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## Original Article

# The influence of metabolic syndrome in the outcomes of colorectal cancer patients

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## ABSTRACT

**Aims:** Determine the influence of metabolic syndrome and its different components in the outcomes of colorectal cancer surgery at 30 days.

**Materials and methods:** Prospective study that included all patients submitted to elective colorectal cancer surgery between August 2015 and August 2016 at Hospital de Braga. Clinical and laboratory parameters evaluated pre-operatively were: central obesity, blood pressure, fasting glucose, triglycerides levels and HDL cholesterol levels. Any complications during the first 30-days after surgery were recorded (readmission, reintervention, anastomotic dehiscence, morbimortality).

**Results:** One hundred and thirty-four patients were included. Metabolic syndrome was diagnostic in 40.7% of patients with the ATPIII definition, 67.5% with the AHA definition and 67.0% with the IDF definition. At 30 days after colorectal cancer surgery, 73.1% patients don't have any complication, 15.7% have minor complications (grade I/II of Clavien-Dindo classification), 11.1% have major complications (grade III/IV/V of Clavien-Dindo classification) and 1.5% have died from surgical complications (grade V of Clavien-Dindo classification). The statistic analysis didn't reveal any association between MS, or its different components, and surgical outcomes.

**Conclusion:** This study seems to indicate that metabolic syndrome don't have any influence in surgical outcomes of colorectal cancer surgery.

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## 1. Introduction

The terms “metabolic syndrome” (MS) stand for a cluster of interrelated risk factors of metabolic origin that have been proved to predict a higher risk of atherosclerotic cardiovascular disease as well as type 2 diabetes mellitus expressing, this way, its clinical importance. With a prevalence of approximately 24,6–30,9% in Europe [1] the development of this syndrome appears to be directly related to abdominal obesity and insulin resistance [2].

Since its initial description (approximately 80 years ago) [1] many different definitions have been proposed by several institutions, but they all agree on the same basic components, namely hypertension, dyslipidemia, insulin resistance and central obesity.

The most popular definitions are those from National Cholesterol Education Program – Third Adult Treatment Panel (NCEP-ATPIII), or just ATPIII, from 2001 [3], the International Diabetes Federation (IDF), from 2005 [4], and, finally, the American Heart Association/National Heart Lung and Blood Institute (AHA/NHLBI), from also 2005 [2].

Besides the cardiovascular consequences of the metabolic syndrome, in several cohort studies and meta-analyses, this entity has been proven to increase cancer risk in general [5,6] with major effects on the gastrointestinal tract, namely increasing the risk of non-neoplastic gastrointestinal disorders, precursor lesions and CRC itself [7]. This relationship between metabolic syndrome and the risk of colorectal cancer is at the moment supported by a large number of studies [1,8,9], and this linkage is mainly explained by abdominal obesity and insulin resistance with a multifactorial mechanism of carcinogenesis involving the action of adipokines, inflammatory cytokines, adiponectin, leptin, IGF-1 and others [1].

Colorectal cancer represents an important health issue, as being the third most common cancer in men and the second in women worldwide (10.0% and 9.2% of the total, respectively) [10]. These

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numbers seem to be rising dramatically worldwide due to urbanization, aging, diet changes and lifestyle [11].

At least one study of our knowledge has already proved the deleterious influence of MS on CRC prognosis, with significantly shorter survival and higher recurrence and liver metastasizing rates, implying that MS is an important prognostic factor for CRC [12]. Moreover, this deleterious influence was also proved for the outcomes of CRC surgery at 30 days, showing a higher rate of postoperative complications and a longer hospital stay in patients classified with the AHA/NHLBI definition of MS. Also in this study from 2009, high blood pressure and high triglyceride levels were as well considered important risk factors for severe complications after CRC surgery, but only the presence of the cluster of metabolic abnormalities that constitute MS was proven to be an independent variable in the multivariate analysis, and not each individual component [13].

Concerning the influence of obesity in surgery outcomes, WC proved to be an independent risk factor for the development of parastomal hernia after permanent colostomy [14]. Another study published in 2013 proved that waist-hip-ration (as a measure of central obesity) had a significant influence in negative outcomes after CRC surgery, namely reoperation, medical complications, intraoperative complications and conversion to open approach, being this prediction effect superior to the one verified when measuring BMI and or WC [15]. Obesity was also associated with an increase in anastomotic leakage after rectal cancer resection [16].

Furthermore, a study concerning the financial implications of CRC surgery in obese patients has detected a significant increase in hospital expenses due to a higher rate of severe complications. The major contributors for these costs were wards stay, operations, and intensive care units [17].

The aim of this study is to determine the influence of MS and different components of MS (high fasting glucose, central obesity, high blood pressure, high triglycerides levels and low HDL cholesterol levels) in the outcomes of CRC surgery at 30 days (reintervention, readmission, dehiscence and morbimortality).

## 2. Methods

### 2.1. Study oversight and patients inclusion

This study included all the patients with a confirmed diagnosis of colorectal adenocarcinoma who underwent elective surgery at Hospital de Braga during August 2015 till August 2016. Patients who presented evidence of metastasis before or at surgery, necessity of removal of other organs due to tumor invasion, synchronous tumors or history of other malignant tumors within 5 years, history of familial adenomatous polyposis and hereditary non-polyposis colorectal carcinoma were excluded.

### 2.2. Data collection

At the first moment of evaluation, during pre-operative consultation, data were collected concerning patient's age, gender, history of arterial hypertension, diabetes mellitus, dyslipidemia, prior neoplasms, usual medication (with special concern for hypertension, diabetes, high triglycerides and low HDL cholesterol specific treatments) and family history of neoplasms. On the day prior to their admission to the hospital for surgery, the patients were requested to present themselves at Clinical Academic Center at Hospital de Braga for an anthropometric evaluation, carried out, all times, by the same nurse, which included height, weight and waist circumference measurement, as well as collection of blood samples for evaluation of fasting glucose, HDL cholesterol and triglycerides levels. During a period of 30 days following surgery, data about complications were collected and registered, namely

morbimortality, readmission, reintervention and anastomotic dehiscence. Morbimortality was posteriorly classified according to Clavien-Dindo's classification [18].

### 2.3. Statistical analysis

Statistical analysis was performed using SPSS – Statistical Package for the Social Science Program, version 23.

Descriptive statistics are presented as absolute frequencies (n) and relative (%) for categorical variables, and mean (M) and standard deviation (SD), or median (Mdn) and interquartile ranges, for quantitative variables, depending on whether or not symmetry of the distributions was ensured. The chi-square test was used to identify associations between dichotomous outcomes (morbimortality, dehiscence, reintervention and readmission) and the independent variables. When the maximum assumed 20% of cells with the expected frequency of less than 5 was exceeded, Fisher's test ( $2 \times 2$  tables) was used. The Mann-Whitney test was used to compare the outcome measured on an ordinal scale (Morbimortality according to Clavien-Dindo classification) with the independent variables. Finally, logistic regressions were used to measure the risk of the independent variables on the dichotomous outcomes. The significance level for rejection of  $H_0$  was 5% ( $p < 0.05$ ).

### 2.4. Ethical issues

The present study was approved by the Ethic Committee of Hospital de Braga. The investigators made sure to safeguard the anonymity and confidentiality of all the participants. A written informed consent was obtained from each patient.

## 3. Results

The present study included a sample of 134 patients with CRC diagnoses, with a mean age of 67.91 years old, 82 males and 52 females. 46 (40.7% in 113) of these patients were diagnoses with MS according to the ATPIII definition, 79 (67.5% in 117) according to the AHA definition and 71 (67.0% in 106) according to the IDF definition. These data are shown in Table 1. We were not able to collect the necessary information for these diagnoses in some of the patients (ND in the table), most often by absence of the patient from the appointments with the nurse for measurement of anthropometric parameters and blood samples collection.

**Table 1**  
Sample characterization; ND = No data.

	Statistics
Age M (SD)	67.91 (12.94)
Gender n (%)	
M	82 (61.2%)
F	52 (38.8%)
MS n (%)	
ATPIII Definition	n = 113
No	67 (59.3%)
Yes	46 (40.7%)
ND	21
AHA Definition	n = 117
No	38 (32.5%)
Yes	79 (67.5%)
ND	17
IDF Definition	n = 106
No	35 (33.0%)
Yes	71 (67.0%)
ND	28

Thirty days after CRC surgery, 98 patients (73.1%) did not suffer from any complication. 11 patients were readmitted to the hospital, 10 patients suffered anastomotic dehiscence and 10 patients were again submitted to surgery. With a total morbimortality percentage of 26.9%, only 2 deaths were registered during this period. Complications distribution according to Clavien-Dindo Classification and the previous data about 30 days after surgery outcomes are shown in Table 2.

**Table 2**  
Sample surgical outcomes.

	n (%)
Readmission	11 (8.3%)
Dehiscence	10 (7.5%)
Reintervention	10 (7.5%)
Morbimortality	36 (26.9%)
Clavien-Dindo Classif.	
No complications	98 (73.1%)
Grade I	8 (6.0%)
Grade II	13 (9.7%)
Grade IIIa	3 (2.2%)
Grade IIIb	6 (4.5%)
Grade IVa	1 (0.7%)
Grade IVb	3 (2.2%)
Grade V	2 (1.5%)
Length of Hospital Stay Mdn (IQR)	5.00 (3.00)

After applying chi-square tests, the results suggest no evidence of association between any of the MS definition diagnosis (or their different components) and the surgical outcomes studied, except for low HDL cholesterol levels by ATPIII definition (HDL - c < 40 mg/dL in men or < 50 mg/dL in women) as a predictor of morbimortality at 30 days, (p = 0.037) (Table 3).

Logistic regression was computed in order to calculate Odds ratio (OR) for the risk of having morbimortality having low HDL cholesterol (by ATPIII definition) as a predictor.

The risk of morbimortality for patients with low HDL cholesterol is 2.42 times increased when compared with patients with high HDL cholesterol (95% CI = [1.04, 5.62]). This result was statistically significant for p = 0.039 (Table 4).

As performing Mann-Whitney Test for ordinal outcomes (Morbimortality according to Clavien-Dindo Classification) we were able to also establish a statistically significant result, which states that patients with low HDL-cholesterol (by ATPIII definition)

**Table 4**  
Logistic Model; In this case: Yes = HDL - C < 40 mg/dL in men or < 50 mg/dL in women and No = HDL - C ≥ 40 mg/dL in men or ≥ 50 mg/dL in women.

	OR	95% CI	p-value
Low HDL cholesterol			
No	1	1	1
Yes	2.42	(1.04-5.62)	p = 0.039

**Table 3**  
Chi square tests results. relation between dichotomous outcomes and independent variables.

	Readmission			Reintervention			Dehiscence			Morbimortality		
	No	Yes	p value	No	Yes	p value	No	Yes	p value	No	Yes	p value
MS ATPIII Definition	43 (93.5%)	3 (6.5%)	0.456	42 (91.3%)	4 (8.7%)	0.361	40 (93.0%)	3 (7%)	0.854	34 (73.9%)	12 (26.1%)	0.790
Central Obesity (ATPIII Definition)	44 (91.7%)	4 (8.3%)	0.787	45 (93.8%)	3 (6.3%)	0.462	44 (93.6%)	3 (6.4%)	0.861	40 (83.3%)	8 (16.7%)	0.056
High Triglycerides level (ATPIII Definition)	42 (91.3)	4 (8.7%)	0.870	45 (97.8%)	1 (2.2%)	0.120	41 (97.6%)	1 (2.4%)	0.088	33 (71.7%)	13 (28.3%)	0.883
Low HDL Cholesterol level (ATPIII Definition)	53 (89.8%)	6 (10.2%)	0.797	54 (90.0%)	6 (10.0%)	0.164	49 (89.1%)	6 (10.9%)	0.297	38 (63.3%)	22 (36.7%)	.037
High Blood Pressure (ATPIII Definition)	82 (91.1%)	8 (8.9%)	0.463	82 (91.1%)	8 (8.9%)	0.185	77 (90.6%)	8 (9.4%)	0.204	62 (68.9%)	28 (31.1%)	0.106
High Fasting Glucose (ATPIII Definition)	44 (91.7%)	4 (8.3%)	0.787	45 (93.8%)	3 (6.3%)	0.462	44 (93.6%)	3 (6.4%)	0.861	40 (83.3%)	8 (16.7%)	0.056
MS AHA Definition	73 (92.4%)	6 (7.6%)	0.595	75 (94.9%)	4 (5.1%)	0.963	70 (94.6%)	4 (5.4%)	0.529	63 (79.7%)	16 (20.3%)	0.054
Central Obesity (AHA Definition)	44 (91.7%)	4 (8.3%)	0.787	45 (93.8%)	3 (6.3%)	0.462	44 (93.6%)	3 (6.4%)	0.861	40 (83.3%)	8 (16.7%)	0.056
High Triglycerides level (AHA Definition)	42 (91.3%)	4 (8.7%)	0.870	45 (97.8%)	1 (2.2%)	0.120	41 (97.6%)	1 (2.4%)	0.088	33 (71.7%)	13 (28.3%)	0.883
Low HDL Cholesterol level (AHA Definition)	85 (90.4%)	9 (9.6%)	0.595	87 (91.6%)	8 (8.4%)	0.095	80 (90.9%)	8 (9.1%)	0.095	68 (71.6%)	27 (28.4%)	0.319
High Blood Pressure (AHA Definition)	105 (92.1%)	9 (7.9%)	0.771	106 (92.2%)	9 (7.8%)	0.232	99 (91.7%)	9 (8.3%)	0.246	86 (74.8%)	29 (25.2%)	0.380
High Fasting Glucose (AHA Definition)	52 (89.7%)	6 (10.3%)	0.686	54 (93.1%)	4 (6.9%)	0.922	50 (94.3%)	3 (5.7%)	0.381	44 (75.9%)	14 (24.1%)	0.425
MS IDF Definition	64 (90.1%)	7 (9.9%)	0.831	66 (93.0%)	5 (7.0%)	0.108	60 (92.3%)	5 (7.7%)	0.363	54 (76.1%)	17 (26.9%)	0.411
Central Obesity (IDF Definition)	75 (90.4%)	8 (9.6%)	0.764	78 (94.0%)	5 (6.0%)	0.200	71 (92.2%)	6 (7.8%)	0.159	65 (78.3%)	18 (21.7%)	0.088
High Triglycerides level (IDF Definition)	42 (91.3%)	4 (8.7%)	0.870	45 (97.8%)	1 (2.2%)	0.120	41 (97.6%)	1 (2.4%)	0.088	33 (71.7%)	13 (28.3%)	0.883
HDL Cholesterol level (IDF Definition)	85 (90.4%)	9 (9.6%)	0.595	87 (91.6%)	8 (8.4%)	0.095	80 (90.9%)	8 (9.1%)	0.323	68 (71.6%)	27 (28.4%)	0.319
High Blood Pressure (IDF Definition)	105 (92.1%)	9 (7.9%)	0.771	106 (92.2%)	9 (7.8%)	0.232	99 (91.7%)	9 (8.3%)	0.246	86 (74.8%)	29 (25.2%)	0.380
High Fasting Glucose (IDF Definition)	52 (89.7%)	6 (10.3%)	0.686	54 (93.1%)	4 (6.9%)	0.922	50 (94.3%)	3 (5.7%)	0.381	44 (75.9%)	14 (24.1%)	0.425

**Table 5**  
Mann-Whitney Test Results. Relation between ordinal outcome (Morbimortality according to Clavien-Dindo classification) and Independent Variables.

	Man-Whitney Test				
	Morbimortality According to Clavien-dindo Classification				
	Mdn (IQR)		p value	U	Z
No	Yes				
MS ATPIII Definition	0 (1)	0 (1)	0.777	1503.00	-0.283
Central Obesity (ATPIII Definition)	0 (2)	0 (0)	0.091	1251.50	-1.691
High Triglycerides level (ATPIII Definition)	0 (1)	0 (1)	0.880	1680.00	-0.151
Low HDL Cholesterol level (ATPIII Definition)	0 (0)	0 (2)	<b>0.033</b>	<b>1400.50</b>	<b>-2.129</b>
High Blood Pressure (ATPIII Definition)	0 (0)	0 (1)	0.133	15670.50	-1.504
High Fasting Glucose (ATPIII Definition)	0 (2)	0 (0)	0.091	1251.50	-1.691
MS AHA Definition	0 (2)	0 (0)	0.067	1260.00	-1.830
Central Obesity (AHA Definition)	0 (2)	0 (0)	0.091	1251.50	-1.691
High Triglycerides level (AHA Definition)	0 (1)	0 (1)	0.880	1680.00	-0.151
Low HDL Cholesterol level (AHA Definition)	0 (0)	0 (2)	0.239	1312.00	0.239
High Blood Pressure (AHA Definition)	0 (2)	0 (1)	0.398	881.00	-0.845
High Fasting Glucose (AHA Definition)	0 (1)	0 (1)	0.452	1685.50	-0.752
MS IDF Definition	0 (1)	0 (1)	0.538	1171.50	-0.616
Central Obesity (IDF Definition)	0 (2)	0 (0)	0.137	918.50	-1.488
High Triglycerides level (IDF Definition)	0 (1)	0 (1)	0.880	1680.00	-0.151
HDL Cholesterol level (IDF Definition)	0 (0)	0 (2)	0.239	1312.00	-1.177
High Blood Pressure (IDF Definition)	0 (2)	0 (1)	0.398	881.00	-0.845
High Fasting Glucose (IDF Definition)	0 (1)	0 (1)	0.452	1685.50	-0.752

present higher grades of complications, according to Clavien-Dion classification (Mdn = 0; IQR = 2;  $p = 0.033$ ), (Table 5).

#### 4. Discussion

It is well known nowadays that MS is a risk factor for the development of CRC, as proven, between many others, by a large cohort study from 2006 [9] or by a recent meta-analysis (reporting 17 studies) from 2013 [8] being the pathophysiological mechanism pointed has responsible mostly related to insulin resistance and abdominal obesity [1]. This fact may perhaps explain the high incidence of MS (in all its definitions) in our sample (constituted only by CRC diagnosed patients) in comparison, for example, with a report that included 1433 inhabitants of Porto city (Portugal). In this study, the investigators obtained an estimated prevalence of MS of 24.0% with the ATPIII criteria, 37.2% with the AHA criteria and, 41.9% with the IDF criteria [19], in contrast with our results of 40.7%, 67.5% and 67.0%, respectively.

On the other hand, the relationship between MS and CRC surgical outcomes, recurrence and survival has been a source of disagreement with discording studies being published over the time.

For instance, a study from 2010 showed that the presence of metabolic syndrome was associated with a significant increase of hepatic metastasis and tumor recurrence [12]. In the same year another prospective study from Thailand peremptorily concluded that MS was an independent risk factor for postoperative complications and longer hospital stay in CRC patients submitted to surgery, with a 30 days follow-up [13]. On the other hand, in 2013, a retrospective cohort investigation concluded that MS had no influence on recurrence and overall survival of CRC patients, perhaps explained by the combined effects of elevated blood glucose and hypertension and the protective effect of dyslipidemia, has proven in the same study [20]. Moreover, two survival analysis from 2016 were able to, again, prove a deleterious effect of MS. On one of them, a prospective study involving 1318 CRC patients, it was proved that MS, specially hyperglycemia, were robust predictors of CRC mortality [21]. On the other one, from October 2016, patients were divided into 4 categories (defined by the presence of MS and/or obesity) and, as a result, the group with MS

and obesity combined obtained a worse survival, overall and CRC related [22].

The pointed mechanism for this interaction might be explain by several theories: first, the insulin-resistant state present in MS influences an abnormal metabolism in adipocytes (especially visceral fat adipocytes) with subsequent increase in levels of Interleukin-6 and tumor necrosis factor- $\alpha$  (both pro-inflammatory) and low levels of adiponectin (protective adipokine) leading to an excessive systemic inflammatory response. Secondly, MS has been correlated with a situation of impaired microvascular circulation, which may cause diminished perfusion and poor tissue healing. And finally, alterations in polymorphonuclear cells has been noticed in patients with MS, which might be caused by the low levels of Leukotriene B4, essential in these cells function, leading this way to alterations in innate immune defense [13].

In our study there was no statistically significant influence of any of the MS definitions or it's components on the studied outcomes (no  $p$  value  $< 0.05$ ), and the only finding that proves influence of HDL-cholesterol (by ATPIII definition) with 30 days morbimortality and with Clavien-Dindo Classification Grade appears to us a statistical finding instead of a valuable finding concerning the context.

#### 5. Conclusion

This study seems to indicate that there is no apparent association between MS, in its different definitions and components, and CRC surgical outcomes (reintervention, readmission, dehiscence and morbimortality) at 30 days.

While a deeper understanding of this relationship could lead to a better clinical management, data remains inconclusive. The question of whether or not a better control of metabolic status could improve CRC patients' prognosis waits for further studies with larger sample sizes and longer follow-up timings.

#### Conflicts of interest

None.

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