

# Visceral obesity enhances inflammatory response after laparoscopic colorectal resection

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## Abstract

**Aims:** C-reactive protein (CRP) is commonly used for monitoring Surgical Stress Response (SSR) and detecting post-operative infectious complications. However, high CRP values can be associated to patient-related factors independently from complications. The aim of this study was to assess the relationship between visceral obesity (VO) and SSR after laparoscopic colorectal resection. **Methods:** Visceral adipose tissue (VAT) area was measured at CT images for 357 patients who underwent elective laparoscopic colorectal resection at our institution. Post-operative outcomes and CRP values were compared between VO and non-VO groups, defined according to VAT cut-offs. Univariate and multivariate analyses were conducted for factors affecting SSR. ROC curves were constructed to assess the most appropriate CRP values for identifying infectious complications in the VO and non-VO populations. **Results:** In the final cohort, 62.2% of patients were classified as VO. No differences were seen in post-operative outcomes and infectious complications. VO was associated with higher CRP values on post-operative day (POD)1, POD2, POD3, and POD5, considering both the overall cohort and patients without infectious complications. A positive correlation was found between VAT and CRP values on all PODs, and VO independently predicted increased CRP on POD1-3 in patients without infectious complications but not in those who developed complications. ROC curves analysis for POD3 CRP showed comparable accuracy for detection of infectious complications in both groups, though the optimal cut-off value was higher in VO group (154 vs. 136 mg/dl). **Conclusions:** Although VO is not associated to increased complications after laparoscopic colorectal resection, it independently predicts increased SSR risk. To achieve accurate identification of infectious complications, different cut-off values of POD3 CRP shall be used in VO and non-VO patients.

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**Aims** : C-reactive protein (CRP) is commonly used for monitoring Surgical Stress Response (SSR) and detecting post-operative infectious complications. However, high CRP values can be associated to patient-related factors independently from complications. The aim of this study was to assess the relationship between visceral obesity (VO) and SSR after laparoscopic colorectal resection.

**Methods** : Visceral adipose tissue (VAT) area was measured at CT images for 357 patients who underwent elective laparoscopic colorectal resection at our institution. Post-operative outcomes and CRP values were compared between VO and non-VO groups, defined according to VAT cut-offs. Univariate and multivariate analyses were conducted for factors affecting SSR. ROC curves were constructed to assess the most appropriate CRP values for identifying infectious complications in the VO and non-VO populations.

**Results** : In the final cohort, 62.2% of patients were classified as VO. No differences were seen in post-operative outcomes and infectious complications. VO was associated with higher CRP values on post-operative day (POD)1, POD2, POD3, and POD5, considering both the overall cohort and patients without infectious complications. A positive correlation was found between VAT and CRP values on all PODs, and VO independently predicted increased CRP on POD1-3 in patients without infectious complications but not in those who developed complications. ROC curves analysis for POD3 CRP showed comparable accuracy for detection of infectious complications in both groups, though the optimal cut-off value was higher in VO group (154 *vs.* 136 mg/dl).

**Conclusions** : Although VO is not associated to increased complications after laparoscopic colorectal resection, it independently predicts increased SSR risk. To achieve accurate identification of infectious complications, different cut-off values of POD3 CRP shall be used in VO and non-VO patients.

## KEY WORDS

visceral obesity, C-reactive protein, inflammation, surgical stress response, laparoscopy

## What's known?

The degree of post-operative inflammation or Surgical Stress Response (SSR) can be assessed in clinical practice through biomarkers such as C-reactive protein (CRP). In colorectal surgery several factors affect CRP levels such as surgical approach, extent of surgery and occurrence of post-operative complications. Among patient-related factors low skeletal muscle mass is a well-known risk factor for increased SSR after surgery.

## what's new?

This is the first paper which assessed the role of visceral adipose tissue (VAT) on CRP levels and SSR. After laparoscopic colorectal resection visceral obese patients present higher SSR compared to normal patients, independently from post-operative complications. When monitoring the post-operative course through CRP levels, VAT should be considered as a risk factors for non-clinically significant higher values.

## Introduction

Hospitalization and surgical procedures affect normal homeostasis and trigger metabolic stress response. This process is commonly called Systemic Inflammatory Response or Surgical Stress Response (SSR), and involves both immune and neuro-endocrine systems <sup>1</sup>.

Several approaches have been proposed for assaying SSR in clinical practice, with C-reactive protein (CRP) measurement remaining the most used and affordable strategy. In colorectal surgery several studies confirmed the usefulness of CRP for safe early discharge, aiming at early detection of adverse events <sup>2</sup>. Conversely, several procedure- and patient-related factors could influence SSR, so that specific subgroups of patients may need the estimation and application of specific cut-off values. Among these factors, surgical approach and nutritional status have been recently found to be associated with SSR <sup>3-5</sup>. In particular, low skeletal muscle mass has been associated with increased SSR <sup>4</sup>, whilst little is known on the post-operative pro-inflammatory role of visceral obesity (VO) and its possible clinical implications.

In this study, we assessed the relationship between visceral adipose tissue (VAT) area measured at CT scan and SSR defined according to peri-operative CRP levels. We assumed that VO, defined as VAT excess, could intensify SSR following laparoscopic colorectal surgery, thus requiring specific cut-off values for detecting post-operative infectious complications in VO patients.

## Patients and methods

### Patients and study design

From January 2012 to February 2020, four-hundred seventy-six patients underwent elective laparoscopic colorectal resection for benign or malignant disease at the Division of General and Hepatobiliary Surgery, University of Verona Hospital Trust. Exclusion criteria were inflammatory bowel disease (n = 21), familial adenomatous polyposis (n = 6), and mortality within post-operative day (POD) 5 (n = 2). All patients with missing data or pre-operative CT imaging in our Picture Archiving and Communication System (PACS) were also excluded from analysis (n = 90).

This study was approved by the Ethics Committee of the University Hospital of Verona, Italy (reference number “58642 - CRINF-1560CESC”). All patients provided written informed consent.

### Clinical and demographic data

Clinic and pathological data collected included age, sex, and Charlson’s comorbidity index (CCI). Patient height, weight, and body mass index (BMI) were recorded from pre-operative assessment. All tumors were confirmed histologically and staged according to the 8<sup>th</sup> Edition of the American Joint Committee on Cancer (AJCC) TNM Classification. Intraoperative variables were tumor location, type of resection, duration of surgical procedure, blood loss, and need for conversion. ERAS protocol enrollment was registered and all patients followed the previously described pathway <sup>6</sup>.

Post-operative complications were graded according to the Clavien-Dindo Classification and divided into minor (grade I-II) and major grade (grade III-V). When several adverse events occurred in the same patient, the highest grade was adopted. Primary outcome was the rate of infectious complications, which included anastomotic leak, pneumonia and surgical site infections<sup>7,8</sup>. Post-operative length of stay (LOS), 30-day readmission, and reoperation rates were registered together with post-operative mortality.

### Laboratory tests

Pre-operative systemic inflammatory condition was assessed through serum CRP within 3 weeks before surgery (Pre-Op CRP). Serum CRP levels in the post-operative period were routinely measured on POD1-3 and on POD4-5, based on clinical indication. The concentration of CRP was measured using a validated immunoturbidimetric assay on a Roche Cobas 8000 (Roche Diagnostics, Basel, Switzerland). The analytical characteristics of this method are as follows: limit of detection, 0.3 mg/L; linearity, 0.3-350 mg/L; intra-assay imprecision, 1.2% to 3.6%; upper limit of the normal reference range: <5 mg/L

### Body composition analysis

Computed tomography (CT) images were retrieved from digital PACS and analyzed using ImageJ software (ImageJ; The National Institutes of Health, Washington, MD, USA; version 1.47) as previously described<sup>9</sup>. Briefly, VAT area (cm<sup>2</sup>) was measured on a single axial CT image at the third lumbar vertebra (L3) using

Hounsfield unit (HU) thresholds of -190 to -30, in line with accepted methodology<sup>10,11</sup>. This parameter is highly correlated with total body adipose tissue<sup>12</sup>. Images analysis was performed by a single researcher specifically trained for the task. VO was defined using sex-specific VAT cut-off values<sup>11,13</sup> as follows: VO group with VAT > 163.8 cm<sup>2</sup> in males and VAT > 80.1 cm<sup>2</sup> in females and non-visceral obese (Non-VO) group with VAT below these thresholds.

## Statistical analysis

Results are presented as percentages (%) and means ( $\pm$ SD) or medians and interquartile range (IQR). Normality was assessed using the Kolmogorov-Smirnov test. Chi-square and Fisher exact tests were used for categorical variables while Student t-test or Mann-Whitney U test were used for quantitative variables as appropriate. Relationships between continuous variables were assessed using Spearman rank correlation coefficient analysis and the correlation coefficient ( $\rho$ ) was calculated.

Univariate analysis was conducted to assess the factors affecting CRP values in the overall population. Subgroup analysis was performed separately for patients who presented infectious complications. The factors analyzed were VO (*vs.* Non-VO), ERAS (*vs.* standard care), male gender (*vs.* female), CCI >4 (*vs.* <4), cancer (*vs.* benign disease), extent of resection (right hemicolectomy *vs.* left hemicolectomy *vs.* rectal resection), need for conversion (*vs.* no conversion), and surgical time > median (*vs.* < median). A screened p-value of <0.10 at univariate analysis was then considered for entering the multivariate model after validating the absence of multicollinearity. In multivariate logistic regression, a p value <0.05 was considered statistically significant.

Since POD3 CRP value is used in our clinical practice as one of the discharge criteria, we tested it as predictor of infectious complications by receiver operating characteristic (ROC) curves analysis. The area under the curve (AUC) is a direct measure of diagnostic accuracy of a test. A test with an AUC between 0.7-0.8 is considered as having a good diagnostic accuracy. Cut-off values with the highest sensitivity and specificity were determined by using the Youden's index. To compare accuracy between ROC curves in subgroup analysis, the DeLong method was applied<sup>14</sup>.

Results were considered statistically significant when p value was found to be <0.05. SPSS software (version 23, SPSS, Inc.) was used for statistical analysis. Graphics were outlined using GraphPad Prism version 9.0.

## Results

### Cohort under study

After the selection process, a cohort of 357 patients was included for study purpose. Median (IQR) BMI in the overall population was 25.0 (22.9-28.1) kg/m<sup>2</sup>. Median (IQR) VAT area was 150.4 (95.7-212.6) cm<sup>2</sup> and, as predictable, was higher in males than in females (183.8 [125.4-251.7] cm<sup>2</sup> *vs.* 103.3 [57.5-167.2] cm<sup>2</sup>; p <0.001). After application of sex-specific cut-offs, 222 patients (62.2%) were classified as VO and 135 patients (37.8%) as non-VO, with no differences in VO incidence between males and females (60.3% *vs.* 64.6%; p = 0.41).

Baseline clinical and pathological characteristics are shown in Table 1. VO patients were older and had higher BMI (p<0.001) and CCI (p=0.01). No relevant differences were found in terms of extent of surgery or staging of malignant disease.

Post-operative outcomes are shown in Table 1. In the overall population, 158 patients (42.3%) developed post-operative complications, and 30 patients (8.4%) suffered a severe complication according to the Clavien-Dindo classification. No differences were found between the VO and non-VO cohorts, as for overall, major grade and infectious complications. Post-operative LoS was also comparable between groups.

### Visceral obesity and SSR

Baseline pre-operative CRP values were significantly associated with VAT both in females ( $\rho$ =0.36, p=0.001) and males ( $\rho$ =0.19; p=0.04). A positive correlation between VAT and post-operative CRP values was found

both in females and males on POD1 ( $\rho=0.24$ ,  $p=0.001$  and  $\rho=0.20$ ,  $p=0.04$ ), POD2 ( $\rho=0.32$ ,  $p<0.001$  and  $\rho=0.15$ ,  $p=0.03$ ) and POD3 ( $\rho=0.31$ ,  $p<0.001$  and  $\rho=0.17$ ,  $p=0.02$ ), but not on POD4 and POD5.

VO patients displayed higher baseline CRP levels compared to non-VO patients (3, 1-6 mg/L *vs.* 1, 1-3 mg/L;  $p<0.001$ ). Higher CRP values were also observed in the VO group on POD1, POD2, POD3 and POD5 (Figure 1 and Table 2).

Linear regression analysis showed that VO was positively correlated with CRP from POD 1 to 3, with the highest coefficient on POD2 ( $\beta=0.164$ ;  $p<0.001$ ). As showed in Supplementary Table 3, conversion to open surgery and surgical time were positively associated with CRP levels. Conversely, ERAS protocol displayed a negative correlation.

In multivariate analysis (Table 4), VO was confirmed as independent risk factor for increased CRP on POD1 and POD2 but not on POD3 ( $\beta=0.062$ ;  $p=0.23$ ). ERAS enrollment was independently associated with reduced CRP values from POD2 to POD5, while conversion to open surgery or duration of surgery were associated with increased CRP values on POD1 and POD1, or with POD 2 and POD3, respectively.

### Infectious complications and SSR

No differences in CRP levels according to the presence of VO were observed in patients with infectious complications (Figure 2b). Univariate analysis in this subgroup of patients did not reveal any association with abnormal CRP values in the post-operative period, so that multivariate analysis was unnecessary (Supplementary Table 1). Further analysis was therefore conducted only for patients without infectious complications. In this subgroup, CRP values were significantly higher in VO compared to non-VO patients on POD1, POD2, POD3 and POD5 (Figure 2a). Univariate analysis showed a positive correlation between CRP from POD 1 to 3, and VO (Supplementary Table 2), with the highest coefficient on POD2 ( $\beta=0.200$ ;  $p=0.001$ ). In multivariate analysis (Table 5), VO was confirmed as independent risk factor for increased CRP values between POD1-3. Other factors associated with high CRP values were conversion to open surgery (POD1-2) and time of surgery (POD 1-4). ERAS enrollment was independently associated with lower CRP values on POD2, POD3 and POD5.

### Assessment of POD3 CRP cut-off values

Considering the outcome of infectious complications, ROC curve analysis revealed an AUC of 0.86 (95% CI: 0.78-0.95,  $p<0.001$ ), thus confirming the clinical significance of measuring CRP on POD3, as reliable predictor of infectious complications. In the overall population, the optimal cut-off was 134 mg/L, associated with 80% sensitivity and 78.9% specificity. Even considering VO and non-VO separately, CRP value on POD3 was an efficient predictor of infectious complications, displaying an AUC value  $>0.85$  (Figure 3). According to the Youden's index, the optimal cut-off value of CRP on POD3 was 136 mg/dL (87.5% sensitivity and 88% specificity) for non-VO patients, and 154 mg/dL (83.3% sensitivity and 81.2% specificity) for VO patients, respectively.

## Discussion

Body composition assessment in surgical patients has recently gained attention due to the possible clinical implications in developing complications and for long-term survival. For example, low skeletal muscle mass seem to be strongly associated with poor post-operative outcomes especially in cancer patients<sup>15-17</sup>. Reduced skeletal muscle mass may promote the development of a pro-inflammatory environment, basically through onset of insulin resistance,<sup>18</sup> which is responsible for enhanced SSR after colorectal resection<sup>4</sup>. Similarly, insulin resistance and higher levels of pro-inflammatory cytokines such as IL-6 and TNF- $\alpha$  are associated with abnormal adipose tissue accumulation, in particular excess of visceral adipocytes<sup>19</sup>. Although the chronic systemic inflammation which characterizes VO is a well-known risk factor for development of several diseases associated with metabolic syndrome<sup>19,20</sup>, the role of VO in worsening surgical outcomes is still debated<sup>19,21,22</sup>. Little is known about the role of VO on acute inflammatory response after colorectal resection. Our study aimed to characterize the magnitude of SSR after laparoscopic colorectal resection according to VO, trying to assess its role in development of infectious complications. We hypothesized that

VO patients presented higher degree of SSR, thus requiring separate cut-offs for predicting safe discharge on POD3.

Although procalcitonin (PCT) presents higher specificity than CRP in differentiating between inflammation and infection <sup>23</sup>, its use in the clinical practice after colorectal surgery is still limited, and mostly influenced development of severe bacterial infections <sup>23–25</sup>. We therefore chose CRP as an objective marker of SSR, due to its widespread use in clinical practice and its role as predictor of complications <sup>2</sup>. In uncomplicated surgery, CRP is generally low on POD1, then exhibits a maximal increase on POD2 and decreases by POD3. Nonetheless, CRP further increases after POD2 in patients developing adverse events. Consequently, CRP on POD3 is widely considered a reliable marker of severe post-operative adverse events, especially infectious complications. Combined with negative clinical findings, a CRP value below the specific cut-offs on POD3 was found an important marker for allowing safe discharge <sup>2</sup>.

The results of this study confirm our original hypothesis of an association between VO and a pro-inflammatory environment, as shown by higher baseline and post-operative CRP values in the overall population. Multivariate analysis confirmed VO as an independent risk factor for increased SSR, with higher CRP values on POD1 and 2. Interestingly, the increase in SSR was stronger in patients who did not develop infectious complications. Our results are in line with recent evidence of low SSR due to reduced surgical stress from the synergistic effect of laparoscopy and ERAS protocol <sup>1,26</sup>. Nevertheless, whilst conversion to open surgery and surgical time are well-known factors associated with increased SSR, we demonstrate here for the first time that VO may be responsible for a larger inflammatory response after laparoscopic colorectal resection. However, this association was not confirmed in patients who developed infectious complications. We can speculate that whether VO is associated with higher SSR even in complicated cases, its effect on CRP may be concealed by the greater inflammatory response fostered by infection.

Previous studies evaluating the role of VO on SSR were carried out in patients who underwent minimally invasive esophagectomy. Doyle et al. reported altered patterns of cytokine expression in VO patients both pre- and post-operatively. Despite a heightened immune and inflammatory response, this appeared to have no clinical adverse sequelae for VO subjects <sup>27</sup>. In accordance with these findings, Okamura et al. showed that VAT quartiles were significantly associated with CRP levels both in the overall population and in patients who did not develop post-operative infectious complications <sup>28</sup>. Following the results of these studies, our findings confirm that VO could intensify SSR following laparoscopic colorectal resection, though VO was not responsible for worse post-operative course, since the complication rates appeared to be similar between VO and non-VO patients. Whether increased SSR in VO patients is related to higher magnitude of tissue damage, enhanced inflammatory response, or both these elements would coexist, this cannot be elucidated from the present study.

Infectious complications after colorectal surgery have a major clinical impact as they increase LOS, treatment costs and worsen long-term survival in cancer patients <sup>29,30</sup>. When early diagnosed, they can be treated effectively, and their impact is minimized. In the era of fast-track protocols, several CRP cut-off values have been proposed to ensure safe discharge. Different thresholds has been used depending on surgical procedure and surgical approach, since the amount of normal SSR varies between open <sup>31–33</sup> and laparoscopic surgery <sup>2,34</sup>. In our opinion, all parameters that could influence SSR should be considered when proposing CRP cut-off values for safe discharge, so that its diagnostic efficiency could be increased. Our study, following previous evidences in minimally invasive esophageal surgery <sup>27,28</sup>, demonstrates increased SSR and CRP production after laparoscopic colorectal resection in patients with increased VAT, both in the overall population and in uncomplicated cases. Consequently, high levels of CRP at POD3 may have different clinical significance in VO and non-VO patients. Notably, avoidance to consider different thresholds for these two groups would decrease the diagnostic performance (i.e., both sensitivity and specificity) of this test. Our analysis with ROC curves demonstrated that the CRP cut-off value at POD3 after minimally invasive colorectal surgery should be differentiated according to patient's body composition, with VO patients presenting higher threshold for safe discharge.

Our study has some limitations, which shall be mentioned. First, the sample size was relatively small since

we focused on patients undergoing elective surgery with minimally invasive approach. However, this decision allowed us to analyze a more homogeneous population, thus reducing the negative effect of many other confounding factors. Second, this is a retrospective observational study conducted at a single institution. The findings presented in this paper would hence need to be validated in larger and prospective cohorts. Third, since introduction of ERAS protocol, more and more patients have been discharged before POD4, thus reducing the availability of data on CRP values on POD4 and 5.

Our paper also has many strengths. The analysis of CT images and VAT was conducted by a single researcher, with large experience in body composition analysis, who was blinded to post-operative outcomes. Then, as previously mentioned, we selected a homogeneous cohort that limited the differences in clinical, pathological, and surgical variables between the two groups. Moreover, to our knowledge, this is one of the few studies analyzing the impact of VAT and VO on SSR after surgery, and it is the sole to consider patients undergoing minimally invasive colorectal resections.

In conclusion, our findings seemingly confirm the presence of a proinflammatory environment before surgery, highlighting enhanced SSR in VO patients. This increased inflammatory response was significant in the overall population and in patients without infectious complications, whilst our analysis failed to find significant difference in those who developed infectious complications. Interestingly, despite the SSR was increased in VO patients, no differences in post-operative complications could be found. We also confirmed that CRP measured on POD3 may present high sensitivity and specificity in predicting infectious complications, though different cut-off values should be considered for VO and non-VO. Future studies in larger cohorts should hence aim at elucidating the relationship between VAT, increased SSR, and incidence of post-operative complications.

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All authors read and approved the final version of this manuscript.

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## TABLES

**Table 1.** Clinic and pathological characteristics in the VO and Non-VO groups

Parameter	Parameter	Parameter	VO n = 222	Non-VO n = 135	p
Gender, male	Gender, male	Gender, male	120 (54.1)	79 (58.5)	0.41
Age, years	Age, years	Age, years	68.9+11.3	63.3+12.7	<0.001
BMI, kg/m <sup>2</sup>	BMI, kg/m <sup>2</sup>	BMI, kg/m <sup>2</sup>	26.5 (24.2-29.4)	23.6 (21.6-24.8)	<0.001
ERAS	ERAS	ERAS	150 (67.6)	99 (73.3)	0.25

Charlson's comorbidity index	Charlson's comorbidity index	Charlson's comorbidity index	4 (3-5)	3 (2-5)	0.01
Surgical indication	Surgical indication	Surgical indication			0.93
	Colon cancer	Colon cancer	116 (52.3)	72 (53.3)	
	Rectal cancer	Rectal cancer	54 (24.3)	29 (21.5)	
	Adenoma	Adenoma	18 (8.1)	11 (8.1)	
	Diverticular disease	Diverticular disease	34 (15.3)	23 (17)	
Neoadjuvant therapy*	Neoadjuvant therapy*	Neoadjuvant therapy*	25 (14.7)	13 (12.9)	0.67
TNM stage*	TNM stage*	TNM stage*			0.17
	TNM stage I / II	TNM stage I / II	111 (65.3)	57 (56.4)	
	TNM stage III / IV	TNM stage III / IV	59 (34.7)	44 (43.6)	
Surgical procedure	Surgical procedure	Surgical procedure			0.84
	Right hemicolectomy	Right hemicolectomy	73 (32.9)	43 (31.9)	
	Left hemicolectomy	Left hemicolectomy	79 (35.6)	51 (37.8)	
	Rectal resection	Rectal resection	70 (31.6)	41 (30.4)	
Associated resections	Associated resections	Associated resections	47 (21.2)	23 (17)	0.34
Surgical time, min	Surgical time, min	Surgical time, min	237 (190-297)	220 (191-270)	0.18
Blood loss, ml	Blood loss, ml	Blood loss, ml	50 (30-100)	40 (30-90)	0.16
Conversion	Conversion	Conversion	18 (8.1)	6 (4.4)	0.18
Overall complications	Overall complications	Overall complications	94 (42.3)	57 (42.2)	0.98
		Minor grade	77 (34.7)	44 (32.6)	0.78
		Major grade	17 (7.7)	13 (9.6)	0.52
Infectious complications	Infectious complications	Infectious complications	34 (15.3)	23 (17)	0.67
		Pneumonia	8 (3.6)	7 (5.2)	0.47
		Anastomotic leak	12 (5.4)	8 (5.9)	0.84
		Surgical site infections	11 (5)	7 (5.2)	0.92
Time to infectious complication, days	Time to infectious complication, days	Time to infectious complication, days	4 (2-5.25)	4 (3-7)	0.44
Mortality	Mortality	Mortality	1 (0.5)	1 (0.7)	0.72
Readmission	Readmission	Readmission	7 (3.2)	5 (3.7)	0.78
Redo surgery	Redo surgery	Redo surgery	10 (4.5)	9 (6.7)	0.38
Length of stay, days	Length of stay, days	Length of stay, days	6 (5-8)	6 (4-8)	0.30

\* Percentage on 271 colon and rectal cancers.

**Table 2.** Surgical stress response expressed as CRP values in the overall population and according to visceral obesity

Parameter	Overall population n = 357	Visceral obesity  VO n = 222	Visceral obesity  Non-VO n = 125	Visceral obesity  p
Pre-operative CRP	2 (1-5)	3 (1-6)	1 (1-3)	<0.001
CRP POD1	62 (43-95)	65 (45-99)	54 (40-81)	0.002
CRP POD2	102 (61-156)	112 (71-169)	88 (53-138)	0.001
CRP POD3	85 (45-132)	92 (52-143)	71 (34-111)	0.003
CRP POD4	74 (36-135)	83 (36-150)	73 (36-117)	0.50
CRP POD5	52 (23-103)	57 (26-113)	44 (19-79)	0.04

POD: post-operative day

**Table 3.** Univariate analysis for factors affecting CRP values

Factor	Crp POD1 $\beta$	Crp POD1 P	Crp POD2 $\beta$	Crp POD2 p	Crp POD3 $\beta$	Crp POD3 p	Crp POD4 $\beta$	Crp POD4 p
VO	0.151	0.004	0.164	0.003	0.125	0.02	0.029	0.74
ERAS	-0.151	0.004	-0.292	<0.001	-0.332	<0.001	-0.281	0.001
Male gender	0.047	0.38	0.081	0.14	0.043	0.39	0.074	0.39
CCI	0.075	0.16	0.136	0.01	0.154	0.004	0.017	0.84
Cancer	0.089	0.09	0.128	0.02	0.126	0.02	0.011	0.90
Specimen length	-0.006	0.91	0.034	0.53	0.103	0.05	0.137	0.11
Conversion	0.170	0.001	0.143	0.01	0.085	0.11	0.098	0.25
Surgical time	0.208	<0.001	0.261	<0.001	0.245	<0.001	0.176	0.04

VO: visceral obesity; CCI: Charlson's comorbidity index

**Table 4.** Multivariate analysis for factors affecting CRP values in the overall population

Factor	Crp POD1 $\beta$	Crp POD1 p	Crp POD2 $\beta$	Crp POD2 p	Crp POD3 $\beta$	Crp POD3 p	Crp POD4 $\beta$	Crp POD4 p
VO	0.119	0.02	0.121	0.02	-	-	-	-
ERAS	-	-	-0.144	0.01	-0.279	<0.001	-0.255	0.004
Male gender	-	-	-	-	-	-	-	-
CCI	-	-	-	-	-	-	-	-
Cancer	-	-	-	-	-	-	-	-
Specimen length	-	-	-	-	-	-	-	-
Conversion	0.146	0.01	-	-	-	-	-	-
Surgical time	0.137	0.01	0.177	0.01	0.193	<0.001	-	-

VO: visceral obesity; CCI: Charlson's comorbidity index

**Table 5.** Multivariate analysis for factors affecting CRP values in patients without infectious complications

Factor	Crp POD1 $\beta$	Crp POD1 p	Crp POD2 $\beta$	Crp POD2 P	Crp POD3 $\beta$	Crp POD3 p	Crp POD4 $\beta$	Crp POD4 p
VO	0.141	0.01	0.156	0.01	0.124	0.03		
ERAS	-	-	-0.165	0.01	-0.199	0.001	-	-
Male gender								
CCI			-	-	-	-		
Cancer			-	-	-	-		
Specimen length								
Conversion	0.218	<0.001	0.163	0.004	-	-	-	-
Surgical time	0.195	0.001	0.251	<0.001	0.267	<0.001	0.289	0.01

VO: visceral obesity; CCI: Charlson's comorbidity index

**Supplementary Table 1.** Univariate analysis for factors affecting CRP values in patients with infectious complications

Factor	Crp POD1 $\beta$	Crp POD1 p	Crp POD2 $\beta$	Crp POD2 p	Crp POD3 $\beta$	Crp POD3 p	Crp POD4 $\beta$	Crp POD4 p
VO	0.113	0.40	0.113	0.42	0.092	0.50	0.146	0.45
ERAS	0.041	0.76	-0.038	0.79	-0.259	0.05	-0.211	0.27
Male gender	0.197	0.14	0.294	0.03	0.301	0.02	0.326	0.10
CCI	0.021	0.88	-0.027	0.85	-0.005	0.97	-0.117	0.55
Cancer	0.148	0.27	0.082	0.59	0.159	0.24	0.113	0.56
Specimen length	-0.085	0.53	-0.132	0.35	0.026	0.85	-0.005	0.98
Conversion	-0.075	0.58	-0.230	0.10	-0.200	0.14	-0.081	0.68
Surgical time	0.028	0.85	-0.052	0.72	-0.052	0.72	-0.142	0.47

VO: visceral obesity; CCI: Charlson's comorbidity index

**Supplementary Table 2.** Univariate analysis for factors affecting CRP values in patients without infectious complications

Factor	Crp POD1 $\beta$	Crp POD1 p	Crp POD2 $\beta$	Crp POD2 P	Crp POD3 $\beta$	Crp POD3 p	Crp POD4 $\beta$	Crp POD4 p
VO	0.168	0.003	0.200	0.001	0.173	0.003	0.081	0.40
ERAS	-0.144	0.01	-0.293	<0.001	-0.296	<0.001	-0.197	0.04
Male gender	0.018	0.75	0.040	0.50	0.060	0.31	-0.029	0.77
CCI	0.055	0.34	0.139	0.02	0.168	0.004	0.065	0.51
Cancer	0.082	0.16	0.153	0.01	0.138	0.02	0.040	0.68
Specimen length	-0.014	0.80	0.035	0.56	0.097	0.10	0.095	0.33
Conversion	0.220	<0.001	0.250	<0.001	0.196	0.001	0.185	0.05
Surgical time	0.220	<0.001	0.321	<0.001	0.334	<0.001	0.329	0.001

VO: visceral obesity; CCI: Charlson's comorbidity index

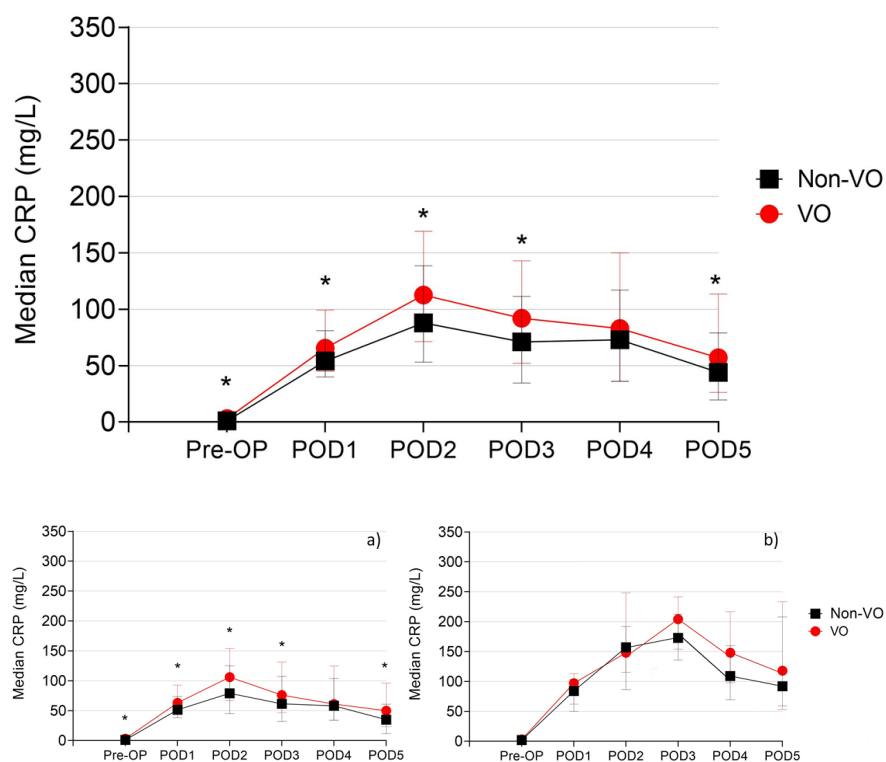
## FIGURE LEGENDS

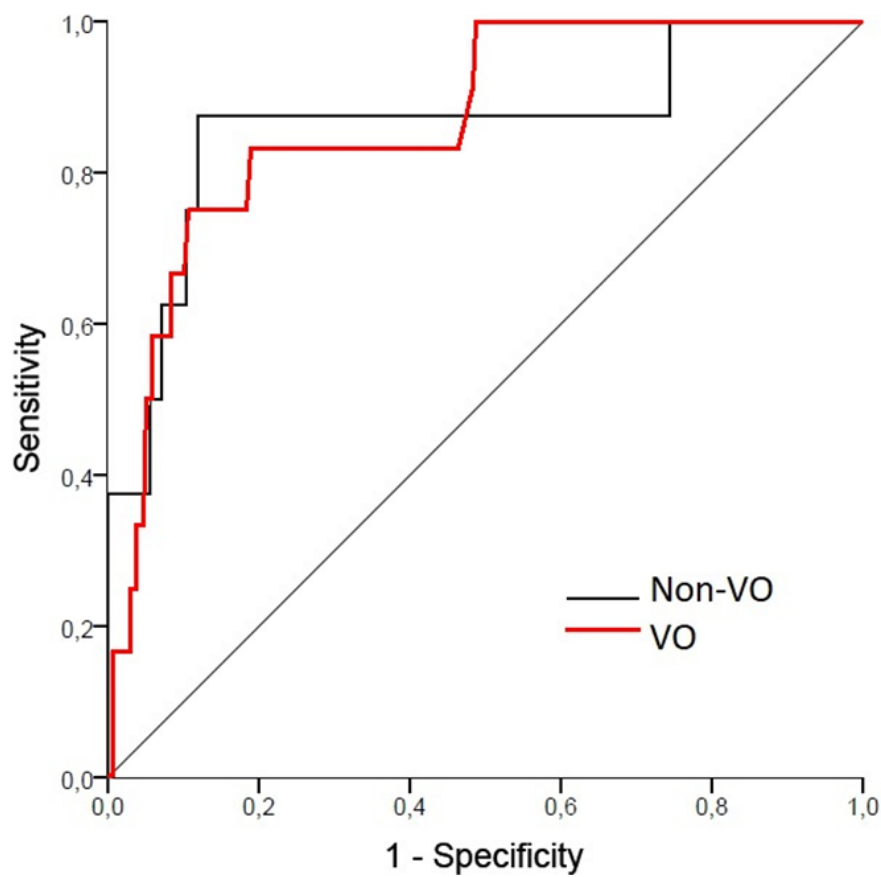
**Figure 1 :** trend in post-operative CRP in the overall population according to VO status (\*p<0.05)

**Figure 2 :** trend in post-operative CRP values in a) patients without infectious complications and b)

patients with post-operative infectious complications according to VO status (\* $p < 0.05$ )

**Figure 3 :** ROC curves for CRP levels on POD3 show good sensitivity and specificity for detection of infectious complications both in VO and Non-VO patients





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