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Visceral obesity enhances inflammatory response after laparoscopic colorectal resection

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Abstract

Aims: C-reactive protein (CRP) is used for monitoring postoperative inflammation (POI) and detecting infectious complications. The aim of this study was to assess the effect of visceral obesity (VO) on acute POI measured through CRP after elective laparoscopic colorectal resection.

Methods: Pre-operative Computed tomography images of 357 patients who underwent laparoscopic colorectal resection were analyzed. Visceral adipose tissue (VAT) area was measured for each patient. VO was defined as VAT area >163.8 cm² in men and >80.1 cm² in women according to accepted sex-specific cut-offs. Postoperative outcomes and CRP values were compared between VO and non-VO groups. The most appropriate CRP value for identifying infectious complications in the two groups was assessed with receiver operating characteristic (ROC) curves. Univariate and multivariate analyses were conducted for factors affecting POI including VO.

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

Conclusions: VO is not associated to increased complications after laparoscopic colorectal resection. Nevertheless, it is independently associated to higher CRP in the overall population and in patients without infectious complications. Consequently, CRP values on POD3 higher than cut-offs commonly adopted in the clinical practice should be carefully evaluated in VO patients to assess the occurrence of infectious complications.

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1 | 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, and involves both immune and neuro-endocrine systems.¹ Several approaches have been proposed for measuring the degree of surgical stress response in clinical practice, and C-reactive protein (CRP) remains the most used and affordable method despite it reflects only the amount of postoperative inflammation (POI) which can be used as a surrogate of the surgical stress response. In colorectal surgery, several studies confirmed the usefulness of CRP for safe early discharge, aiming at early detection of adverse events.²⁻⁵ Conversely, several procedure- and patient-related factors could influence POI, 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 inflammation.⁶⁻⁸ In particular, low skeletal muscle mass has been associated with increased POI,⁷ while little is known about the postoperative 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 POI defined according to postoperative CRP levels. We assumed that VO, defined as VAT excess, could intensify POI following laparoscopic colorectal surgery, thus requiring specific cut-off values for detecting postoperative infectious complications in VO patients.

2 | PATIENTS AND METHODS

2.1 | Patients and study design

From January 2012 to February 2020, 476 patients underwent elective laparoscopic colorectal resection for benign disease (adenomas and diverticular disease) or colorectal adenocarcinoma 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 postoperative 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 ($n = 90$). Since no differences in pre-operative CRP values were found between patients undergoing surgery for diverticular disease and colorectal neoplasia (2, 1-5 mg/L vs 2, 1-7 mg/L, $P = .53$), all patients were considered together for postoperative analysis purposes.

This study was approved by the Ethics Committee of the University Hospital of Verona, Italy (reference number "58642 - CRINF-1560CESC"). Written informed consent for anonymized data collection and analysis was obtained from all the patients included in the study.

What's known?

- The degree of postoperative inflammation (POI) in the surgical stress response 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 postoperative complications. Among patient-related factors, low skeletal muscle mass is a well-known risk factor for increased POI.

What's new?

- This is the first paper which assessed the role of visceral adipose tissue on CRP levels as a marker of POI degree. After laparoscopic colorectal resection, visceral obese (VO) patients present higher CRP values compared with normal patients, independently from postoperative complications. In patients affected by VO, high CRP in the postoperative values could not represent a signal of complications and should be carefully evaluated. Specific cut-off values of CRP should be considered for VO and non-VO patients to detect clinically significant infectious complications.

2.2 | Clinical and demographic data

Clinical 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 8th 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. All patients who followed the enhanced recovery after surgery (ERAS) protocol and achieved all the previously described goals⁹ were registered as "ERAS" while patients excluded from fast-track protocol or with failed ERAS were registered as "non-ERAS."

Postoperative 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. The rate of infectious complications, which included anastomotic leak, pneumonia, and surgical site infections was analyzed.^{10,11} Postoperative length of stay (LOS), 30-day readmission, and reoperation rates were registered together with postoperative mortality.

2.3 | 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 postoperative period were routinely measured on POD1-3 for all the patients in the study group and, additionally, on POD4-5 if patients remained in hospital and according to 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%-3.6%; upper limit of the normal reference range: <5 mg/L.

2.4 | 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.¹² Briefly, VAT area (cm²) was measured on a single axial CT image at the third lumbar vertebra (L3) using Hounsfield unit thresholds of -190 to -30, in line with accepted methodology.^{13,14} This parameter is highly correlated with total body adipose tissue.¹⁵ Images analysis was performed by a single researcher specifically trained for the task. VO was defined using sex-specific VAT cut-off values^{14,16} as follows: VO group with VAT >163.8 cm² in men and VAT >80.1 cm² in women and non-visceral obese (non-VO) group with VAT below these thresholds.

2.5 | Statistical analysis

Results are presented as percentages (%) and means (\pm SD) or medians and interquartile range (IQR) according to normal distribution assessed using the Kolmogorov-Smirnov test. Chi-square and Fisher exact tests were used for categorical variables while Student's *t* test or Mann-Whitney *U* test was used for quantitative variables as appropriate. Relationships between continuous variables were assessed using Spearman's rank correlation coefficient analysis and the correlation coefficient (ρ) 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), men (vs women), CCI >4 (vs \leq 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 \leq median). A screened *P*-value of <.10 at univariate analysis was then considered for entering the multivariate model after validating the absence of multicollinearity. In multivariate logistic regression, a *P* < .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 a 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 and 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.¹⁷

Results were considered statistically significant when *P* value was found to be <.05. SPSS software (version 23, SPSS, Inc) was used for statistical analysis. Graphics were outlined using GraphPad Prism version 9.0.

3 | RESULTS

3.1 | 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/m². Median (IQR) VAT area was 150.4 (95.7-212.6) cm² and, as predictable, was higher in men than in women (183.8 [125.4-251.7] cm² vs 103.3 [57.5-167.2] cm²; *P* < .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 men and women (60.3% vs 64.6%; *P* = .41). According to BMI criteria, 178 patients (49.9%) were classified as normal weight (BMI <25 kg/m²), 126 patients (35.3%) as overweight (BMI 25-29.9 kg/m²) and 53 patients (14.8%) as obese (BMI \geq 30 kg/m²). Within these three BMI categories, VO prevalence was 41%, 77%, and 98.1% respectively (*P* < .001). Relationship between BMI and VAT is depicted in Figure 1. BMI and VAT showed a positive correlation in normal (ρ = 0.40, *P* < .001) and overweight (ρ = 0.24, *P* = .01) patients, but not in obese patients (ρ = -0.04, *P* = .78).

Baseline clinical and pathological characteristics are presented in Table 1. VO patients were older and had higher BMI (*P* < .001) and CCI (*P* = .01). No relevant differences were found in terms of extent of surgery or staging of malignant disease.

Postoperative outcomes are presented in Table 1. In the overall population, 158 patients (42.3%) developed postoperative 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. Postoperative LOS was also comparable between groups.

Thirty-three patients (9.2%) were discharged before POD4, and CRP values were measured only on POD1-3. In the 209 cases (58.5%) discharged after POD5, 219 patients (61.3%) had CRP measured on POD4 and 160 (44.8%) on POD5 according to clinical needs.

3.2 | VO and POI

Baseline pre-operative CRP values were significantly associated with VAT both in women (ρ = 0.36, *P* = .001) and men (ρ = 0.19; *P* = .04). A positive correlation between VAT and postoperative CRP values was found both in women and men on POD1 (ρ = 0.24, *P* = .001, and ρ = 0.20, *P* = .04), POD2 (ρ = 0.32, *P* < .001 and ρ = 0.15, *P* = .03),

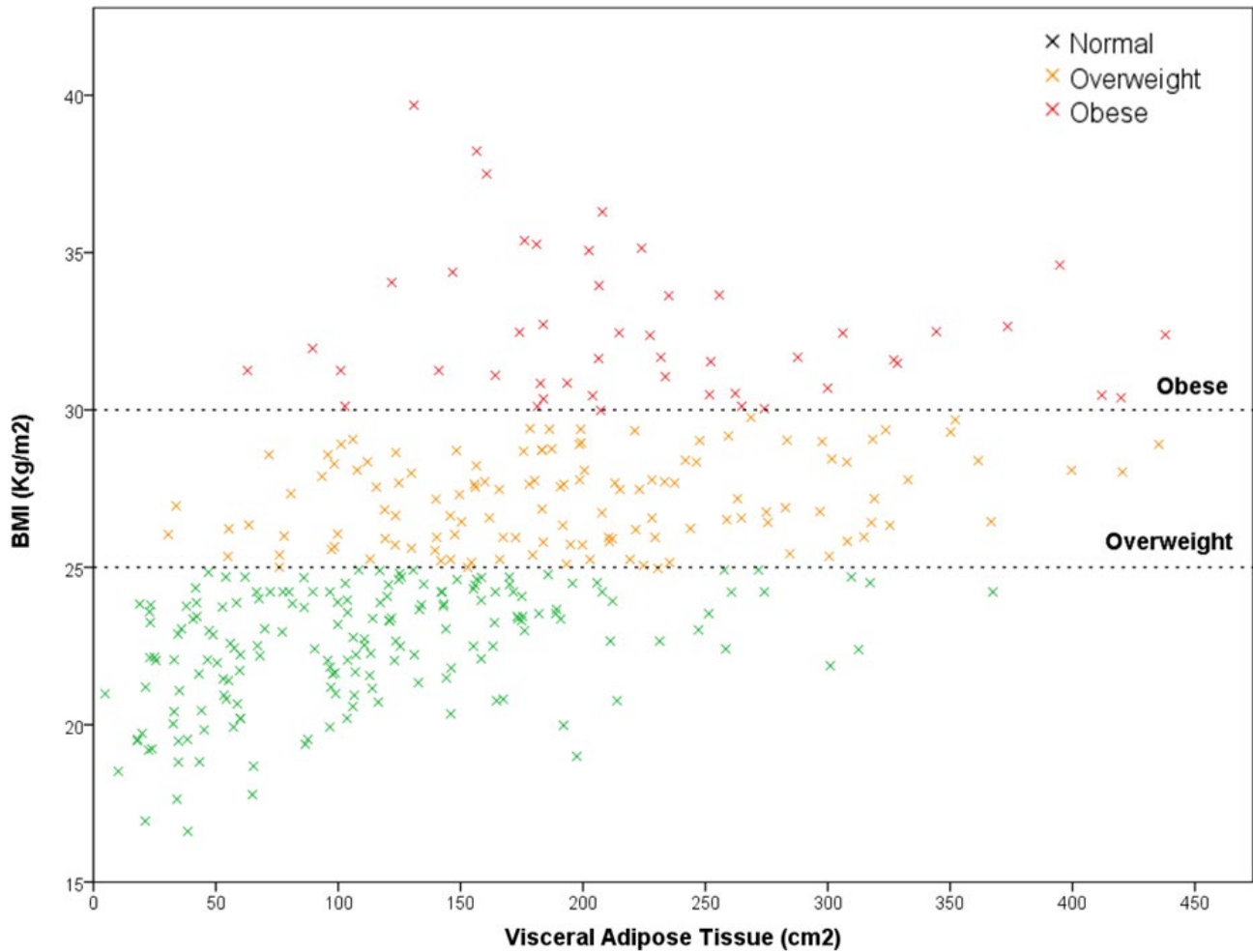


FIGURE 1 Correlation between body mass index (BMI) and visceral adipose tissue (VAT) in normal (BMI <25 kg/m²), overweight (BMI 25-29.9 kg/m²), and obese (BMI ≥30 kg/m²) patients

and POD3 ($\rho = 0.31$, $P < .001$, and $\rho = 0.17$, $P = .02$), but not on POD4 and POD5. No significant correlation between BMI and CRP values was found on each POD.

VO patients displayed higher baseline CRP levels compared with non-VO patients (3, 1-6 mg/L vs 1, 1-3 mg/L; $P < .001$). Higher CRP values were also observed in the VO group on POD1, POD2, POD3, and POD5 (Figure 2 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 ($\beta = 0.164$; $P < .001$). As given in 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 an independent risk factor for increased CRP on POD1 and POD2, but not on POD3 ($\beta = 0.062$; $P = .23$). ERAS enrollment was independently associated with reduced CRP values from POD2 to POD5, while conversion to open surgery or duration of surgery was associated with increased CRP values on POD1 and POD1, or with POD 2 and POD3, respectively.

3.3 | Infectious complications and POI

No differences in CRP levels according to the presence of VO were observed in patients with infectious complications (Figure 3A). Univariate analysis in this subgroup of patients did not reveal any association with abnormal CRP values in the postoperative period (Table 5), so that multivariate analysis was not performed. Further analysis was therefore conducted only for patients without infectious complications. In this subgroup, CRP values were significantly higher in VO compared with non-VO patients on POD1, POD2, POD3, and POD5 (Figure 3B). Univariate analysis showed a positive correlation between VO and CRP on POD 1 to 3 (Table 6), with the highest coefficient on POD2 ($\beta = 0.200$; $P = .001$). In multivariate analysis (Table 7), VO was confirmed as an independent risk factor for increased CRP values between POD1 and 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.

TABLE 1 Clinical and pathological characteristics in the groups analyzed

Parameter	VO n = 222	Non-VO n = 135	P
Men	120 (54.1)	79 (58.5)	.41
Age, y	68.9 ± 11.3	63.3 ± 12.7	<.001
BMI, kg/m ²	26.5 (24.2-29.4)	23.6 (21.6-24.8)	<.001
ERAS	150 (67.6)	99 (73.3)	.25
Charlson's comorbidity index	4 (3-5)	3 (2-5)	.01
Surgical indication			.93
Colon cancer	116 (52.3)	72 (53.3)	
Rectal cancer	54 (24.3)	29 (21.5)	
Adenoma	18 (8.1)	11 (8.1)	
Diverticular disease	34 (15.3)	23 (17)	
Neoadjuvant therapy ^a	25 (14.7)	13 (12.9)	.67
TNM stage ^a			.17
TNM stage I/II	111 (65.3)	57 (56.4)	
TNM stage III/IV	59 (34.7)	44 (43.6)	
Surgical procedure			.84
Right hemicolectomy	73 (32.9)	43 (31.9)	
Left hemicolectomy	79 (35.6)	51 (37.8)	
Rectal resection	70 (31.6)	41 (30.4)	
Associated resections	47 (21.2)	23 (17)	.34
Surgical time, min	237 (190-297)	220 (191-270)	.18
Blood loss, mL	50 (30-100)	40 (30-90)	.16
Conversion	18 (8.1)	6 (4.4)	.18
Overall complications	94 (42.3)	57 (42.2)	.98
Minor grade	77 (34.7)	44 (32.6)	.78
Major grade	17 (7.7)	13 (9.6)	.52
Infectious complications	34 (15.3)	23 (17)	.67
Pneumonia	8 (3.6)	7 (5.2)	.47
Anastomotic leak	12 (5.4)	8 (5.9)	.84
Surgical site infections	11 (5)	7 (5.2)	.92
Time to infectious complication, d	4 (2-5.25)	4 (3-7)	.44
Mortality	1 (0.5)	1 (0.7)	.72
Readmission	7 (3.2)	5 (3.7)	.78
Redo surgery	10 (4.5)	9 (6.7)	.38
Length of stay, d	6 (5-8)	6 (4-8)	.30

Abbreviations: BMI, body mass index; ERAS, enhanced recovery after surgery; VO, visceral obesity.

^aPercentage on 271 colon and rectal cancers.

3.4 | 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, $P < .001$), thus confirming the clinical significance of measuring CRP on POD3 as a reliable predictor of infectious complications. In the overall

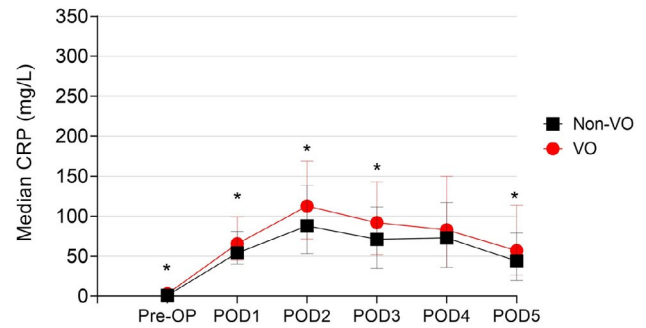


FIGURE 2 Trend in postoperative C-reactive protein in the overall population according to visceral obesity (VO) status (* $P < .05$)

population, the optimal cut-off was 134 mg/L, 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 4). According to the Youden's index, the optimal cut-off value of CRP on POD3 was 136 mg/L (87.5% sensitivity and 88% specificity) for non-VO patients, and 154 mg/L (83.3% sensitivity and 81.2% specificity) for VO patients, respectively.

4 | DISCUSSION

Body composition assessment in surgical patients has recently gained attention because of possible clinical implications in complications and long-term survival. For example, low skeletal muscle mass seems to be strongly associated with poor postoperative outcomes, especially in cancer patients.¹⁸⁻²⁰ Reduced skeletal muscle mass may promote the development of a pro-inflammatory environment, basically through the onset of insulin resistance,²¹ which is responsible for enhanced POI after colorectal resection.⁷ Similarly, insulin resistance and higher levels of pro-inflammatory cytokines such as IL-6 and TNF- α are associated with abnormal adipose tissue accumulation, in particular excess of visceral adipocytes.²² Although the chronic systemic inflammation which characterizes VO is a well-known risk factor for development of several diseases associated with metabolic syndrome,^{22,23} the role of VO in worsening surgical outcomes is still debated.^{22,24,25} Little is known about the role of VO on acute inflammatory response after colorectal resection. Our study aimed to characterize the magnitude of POI 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 POI, thus requiring separate cut-offs for predicting safe discharge on POD3.

Although procalcitonin presents higher specificity than CRP in differentiating between inflammation and infection,²⁶ its use in the clinical practice after colorectal surgery is still limited, and mostly influenced the development of severe bacterial infections.²⁶⁻²⁸ We therefore chose CRP as an objective marker of POI because of its widespread use in clinical practice and its role as predictor of

Parameter	Overall population n = 357	Visceral obesity		P
		VO n = 222	Non-VO n = 125	
Pre-operative CRP	2 (1-5)	3 (1-6)	1 (1-3)	<.001
CRP POD1	62 (43-95)	65 (45-99)	54 (40-81)	.002
CRP POD2	102 (61-156)	112 (71-169)	88 (53-138)	.001
CRP POD3	85 (45-132)	92 (52-143)	71 (34-111)	.003
CRP POD4	74 (36-135)	83 (36-150)	73 (36-117)	.50
CRP POD5	52 (23-103)	57 (26-113)	44 (19-79)	.04

TABLE 2 Surgical stress response expressed as C-reactive protein values in the overall population and according to visceral obesity

Abbreviations: CRP, C-reactive protein; POD, postoperative day; VO, visceral obesity.

TABLE 3 Univariate analysis for factors affecting C-reactive protein values in the overall population

Factor	CRP POD1		CRP POD2		CRP POD3		CRP POD4		CRP POD5	
	β	P	β	P	β	P	β	P	β	P
VO	0.151	.004	0.164	.003	0.125	.02	0.029	.74	0.068	.34
ERAS	-0.151	.004	-0.292	<.001	-0.332	<.001	-0.281	.001	-0.247	<.001
Men	0.047	.38	0.081	.14	0.043	.39	0.074	.39	0.092	.20
CCI	0.075	.16	0.136	.01	0.154	.004	0.017	.84	0.116	.11
Cancer	0.089	.09	0.128	.02	0.126	.02	0.011	.90	0.068	.34
Specimen length	-0.006	.91	0.034	.53	0.103	.05	0.137	.11	0.064	.97
Conversion	0.170	.001	0.143	.01	0.085	.11	0.098	.25	-0.049	.50
Surgical time	0.208	<.001	0.261	<.001	0.245	<.001	0.176	.04	0.069	.36

Abbreviations: CCI, Charlson's comorbidity index; CRP, C-reactive protein; ERAS, enhanced recovery after surgery; POD, postoperative day; VO, visceral obesity.

TABLE 4 Multivariate analysis for factors affecting C-reactive protein values in the overall population

Factor	CRP POD1		CRP POD2		CRP POD3		CRP POD4		CRP POD5	
	β	P	β	P	β	P	β	P	β	P
VO	0.119	.02	0.121	.02	—	—	—	—	—	—
ERAS	—	—	-0.144	.01	-0.279	<.001	-0.255	.004	-0.247	<.001
Men	—	—	—	—	—	—	—	—	—	—
CCI	—	—	—	—	—	—	—	—	—	—
Cancer	—	—	—	—	—	—	—	—	—	—
Specimen length	—	—	—	—	—	—	—	—	—	—
Conversion	0.146	.01	—	—	—	—	—	—	—	—
Surgical time	0.137	.01	0.177	.01	0.193	<.001	—	—	—	—

Abbreviations: CCI, Charlson's comorbidity index; CRP, C-reactive protein; ERAS, enhanced recovery after surgery; POD, postoperative day; VO, visceral obesity.

complications.² 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 postoperative adverse events, especially infectious complications. Combined with negative clinical

findings, a CRP value below the specific cut-offs on POD3 was found as an important marker for allowing safe discharge.²

In our study, we highlighted a significant correlation between VAT measured at pre-operative CT images and CRP values on POD1-3. Higher values of VAT were associated to increased POI. On the contrary, BMI values, which are commonly used in the clinical

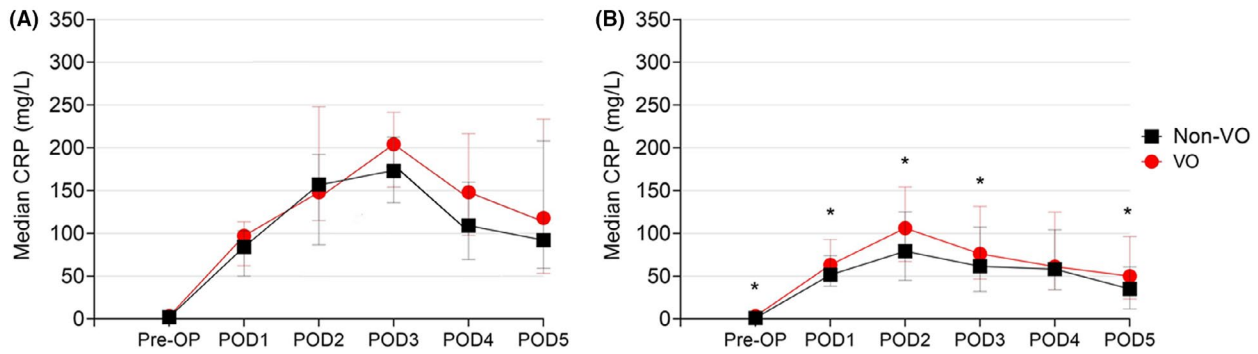


FIGURE 3 Trend in postoperative C-reactive protein values in (A) patients with infectious complications and (B) patients without postoperative infectious complications according to visceral obesity (VO) status (* $P < .05$)

TABLE 5 Univariate analysis for factors affecting C-reactive protein values in patients with infectious complications

Factor	CRP POD1		CRP POD2		CRP POD3		CRP POD4		CRP POD5	
	β	<i>P</i>	β	<i>P</i>	β	<i>P</i>	β	<i>P</i>	β	<i>P</i>
VO	0.113	.40	0.113	.42	0.092	.50	0.146	.45	0.041	.79
ERAS	0.041	.76	-0.038	.79	-0.259	.05	-0.211	.27	-0.147	.34
Men	0.197	.14	0.294	.03	0.301	.02	0.326	.10	0.092	.55
CCI	0.021	.88	-0.027	.85	-0.005	.97	-0.117	.55	-0.197	.20
Cancer	0.148	.27	0.082	.59	0.159	.24	0.113	.56	-0.003	.99
Specimen length	-0.085	.53	-0.132	.35	0.026	.85	-0.005	.98	-0.015	.92
Conversion	-0.075	.58	-0.230	.10	-0.200	.14	-0.081	.68	-0.210	.17
Surgical time	0.028	.85	-0.052	.72	-0.052	.72	-0.142	.47	-0.119	.47

Abbreviations: CCI, Charlson's comorbidity index; CRP, C-reactive protein; ERAS, enhanced recovery after surgery; POD, postoperative day; VO, visceral obesity.

TABLE 6 Univariate analysis for factors affecting C-reactive protein values in patients without infectious complications

Factor	CRP POD1		CRP POD2		CRP POD3		CRP POD4		CRP POD5	
	β	<i>P</i>	β	<i>P</i>	β	<i>P</i>	β	<i>P</i>	β	<i>P</i>
VO	0.168	.003	0.200	.001	0.173	.003	0.081	.40	0.074	.36
ERAS	-0.144	.01	-0.293	<.001	-0.296	<.001	-0.197	.04	-0.220	.01
Men	0.018	.75	0.040	.50	0.060	.31	-0.029	.77	0.083	.31
CCI	0.055	.34	0.139	.02	0.168	.004	0.065	.51	0.227	.01
Cancer	0.082	.16	0.153	.01	0.138	.02	0.040	.68	0.117	.15
Specimen length	-0.014	.80	0.035	.56	0.097	.10	0.095	.33	0.061	.45
Conversion	0.220	<.001	0.250	<.001	0.196	.001	0.185	.05	0.020	.81
Surgical time	0.220	<.001	0.321	<.001	0.334	<.001	0.329	.001	0.124	.15

Abbreviations: CCI, Charlson's comorbidity index; CRP, C-reactive protein; ERAS, enhanced recovery after surgery; POD, postoperative day; VO, visceral obesity.

practice for evaluation of the degree of patients' adiposity, showed no correlation with CRP values on each POD. We can hypothesize that although BMI is associated to VAT amount (Figure 1), BMI evaluation is insufficient for the assessment of the amount of visceral fat which is responsible for the increase in inflammatory response in the

postoperative period. 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 postoperative CRP values in the overall population. Multivariate analysis confirmed VO as an independent risk factor for increased POI, with higher CRP

TABLE 7 Multivariate analysis for factors affecting C-reactive protein values in patients without infectious complications

Factor	CRP POD1		CRP POD2		CRP POD3		CRP POD4		CRP POD5	
	β	P	β	P	β	P	β	P	β	P
VO	0.141	.01	0.156	.01	0.124	.03				
ERAS	—	—	-0.165	.01	-0.199	.001	—	—	-0.220	.01
Men										
CCI			—	—	—	—			—	—
Cancer			—	—	—	—				
Specimen length										
Conversion	0.218	<.001	0.163	.004	—	—	—	—		
Surgical time	0.195	.001	0.251	<.001	0.267	<.001	0.289	.01		

Abbreviations: CCI, Charlson's comorbidity index; CRP, C-reactive protein; ERAS, enhanced recovery after surgery; POD, postoperative day; VO, visceral obesity.

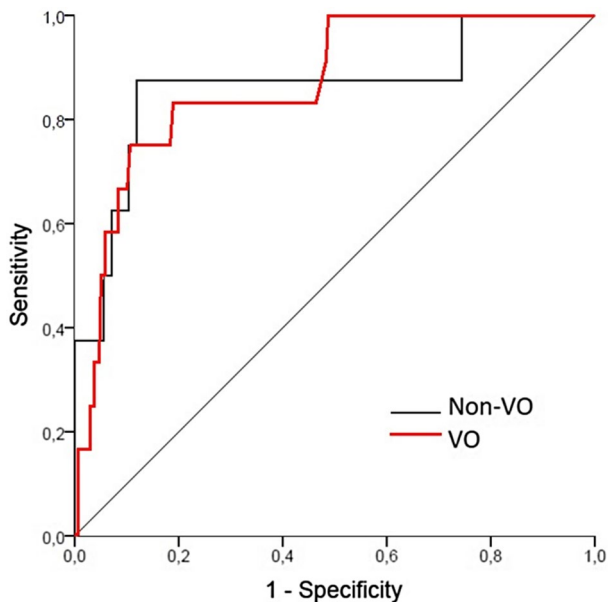


FIGURE 4 ROC curves for C-reactive protein levels on postoperative day 3 show good sensitivity and specificity for detection of infectious complications both in visceral obesity (VO) and Non-VO patients

values on POD1 and 2. Interestingly, the increase in POI was stronger in patients who did not develop infectious complications. Our results are in line with recent evidence of low POI because of reduced surgical stress from the synergistic effect of laparoscopy and ERAS protocol.^{1,29} Nevertheless, while conversion to open surgery and surgical time are well-known factors associated with increased POI, 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 POI 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 POI 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 postoperatively. Despite a heightened immune and inflammatory response, this appeared to have no clinical adverse sequelae for VO subjects.³⁰ 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 postoperative infectious complications.³¹ Following the results of these studies, our findings confirm that VO could intensify POI following laparoscopic colorectal resection, though VO was not responsible for worse postoperative course, since the complication rates appeared to be similar between VO and non-VO patients. Whether increased POI 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.^{32,33} 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 have been used depending on surgical procedure and surgical approach, since the amount of normal POI varies between open³⁴⁻³⁶ and laparoscopic surgery.^{2,37} In our opinion, all parameters that could influence POI 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,^{30,31} demonstrates increased POI after laparoscopic colorectal resection in patients with increased VAT. As an example, a CRP value on POD3 of 150 mg/L could lead to postpone hospital discharge and to look for a source of infection according to our standard fast-track protocol. According to the present results, if this patient was VO the risk of infectious complications would be overestimated being CRP <154 mg/L while it

would be a correct management for a non-VO patient. The use of CRP cut-off values plays a more interesting role in asymptomatic patients who can present an aspecific increased or non-decreasing CRP value on POD3. In these patients, the use of tailored cut-off values which consider VO status would improve diagnostic performance (ie, both sensitivity and specificity), allowing clinicians to better identify patients who require further diagnostics and those who can be safely discharged without risks. 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. Despite this decision allowed us to analyze a more homogeneous population, the low incidence of severe complications such as anastomotic leak prevented from specific ROC curve analysis. Second, this is a retrospective observational study conducted at a single institution. The findings presented in this paper 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 postoperative 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 POI, and it is the sole to consider patients undergoing minimally invasive colorectal resections.

In conclusion, our findings confirm the presence of a pro-inflammatory environment before surgery and highlight an enhanced POI in VO patients. This increased inflammatory response was significant in the overall population and in patients without infectious complications, while our analysis failed to find significant difference in those who developed infectious complications. Interestingly, despite the POI was increased in VO patients, no differences in postoperative 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 POI, and incidence of postoperative complications with specific interest for anastomotic leak.

DISCLOSURES

Conti C., Pedrazzani C., Turri G., Gecchele G., Valdegamberi A., Ruzzenente A., Zamboni GA, Lippi G., Guglielmi A. have no conflict of interests or funding to declare.

AUTHORS' CONTRIBUTIONS

Conti C., Pedrazzani C., Lippi G., Ruzzenente A., and Guglielmi A., provided study concept and design; Conti C., Turri G., Zamboni GA, Gecchele G., and Valdegamberi A. collected data; Pedrazzani C., Conti C. Ruzzenente A., Lippi G., and Valdegamberi A. performed data analysis and interpretation; Pedrazzani C., Conti C., and Turri G. drafted the manuscript; Turri G., Gecchele G., Zamboni GA, Valdegamberi A., Ruzzenente A., Lippi G., and Guglielmi A. provided critical revision of the paper. All authors read and approved the final version of this manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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