessment of cancer patients [17,45].

The present study has limitations inherent to retrospective studies. Some data may have been lost due to possible underreporting and possible confounding factors that are difficult to control may have arisen. The study was also performed in just one cancer treatment center, which may have generated selection bias in the sample. Moreover, the study discusses a relevant topic, has a high number of participants and has potential clinical utility.

The results are important for a better understanding of the clinical characteristics of surgical patients with colorectal cancer and can assist in implementation of future protocols.

Conclusion

In conclusion, our results indicated that pre-treatment high levels of leukocytes and low albumin levels were independent predictors of postoperative complications. These results suggest the use of these markers in surgical colorectal cancer patients, however, further investigation with larger populations is required.

Conflict of interests The authors declare no conflict of interests.

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FIGURE

Fig 1 Patient Selection Flow Diagram

TABLES

Table 1 Surgical complications according to Clavien-Dindo classification (2004)

Table 2 Characteristics of colorectal cancer patients in relation to the proportion of occurrence of postoperative complications (N=673)

Table 3 Logistic regression model of univariate and multivariate analysis by postoperative complications in CRC patients

Table 1. Surgical complications according to Clavien-Dindo classification (2004)

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications Blood transfusions and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade IIIa	Intervention not under general anesthesia
Grade IIIb	Intervention under general anestesia
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU management
Grade IVa	Single organ dysfunction (including dialysis)
Grade IVb	Multiorgan dysfunction
Grade V	Death of a patient
Suffix “d”	If the patient suffers from a complication at the time of discharge, the suffix “d” (for “disability”) is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

*Brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks. CNS: Central nervous system; IC: Intermediate Care; ICU: Intensive care unit. Adapted from Dindo et al (2004)

Figure

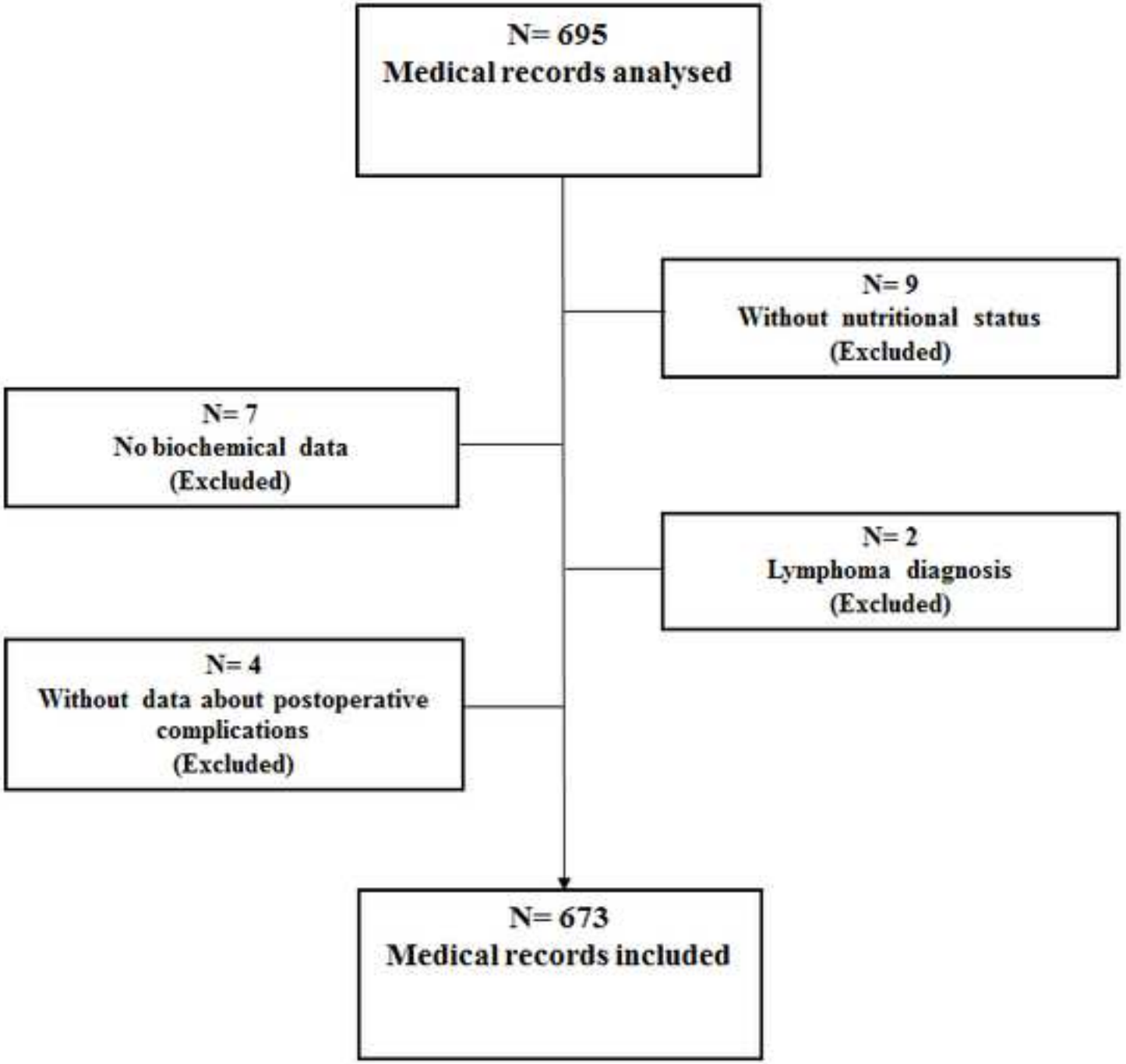

Table 2. Characteristics of colorectal cancer patients in relation to the proportion of occurrence of postoperative complications (N=673)

Variables	Categories	Postoperative complications (CD Grade I-V)		p-value
		Yes	No	
Sex	Female	78 (44.1)	265 (53.4)	0.032
	Male	88 (55.9)	231 (46.6)	
Age	<64	72(40.7)	271 (54.6)	0.001
	≥64	105(59.3)	225 (45.4)	
Alcohol consumption	Never	105(60.7)	283(58.1)	0.164
	Yes	47(27.2)	163(33.5)	
	Ex-alcoholist	21(12.1)	41(8.4)	
Smoking	Never	105(60.7)	270(55.1)	0.414
	Yes	23(13.3)	80(16.3)	
	Ex-smoker	45(26.0)	140(28.6)	
Tumor side	Left	122(68.9)	348(70.2)	0.759
	Right	55(31.1)	148(29.8)	
Histological Type	Adenocarcinoma	170(96.0)	483(97.6)	0.292
	Carcinoma	7(4.0)	12(2.4)	
Differentiation degree	Well differentiated	7(4.0)	15(3.0)	0.091
	Moderately differentiated	145(83.4)	442(89.5)	
	Poorly differentiated	22(12.6)	37(7.5)	
T stage	I / II	15(10.7)	33(7.4)	0.215
	III / IV	125(89.3)	412(92.6)	
Limph node involvement	Yes	84(52.8)	278(59.9)	0.118
	No	75(47.2)	186(40.1)	
Tissue invasion	Yes	121(74.2)	412(87.3)	<0.001
	No	42(25.8)	60(12.7)	
Glicemia	1 st tercile	50(31.8)	149(37.1)	0.511
	2 nd tercile	51(32.5)	121(30.1)	
	3 rd tercile	56(35.7)	132(32.8)	
Hypertension	Yes	68(44.7)	186(42.1)	0.568
	No	84(55.3)	256(57.9)	
Diabetes	Yes	10(6.6)	17(3.8)	0.163
	No	142(93.4)	425(96.2)	
Hypertension plus Diabetes	Yes	25(14.1)	54(10.9)	0.251
	No	152(85.9)	442(89.1)	
BMI classification	Eutrophy	78(44.1)	212(42.7)	0.344
	Malnourished/Low weight	34(19.2)	76(15.4)	
	Overweight/Obesity	65(36.7)	208(41.9)	
Weight Loss	No loss	24(27.9)	76(39.0)	0.203
	Significant loss	44(51.2)	84(43.1)	
	Severe loss	18(20.9)	35(17.9)	
ASG-PPP	A	36(38.3)	128(42.5)	0.001
	B	46(48.9)	164(54.5)	
	C	12(12.8)	9(3.0)	

Table 2. Clinical characteristics of the colorectal cancer patients (n=678) (Cont. 1)

Variables	**Categories**	**Postoperative complications**		**p-value**
		No	**Yes**	
NLR	1 st tercile (0.0-2.13)	55 (31.4)	167 (33.9)	
	2 nd tercile (2.14-3.87)	47(26.9)	173 (35.1)	0.027
	3 rd tercile (≥3.88)	73(41.7)	153(31.0)	
PLR	1 st tercile (0-132)	58(32.8)	166(33.5)	
	2 nd tercile (133-213)	52(29.3)	170(34.3)	0.321
	3 rd tercile (≥214)	67(37.9)	159(32.2)	
LMR	1 st tercile (0.0-2.17)	68 (38.9)	150(30.5)	
	2 nd tercile (2.18-3.54)	52(29.7)	172(35.0)	0.123
	3 rd tercile (≥3.55)	55(31.4)	170(34.5)	
Leucocyte	1 st tercile (0-7062)	42(23.7)	182(36.8)	
	2 nd tercile (7063-9409)	57(32.2)	165(33.3)	0.001
	3 rd tercile (≥9410)	78(44.1)	148(29.9)	
Albumin	3 rd tercile (≥4.2)	36(44.5)	77(27.6)	
	1 st tercile (0.0-3.7)	24(29.6)	96(34.4)	0.013
	2 nd tercile (3.8-4.1)	21(25.9)	106(38.0)	
SGA-TOTAL SCORE	1 st tercile (0-96)	28(29.8)	92(30.7)	
	2 nd tercile (97-119)	29(30.9)	105(35.0)	0.641
	3 rd tercile (≥120)	37(39.3)	103(34.3)	

CD: Clavien-Dindo; N: Number of observations; BMI: Body Mass Index; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; LMR: Lymphocyte-to-monocyte ratio.

*Pearson´s Chi Square test.

Table 3. Logistic regression model of univariate and multivariate analysis by postoperative complications in CRC patients (n=673)

Variables	**Categories**	**N**	Univariate Analysis Postoperative Complications (CD Grade I-V)			Multivariate Analysis Postoperative Complications (CD Grade I-V)		
			OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Sex	Female	343	1	-	-	1	-	-
	Male	330	1.46	1.03-2.06	0.033	1.86	0.97-3.55	0.061
Tumor side	Left	470	1	-	-	-	-	-
	Right	203	1.06	0.73-1.54	0.759	-	-	-
Histological Type	Adenocarcinoma	653	1	-	-	-	-	-
	Carcinoma	19	1.66	0.64-4.28	0.296	-	-	-
Differentiation degree	Well differentiated	22	1	-	-	-	-	-
	Moderately differentiated	587	0.70	0.28-1.76	0.451	-	-	-
	Poorly differentiated	59	1.27	0.45-3.61	0.648	-	-	-
T stage	I / II	48	1	-	-			
	III / IV	537	0.67	0.35-1.27	0.217	0.39	0.14-1.05	0.062
Limph node involvement	Yes	362	0.75	0.52-1.01	0.119	1.19	0.62-2.28	0.607
	No	261	1	-	-	1	-	-
BMI classification	Eutrophy	290	1	-	-	1	-	-
	Malnourished/Low weight	110	1.18	0.80-1.72	0.401	0.44	0.16-1.22	0.114
	Overweight/Obesity	273	1.43	0.88-2.34	0.152	1.33	0.67-2.64	0.409
Weight Loss[a]	No loss	100	1	-	-	1	-	-
	Significant loss	128	1.66	0.92-2.98	0.091	1.08	0.37-3.14	0.888
	Severe loss	53	1.63	0.78-3.38	0.191	0.51	0.09-2.85	0.447
PG-SGA-total score	1 st tercile (0.0-3.9)	120	1	-	-	-	-	-
	2 nd tercile (4.0-8.9)	134	0.91	0.50-1.64	0.747	-	-	-
	3 rd tercile (≥9.0)	140	1.18	0.67-2.08	0.566	-	-	-
NLR[b]	1 st tercile (0.0-2.13)	222	1	-	-	1	-	-
	2 nd tercile (2.14-3.87)	220	0.82	0.53-1.28	0.395	0.78	0.36-1.7	0.531
	3 rd tercile (≥3.88)	226	1.45	0.96-2.19	0.079	0.79	0.31-2.01	0.622
PLR	1 st tercile (0-132)	224	1	-	-	-	-	-
	2 nd tercile (133-213)	222	0.87	0.57-1.35	0.545	-	-	-
	3 rd tercile (≥214)	226	1.21	0.8-1.82	0.374	-	-	-
LMR[c]	1 st tercile (0.0-2.17)	218	1	-	-	1	-	-
	2 nd tercile (2.18-3.54)	224	0.67	0.44-1.02	0.060	0.52	0.21-1.32	0.169
	3 rd tercile (≥3.55)	225	0.71	0.47-1.08	0.114	0.65	0.30-1.38	0.260
Leucocyte	1 st tercile (0-7062)	224	1	-	-	1	-	-
	2 nd tercile (7063-9409)	222	1.5	0.95-2.35	0.079	1.87	0.86-4.08	0.114
	3 rd tercile (≥9410)	226	2.28	1.48-3.52	0.000	2.76	1.22-6.27	0.015
Albumin	3 rd tercile (≥4.2)	127	1	-	-	1	-	-
	1 st tercile (0.0-3.7)	113	2.36	1.28-4.36	0.006	2.35	1.05-5.24	0.037
	2 nd tercile (3.8-4.1)	120	1.26	0.66-2.41	0.481	1.45	0.67-3.14	0.342
Glicemia	1 st tercile (0-96)	199	1	-	-	-	-	-
	2 nd tercile (97-119)	172	0.79	0.51-1.24	0.305	-	-	-
	3 rd tercile (≥120)	188	0.99	0.63-1.56	0.977	-	-	-

Table 3. Univariate and multivariate logistic regression for postperative complication by clinical characteristics of the colorectal cancer patients (n=673)(Cont 1)

Variables	**Categories**	**N**	Univariate Analysis Postoperative Complications (CD Grade I-V)			Multivariate Analysis Postoperative Complications (CD Grade I-V)		
			OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Hypertension	Yes	254	1.11	0.77-1.61	0.568	-	-	-
	No	340	1	-	-	-	-	-
Diabetes	Yes	27	1.76	0.79-3.93	0.168	2.88	0.64-13.04	0.169
	No	567	1	-	-	1	-	-
Hypertension plus Diabetes	Yes	79	1.35	0.81-2.24	0.252	-	-	-
	No	594	1	-	-	-	-	-
Age	<64	343	1	-	-	1	-	-
	≥64	330	1.76	1.24-2.49	0.002	2.37	1.22-4.6	0.011
PG-SGA Classification [d]	A	164	1	-	-	1	-	-
	B	210	0.99	0.61-1.63	0.991	0.78	0.27-2.22	0.640
	C	21	4.74	1.85-12.14	0.001	6.36	0.27-149.18	0.250

CD: Clavien-Dindo; N= number of observation; OR: Odds ratio; CI: Confidence interval; BMI: Body mass index; PG-SGA: Patient-Generated Subjective Global Assessment; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; LMR: Lymphocyte-to-monocyte ratio.

[a] Multivariate analysis adjusted without NLR, LMR and PG-SGA classification; [b] Multivariate analysis adjusted without Weight Loss, LMR and PG-SGA; [c] Multivariate analysis adjusted without Weight loss, NLR and PG-SGA classification; [d] Multivariate analysis adjusted without NLR, LMR and Weight loss.