



# C-Reactive Protein on Postoperative Day 1: a Predictor of Early Intra-abdominal Infections After Bariatric Surgery

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## Abstract

**Background** Early intra-abdominal infections (IAI) compromise short-term outcomes in bariatric surgery. The timely detection of IAI is challenging but essential to prevent major sequelae of such complications. C-reactive protein (CRP) is a reliable marker for detecting IAI after colorectal surgery. In bariatric surgery, data on CRP as a marker for IAI are limited, particularly for postoperative day one (POD1).

**Objective** The objective of this study was to assess CRP on POD1 as a predictor for early IAI (within 7 days following surgery) in patients after laparoscopic sleeve gastrectomy (LSG) and Roux-en-Y gastric bypass (LRYGB).

**Methods** Patients with bariatric surgery between 08/2010 and 06/2017 were included. The predictive capacity of CRP for early IAI was determined using a receiver operating characteristics (ROC) analysis.

**Results** In 523 patients (68.5% female, LSG = 358, LRYGB = 165), 16 (3%) early IAI were observed. ROC analysis revealed a significant predictive capacity of POD1 CRP for early IAI, with a sensitivity and a specificity of 81.2 and 94.3%, respectively, at a CRP cut-off value of 70 mg/L. In patients with confirmed early IAI, 81.3% had a CRP level  $\geq$  70 mg/L (LSG 85.7%, LRYGB 77.8%). The negative predictive value for a CRP level  $<$  70 mg/L was 99.4% overall and was 100 and 98% for LSG and LRYGB, respectively.

**Conclusion** In patients with a CRP level  $<$  70 mg/L on POD1, early IAI can be excluded with high accuracy in bariatric patients. Thus, early postoperative CRP may be used to assess the risk of early IAI in enhanced recovery programs.

**Keywords** Roux-en-Y gastric bypass · Sleeve gastrectomy · Postoperative complications · C-reactive protein · ROC curve analysis · Organ space surgical site infections · Intra-abdominal infections

## Introduction

The number of bariatric procedures performed worldwide is on the rise, with Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) accounting for approximately 75%

of all procedures today [1]. For decades, the long- and short-term mortality and morbidity have greatly diminished. However, short-term complications that necessitate timely treatment are still a matter of concern [2]. Of these complications, intra-abdominal infections (IAI) have a significant

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impact on the perioperative outcomes, duration of hospital stay, readmission rates, and long-term outcomes [2, 3], particularly if the diagnosis is delayed.

The early identification of IAI after bariatric surgery is crucial but remains a challenge for the treating surgical team. The predictive accuracy of clinical features during the early postoperative phase is not ideal, and the occurrence of a gastrointestinal leak may be more subtle or delayed in obese patients [4]. Unfortunately, there is currently no marker for the early prediction of IAI. Clinical parameters, laboratory markers, and imaging findings together may all contribute to the identification of postoperative complications. However, routine radiological assessment for the diagnosis of IAI is controversial, and upper gastrointestinal swallow studies are of limited value [5, 6]. Overall, it is difficult to distinguish IAI from postoperative inflammatory responses related to surgical stress.

The value of C-reactive protein (CRP) as an essential marker for the assessment of infectious complications in the postoperative period has gained clinical acceptance due to the broad availability, low cost, and good reliability of CRP testing, which has mostly been assessed in the setting of laparoscopic colorectal surgery [7, 8].

In bariatric surgery, data on the use of CRP are limited and diverging with regard to the time of measurement, sensitivity, and specificity [9–11]. Nevertheless, CRP measured on postoperative day 2 has been shown to be a predictor of both minor and major complications after RYGB [12, 13].

In the era of enhanced recovery programs, with patients being discharged from the hospital 24–36 h after surgery and potentially before developing any clinical signs of IAI [14], an accurate indicator of early postoperative complications, including IAI, is of uttermost importance.

The aim of this study was to investigate the predictive value of postoperative day 1 (POD 1) CRP for IAI in patients undergoing laparoscopic bariatric surgery.

## Materials and Methods

This study was performed at a reference center and teaching hospital for bariatric surgery. Data for the analysis were retrospectively extracted from the bariatric surgery registry and the electronic medical records. All patients undergoing primary LSG or LRYGB from August 2010 to April 2017 were included. The procedures were performed by at least one of the three bariatric surgeons.

The inclusion criteria were as follows: a BMI above 35 kg/m<sup>2</sup>, 18 years or older, and a CRP level measured on POD1 (standard of care procedure). Patients who underwent a primary open procedure or conversion to an open procedure, who had undergone previous bariatric procedures, who had a history of chronic inflammatory diseases (e.g., Crohn's disease), and who used antibiotics within 2 weeks prior to the

bariatric surgery were excluded. The study was approved by an independent ethics committee.

## Definition

IAI were assessed according to the guidelines of the US Centers for Disease Control and Prevention for surgical site infections [15]. Since 2015, the incidence of organ space surgical site infections has been monitored via participation in the Swiss-NOSO Network [16]. Early IAI were defined as occurring within the first 7 days following bariatric surgery. Anastomotic leakage was counted as IAI if it was radiologically verified or diagnosed during gastro-duodenoscopy or reoperation.

## CRP Measurements

The plasma levels of CRP were routinely determined in an ISO17025-accredited laboratory. The measurement range was 0.3 to 350 mg/L (maximum value 700 mg/L with dilution). The normal range for CRP is defined as less than 5 mg/L.

## Statistical Analysis

The normality of the distribution of continuous variables was assessed using histograms, skewness, and the Shapiro-Wilk test. Categorical variables were reported as numbers and percentages, and continuous variables were reported as medians and interquartile ranges (IQR). The predictive capacity of CRP level on POD 1 for early IAI was assessed using a receiver operating characteristic (ROC) curve analysis. The CRP cut-off value with the best sensitivity and specificity for the detection of early IAI was calculated using Youden's index [sensitivity – (1 – specificity)]. The ROC curve analysis results were reported as the area under the curve (AUC) with corresponding 95% confidence intervals (CI) and *p* values. Based on the best CRP cut-off value for the detection of early IAI, the sensitivity, specificity, and positive and negative predictive values (PPV, NPV) were calculated. The association of the CRP cut-off value with the best sensitivity and specificity and early IAI was subsequently analyzed in a univariate analysis using Fisher's exact test. The association of other clinically important factors (age, sex, weight, BMI, ASA score, and duration of surgery) with early IAI was also analyzed in a univariate analysis using Fisher's exact and the Mann-Whitney test. *p* values <0.05 were considered statistically significant. All statistical analyses were performed using SPSS Statistics, Version 25 (IBM Corporation, Armonk, NY, USA).

## Results

A total of 523 patients were included. Of these, 358 (68.5%) underwent LSG, and 165 (31.5%) underwent LRYGB. The

overall median hospital stay was 3.0 days (IQR 1.0); the median hospital stay for LSG and LRYGB patients was 3.0 (1.0) days and 3.0 (2.0) days, respectively. The baseline characteristics of the patients are outlined in Table 1.

### Incidence of IAI

Overall, 16 patients (3.1%) developed early IAI. In the subgroups of patients undergoing LSG and LRYGB, early IAI were found in 7 (2.0%) and 9 (5.5%) patients, respectively. The median duration from surgery until the diagnosis of early IAI was 2.5 days (IQR 3.0) overall, 4.0 days (3.0) for LSG patients, and 1.0 (3.0) day for LRYGB patients. Eleven patients were considered to have a significant leak, including one leak at the enteroenterostomy site and one perforation of the colon. An abscess was identified in five patients.

### CRP as a Predictor for IAI

Compared with patients without early IAI, the median CRP values on POD1 were significantly higher in both LSG and LRYGB patients with early IAI (Fig. 1).

The ROC curve analysis revealed a significant predictive value of CRP level on POD1 for early IAI (Fig. 2, Table 3). Based on Youden's index, the optimal CRP cut-off value for predicting early IAI was 70 mg/L. The sensitivity, specificity, and positive and negative predictive values of a POD1 CRP level  $\geq 70$  mg/L for the detection of early IAI are outlined in Table 2.

Early IAI were significantly more frequent in patients with POD1 CRP levels  $\geq 70$  mg/L than in patients with POD1 CRP levels  $< 70$  mg/L (81.3 vs. 18.7%,  $p < 0.001$ ); this was also true

for patients in the LSG (85.7 vs. 14.3%,  $p < 0.001$ ) and the LRYGB subgroups (77.8 vs. 22.2%,  $p = 0.001$ ) (Table 3).

No significant association between other clinically important factors (i.e., sex, age, BMI, ASA) and early IAI was found in the univariate analysis. Consequently, no multivariate regression analysis for early IAI was performed.

### Discussion

To our knowledge, this is the first study to investigate the postoperative CRP levels in patients undergoing two different types of surgery (LSG and LRYGB) to detect early IAI after bariatric surgery.

The present study demonstrates that CRP measured on POD1 is a good marker for excluding IAI occurring within 7 days after bariatric surgery. A CRP cut-off value of  $< 70$  mg/L is associated with a minimal risk of IAI (NPV 95%), whereas a CRP level  $\geq 70$  mg/L can be used to identify patients with a high risk of early IAI.

The utility of CRP measurements to rule out infection has been established in other surgical fields; for instance, after elective colorectal surgery, the high NPV ( $> 95\%$ ) of CRP measurements allows the patient's safe and early discharge from hospital [18]. In a meta-analysis investigating different open and laparoscopic surgical procedures, CRP levels measured 4 days after RYGB had the highest accuracy in predicting postoperative infections [7]. However, a postoperative day 4 CRP assessment is not clinically feasible in most patients since they are discharged before this day and because routine monitoring after discharge is neither recommended nor performed on a regular basis.

**Table 1** Patient characteristics

	LSG/LRYGB ( $n = 523$ )	LSG ( $n = 358$ )	LRYGB ( $n = 165$ )
Age (years)	40.0 (20.0)	43.0 (21.0)	36.0 (18.0)
Sex (male/female)*	165/358 (31.5/68.5)	141/217 (39.4/60.6)	24/141 (14.5/85.5)
Weight (kg)	125.0 (31.1)	132.0 (33.0)	115.0 (22.2)
BMI (kg/m <sup>2</sup> )	43.0 (8.7)	44.8 (10.0)	41.3 (5.5)
ASA score 2*	130 (24.9)	73 (20.4)	57 (34.5)
ASA score 3*	388 (74.2)	280 (78.2)	108 (65.5)
ASA score 4*	5 (1.0)	5 (1.4)	0 (0.0)
Diabetes mellitus	112 (21.4)	97 (27.1)	15 (9.1)
Obstructive sleep apnea	201 (38.4)	164 (45.8)	37 (22.4)
Arterial hypertension	244 (46.7)	185 (51.7)	59 (35.8)
Dyslipidemia	235 (44.9)	177 (49.4)	58 (35.2)
Liver steatosis	243 (46.5)	171 (47.8)	72 (43.6)
Orthopedic disorders	308 (58.9)	208 (58.1)	100 (60.6)

Values are medians (interquartile ranges) unless indicated otherwise. \*Values are numbers (percentages)

LSG laparoscopic sleeve gastrectomy, LRYGB laparoscopic Roux-en-Y gastric bypass, BMI body mass index, ASA American Society of Anesthesiologists Physical Status Classification System, EOSS Edmonton Obesity Staging System

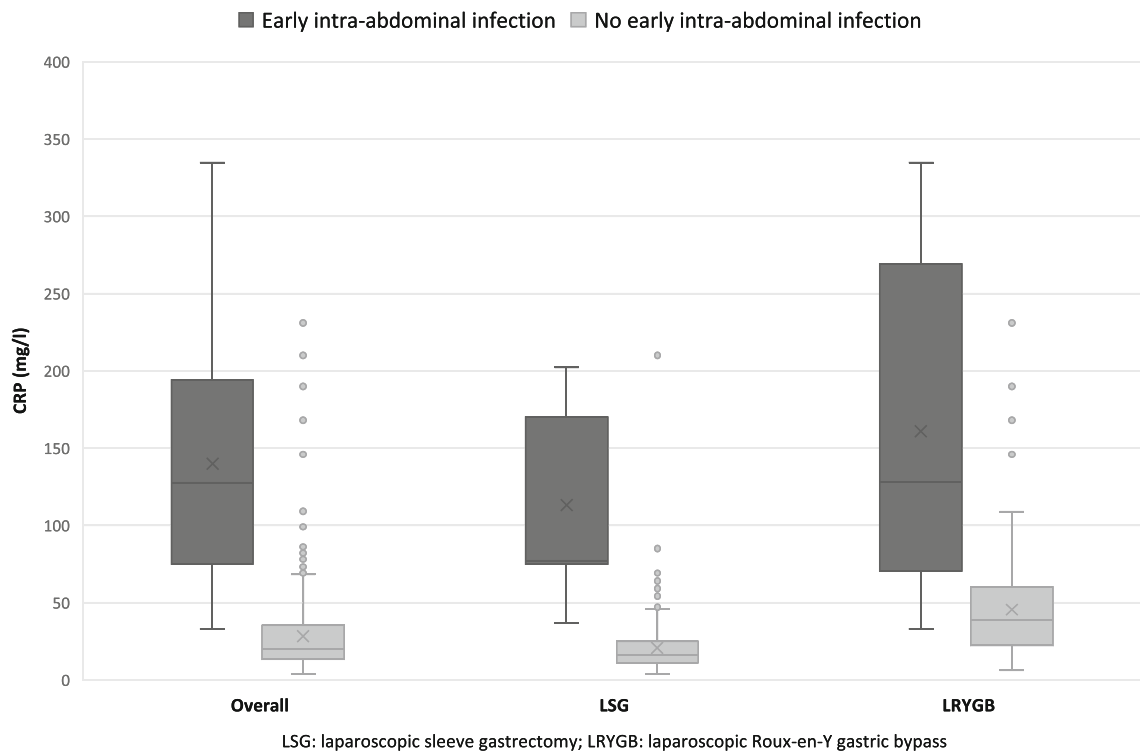
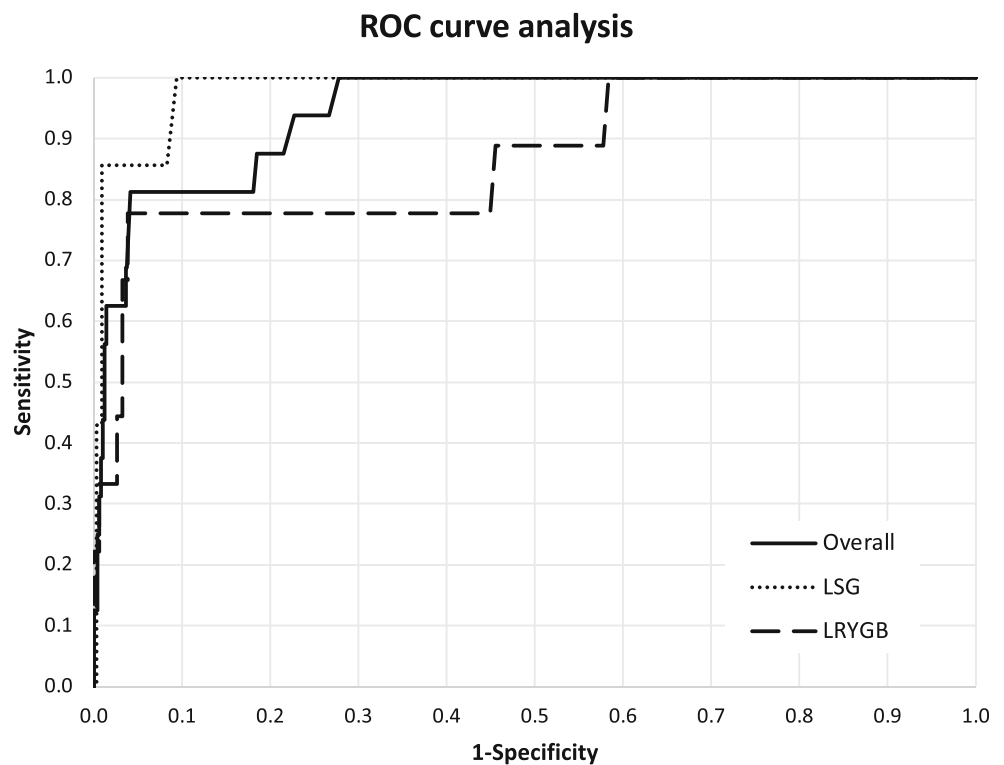


Fig. 1 CRP values on postoperative day 1

Recent studies have suggested that CRP measured on postoperative day 2 is a predictor of complications after LRYGB [12, 13]. In a retrospective study, Warschkow et al. evaluated the diagnostic value of CRP on day 2 (cut-off level 229 mg/L)

in predicting overall complications after laparoscopic gastric bypass (sensitivity 0.53, 95% CI 0.31–0.74 and specificity 0.91, 95% CI 0.79–0.96). They found that the postoperative day 2 CRP levels were predictive for the diagnosis of intestinal

Fig. 2 CRP on postoperative day 1 as a predictor of early intra-abdominal infections



**Table 2** CRP day 1 as a predictor of early ( $\leq 7$  days) intra-abdominal infections

	CRP day 1*			CRP day 1 $\geq 70$ mg/L			
	AUC	95% CI	<i>p</i> value	Sensitivity	Specificity	PPV	NPV
LSG and LRYGB ( <i>n</i> = 523)	0.946	0.903–0.989	<0.001	0.81	0.94	0.31	0.99
LSG ( <i>n</i> = 358)	0.982	0.959–1.000	<0.001	0.86	0.99	0.60	1.00
LRYGB ( <i>n</i> = 165)	0.870	0.731–1.000	<0.001	0.78	0.84	0.22	0.98

\*Receiver operating characteristic analysis

CRP C-reactive protein, AUC area under the curve, CI confidence interval, PPV positive predictive value, NPV negative predicting value

leaks (sensitivity 100%, 95% CI 0.51–1.00) [12]. Notably, the cut-off value described by Warschkow is considerably higher than the cut-off value determined by our analysis and may not be clinically useful because of its low sensitivity.

Research findings on the diagnostic accuracy of POD1 CRP measurements are limited, and the results are conflicting. A few studies concluded that CRP measured on POD1 had no predictive value [11, 13], while others showed the good diagnostic performance of CRP for detecting postoperative complications, similar to our results.

In 112 patients who underwent LRYGB, Pike et al. demonstrated that CRP <100 mg/L on POD1 was a good predictor of safe discharge. Late major complications were detected with a sensitivity of 100% and a specificity of 95% [19]. Their primary endpoint was major complications according to Clavien-Dindo classification [20]. However, in this classification system, there is no stratification by the type or localization of complications. Furthermore, these results reflect a single-surgeon experience with a small sample size, which limits the generalization of the findings.

In 115 morbidly obese patients, Munoz et al. investigated whether the CRP and procalcitonin levels measured on the first two postoperative days could predict septic complications after LSG [21]. They found a CRP cut-off value of 70 mg/L to be a good discriminator on POD1. On POD2, the corresponding CRP cut-off value was 150 mg/L. In a recent study, the same group focused specifically on staple line leaks in 208 LSG patients. A CRP cut-off value of 90 mg/L was associated with an 85% sensitivity and a 90% specificity [22].

Overall, the CRP cut-off values differ significantly between studies due to incongruent patient populations in terms of BMI, ethnicity, procedure type, and definitions of outcomes

and complications. There is no uniform consensus on the classification of postoperative leaks or septic complications after bariatric surgery, and various classifications differ with regard to the time of onset, clinical presentation, location, and radiographic appearance.

Of the 16 patients with IAI in our study, two thirds of the patients presented with leaks, and one third suffered from abscesses involving an organ/space. Early IAI were observed more frequently in patients with LRYGB than in patients with LSG (2.0 vs. 5.5%).

Out of 422 patients, there were three patients who had IAI but false negative CRP results (< 70 mg/L) on POD 1. Of these, two patients had stenotic anastomoses after LRYGB, and one patient developed an abscess within the first 7 days; all three presented with leaks. One LSG patient who did not have a relevant increase in CRP level on POD1 suffered from a perforation of the colon within 1 week after surgery. The reason for the lower CRP values in these three patients is not entirely clear. However, one might speculate that during the initial phase of stenosis, CRP values may have remained low and increased only when IAI became clinically apparent.

Due to several false positive CRP values, the positive predictive values were relatively lower than the negative predictive values (the overall PPV, PPV for LSG patients, and PPV for LRYGB patients were 31, 60, and 22%, respectively). This finding is consistent with a review by Singh et al., who evaluated patients after colorectal surgery [17].

In obese patients, the CRP baseline is higher than in normal weight patients and may lead to “inflammatory noise” that can be difficult to interpret [27]. This is particularly true when adipose tissue is centrally deposited and insulin resistance is present [28]. For this reason, some authors think that measuring

**Table 3** Early ( $\leq 7$  days) intra-abdominal infections

	Overall	CRP day 1 < 70 mg/L	CRP day 1 $\geq 70$ mg/L	<i>p</i> value
LSG and LRYGB ( <i>n</i> = 523)	16 (3.1)	3 (18.7)	13 (81.3)	<0.001
LSG ( <i>n</i> = 358)	7 (2.0)	1 (14.3)	6 (85.7)	<0.001
LRYGB ( <i>n</i> = 165)	9 (5.5)	2 (22.2)	7 (77.8)	<0.001

Univariate analysis using Fisher’s exact test. Variables are numbers (percentages)

LSG laparoscopic sleeve gastrectomy, LRYGB laparoscopic Roux-en-Y gastric bypass, CRP C-reactive protein (mg/L)



CRP on POD1 is too early because the discrimination between “inflammatory noise” induced by the surgical trauma (tissue damage) and the beginning of a complication may not be possible. However, the CRP cut-off value reported in our study is certainly above the expected “inflammatory noise” threshold.

In clinical practice, the early discharge of patients is mainly based on early clinical evolution and on biomarkers. Nevertheless, the timely diagnosis of major complications remains difficult, and complications cannot always be predicted based on the current knowledge [23]. The measurement of CRP is an additional tool to assess patients in the early post-operative period that is separate from their clinical signs. CRP should therefore be added to the discharge criteria for POD1, particularly if early discharge becomes standard. In patients with an elevated CRP level, an in-hospital observation period of 2 or more days may be justified, depending on the evolution of the clinical and laboratory parameters.

The present study has some limitations including its retrospective design. It was a single-center study performed in a teaching environment. However, the surgical procedures were standardized and supervised by three different bariatric surgeons, and the prevalence of IAI identified in our study was similar to other data reported in the literature [24–26].

## Conclusion

The current study revealed that a CRP level < 70 mg/L on POD 1 is a highly accurate negative predictor of early IAI in bariatric patients who have undergone LSG or LRYGB. This finding is particularly helpful for evaluating patients for early discharge after bariatric surgery. The predictive value and cost-effectiveness of CRP measurements should be further validated in a prospective study.

## Compliance with Ethical Standards

**Conflict of Interest** All authors declare no commercial associations that might represent conflicts of interest with this article.

**Human and Animal Rights and Informed Consent** All procedures were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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