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C-Reactive Protein as a Marker of Postoperative Complication of Emergency Colorectal Surgery

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Abstract

Introduction The literature converges regarding the use of C-reactive protein (CRP) tests between postoperative days (PODs) 3 and 5 of elective procedures. In this period, they have great sensitivity and negative predictive value (NPV) for severe and anastomotic complications about two days before the first clinical sign. The few studies on colorectal urgency suggest that, despite the different initial values according to the surgical indication, following POD 3, the level of CRP is similar to that of elective procedures. However, given the heterogeneity of the studies, there is no consensus on the cutoff values for this use.

Objective To validate the use and propose a PO CRP cut-off value in urgent colorectal procedures as an exclusion criterion for complications of anastomosis or the abdominal cavity.

Method Retrospective analysis of the medical records of 308 patients who underwent urgent colorectal surgical procedures between January 2017 and December 2019. The following data were considered: age, gender, surgical indication, type of procedure performed, complications, CRP levels preoperatively and from POD 1 to 4, and the severity of the complications. We compared the CRP levels and the percentage variations between the preoperative period and PODs 1 to 4 as markers of severe complications using the receiver operating characteristic (ROC) curve.

Keywords
- colorectal surgery
- C-reactive protein
- postoperative complications
- acute surgery

In this manuscript, we show the use of C-reactive protein (CRP) as a tool to exclude severe postoperative complications of urgent colon and rectal surgery, allowing a safe early discharge, as it is currently used in elective procedures. To our knowledge, this is the first study concerning a formal cut-off for CRP and this use of CRP variation in emergency colorectal surgery.

Introduction

Colorectal surgical procedures have a high incidence of complications, reaching up to 65%.[1] Although these procedures are frequently performed, there are reports of up to 20% of anastomotic leaks when they are performed electively,[2,3] with a mortality of ~ 22% for this diagnosis.[2,4] However, ~ 30% of colorectal operations are performed as a matter of

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Results The levels of CRP on POD4, and their percentage drops between PODs 2 to 4 and PODs 3 to 4, were better to predict severe complications. A cutoff of 7.45 mg/dL on POD 4 had 91.7% of sensitivity and NPV. A 50% drop between PODs 3 and 4 had 100% of sensitivity and NPV.

Conclusion Determining the level of CRP is useful to exclude severe complications, and it could be a criterion for hospital discharge in POD 4 of emergency colorectal surgery.

urgency,[5] and, in this condition, the overall mortality reaches around 25%.[6]

In the last decade, there has been an increase in the number of studies aimed at reducing the impact of surgical complications. Measures for the optimization of interventions in the postoperative (PO) period and the detection of complications before the onset of clinical manifestations have helped reduce the severity of complications, the length of the hospital stay, and mortality.[2] For this purpose, the use of serum inflammatory markers is already well established.

The most commonly used inflammation marker is C-reactive protein (CRP). It is synthesized by hepatocytes as part of the acute phase response after stimulation by interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and IL-1β originated from the site of inflammation. C-reactive protein is a valuable marker to detect disease activity, inflammatory response, and PO recovery due to its short half-life (19 hours).[2]

The literature converges regarding the use of CRP tests between postoperative days (PODs) 3 and 5 of elective procedures. In this period, there is great sensitivity and negative predictive value (NPV) for severe and anastomotic complications about two days before the first clinical sign.[7] The few studies on colorectal urgency suggest that despite the different initial values according to the surgical indication, following POD 3, the level of CRP is similar to that of elective procedures.[8]

A recent review[9] validated the value of 10 mg/dL as a safe level for hospital discharge in POD 4 free of any complications of the surgical act, regardless of whether it is urgent or elective. However, given the heterogeneity of published studies, there is no consensus on the cutoff values for this use. Similarly, we found a single study[10] using the variation in CRP levels as a prognostic factor in the PO period, but the procedure evaluated was gastrectomy, and, as far as we know, there is no publication with this assessment in colorectal emergency surgery. Thus, the present study aimed to validate the use and propose a PO CRP cut-off value in urgent colorectal procedures as an exclusion criterion for complications of anastomosis or the abdominal cavity.

Methods

A retrospective analysis of the medical records of patients older than 18 years of age submitted to urgent colorectal surgical between January 2017 and December 2019 by the General and Oncologic Surgery Service of Hospital do Servidor Publico Estadual – Francisco Morato de Oliveira, in São Paulo, Brazil.

The procedures considered were performed with broad access to the abdominal cavity by both laparotomy and laparoscopy, followed by decompressive ostomies or colorectal resections, excluding appendectomy for the persent analysis.

We assessed the following data: gender, age, surgical indication, type of procedure, PO complication, preoperative, and PO CRP levels from PODs 1 to 4. We stratified the severity of PO complications based on the Clavien-Dindo classification,[11] and considered Clavien-Dindo I and II mild complications, and III and IV, severe complications. Surgical-site infections (SSIs) were defined according to the guideline of the Centers for Disease Control and Prevention (CDC).[12]

We compared the median CRP level between PODs 1 to 4, as well as the percentage of variation between these days when infection and anastomotic complications were present.

Statistics

The continuous variables were expressed as means ± standard deviations or medians with interquartile ranges. The means were compared by the Student *t*-test or the Mann-Whitney, test according to the distribution. The qualitative variables were expressed as percentages and compared with the Chi-Squared or Fisher exact tests, when the expected value was lower than 5. We used the receiver operating characteristic (ROC) curve for CRP dosages and the percentage variation between subsequent PODs, setting the best areas under the curve (AUCs) to predict severe complications and deaths, and for intra-abdominal infections characterized as intracavitary abscesses, anastomotic leaks, or stoma collapses. For the best AUC, we then used the ROC individually to calculate the cutoff values for better sensitivity and NPV.

The threshold for statistical significance was established as $p < 0.05$ for all analyses. The data were analyzed using the Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, IBM Corp., Armonk, NY, US) software, version 23.0.

Results

We assessed the medical records of 308 patients (►**Table 1**), with a mean age of 70.3 ± 12.65 years, 45.1% of whom were male. A total of 176 patients (57.1%) underwent surgery for

Table 1 Characteristics of the study sample

	Neoplasia		Benign disease		Total		*p*-value
Gender							
Male – n (%)	81	(46.0%)	58	(43.9%)	139	(45.1%)	0.716
Female – n (%)	95	(54.0%)	74	(56.1%)	169	(54.9%)	
Age (years)							
Average	70.3	± 14.82	70.3	± 0.11	70.3	± 12.65	0.999
Indication							
Inflammation/Infection – n (%)	30	(17.0%)	36	(27.3%)	66	(21.4%)	< 0.001
Obstruction – n (%)	124	(70.5%)	42	(31.8%)	166	(53.9%)	
Ischemia – n (%)	0	(0.0%)	13	(9.8%)	13	(4.2%)	
Bleeding – n (%)	5	(2.8%)	4	(3.0%)	9	(2.9%)	
Perforation – n (%)	17	(9.7%)	37	(28.0%)	54	(17.5%)	
Procedure							
Right colectomy – n (%)	77	(43.8%)	55	(41.7%)	132	(42.9%)	0.850
Transverse colectomy – n (%)	3	(1.7%)	3	(2.3%)	6	(1.9%)	
Left colectomy – n (%)	20	(11.4%)	13	(9.8%)	33	(10.7%)	
Right + left colectomy – n (%)	4	(2.3%)	1	(0.8%)	5	(1.6%)	
Total colectomy – n (%)	15	(8.5%)	9	(6.8%)	24	(7.8%)	
Anterior resection – n (%)	54	(30.7%)	49	(37.1%)	103	(33.4%)	
Loop ostomy – n (%)	3	(1.7%)	2	(1.5%)	5	(1.6%)	
Primary anastomosis – n (%)	66	(37.5%)	44	(33.3%)	110	(35.7%)	0.418
Complications							
None – n (%)	13	(7.4%)	5	(3.8%)	18	(5.8%)	0.006
Clavien-Dindo I – n (%)	16	(9.1%)	9	(6.8%)	25	(8.1%)	
Clavien-Dindo II – n (%)	80	(45.4%)	35	(26.5%)	115	(37.3%)	
Clavien-Dindo III – n (%)	14	(8.0%)	8	(6.1%)	22	(7.1%)	
Clavien-Dindo IV – n (%)	19	(10.8%)	25	(18.9%)	44	(14.3%)	
Clavien-Dindo V – n (%)	34	(19.3%)	50	(37.9%)	84	(27.3%)	
Abdominal complications – n (%)	24	(13.6%)	18	(13.6%)	42	(13.6%)	> 0.999
Infectious complications – n (%)	66	(37.5%)	74	(56.1%)	140	(45.5%)	0.001
Surgical-site infections							
Superficial incisional – n (%)	19	(10.8%)	16	(12.1%)	35	(11.4%)	0.717
Deep Incisional – n (%)	35	(19.9%)	43	(32.6%)	78	(25.3%)	0.011
Organ/space – n (%)	42	(23.9%)	51	(38.6%)	93	(30.2%)	0.005
Distance – n (%)	32	(18.2%)	46	(34.8%)	78	(25.3%)	0.001
Noninfectious complications – n (%)	77	(43.8%)	77	(58.3%)	154	(50.0%)	0.011
Length of stay (days)							
Average	13.7	± 17.46	15.68	± 16.78	14.58	± 17.17	0.332
Median	8.0		10.00		8.0		
Total – n (%)	176	(57.1%)	132	(42.9%)	308	(100.0%)	

neoplastic urgencies, with no difference between genders ($p = 0.716$).

The main surgical indication was colon obstruction (53.9%), followed by inflammation (21.4%) and perforation (17.5%). All indications had different frequencies between the groups ($p < 0{,}001$): the neoplastic group had more cases of obstruction (70.5%), but fewer cases of inflammation, ischemia, and perforation. An equal percentage for all groups

Table 2 Postoperative complications of the study sample

Complication	Uncomplicated		Mild		Severe		Death	
Inflammation/infection – n (%)	6	(9.1%)	31	(47.0%)	14	(21.2%)	15	(22.7%)
Obstruction – n (%)	8	(4.8%)	95	(57.2%)	28	(16.9%)	35	(21.1%)
Ischemia – n (%)	1	(7.7%)	0	(0.0%)	4	(30.8%)	8	(61.5%)
Bleeding – n (%)	2	(22.2%)	1	(11.1%)	2	(22.2%)	4	(44.4%)
Perforation – n (%)	1	(1.9%)	13	(24.1%)	18	(33.3%)	22	(40.7%)
Total – n (%)	18	(5.8%)	140	(45.5%)	66	(21.4%)	84	(27.3%)

was only observed in the Bonferroni post-hoc test for colorectal bleeding (►**Table 1**). Among the procedures, regardless of the etiological group ($p = 0.850$), the most performed were right colectomy (42.9%) and anterior resection (33.4%). Anastomosis was performed in 110 patients (35.7%).

We observed a total of 51.3% of absent or mild complications, with the Bonferroni test showing that patients operated due to neoplastic disease had a greater number of Clavien-II complications (45.4% versus 26.5%) and lower mortality (19.3% versus 37.9%). There was a greater severity of PO complications among patients operated due to diseases of benign etiology ($p = 0.006$). The overall mortality was of 27.3%, with 10% of cases of colonic ischemia (►**Table 2**).

The analysis of the CRP values for anastomotic/abdominal complications (►**Figs. 1** and **2**) showed a better AUC (0.744) for the variation between PODs 2 to 4. For this period, an 83.5% drop had 100% of sensitivity and NPV. The variation between PODs 3 to 4 (AUC = 0.695) had, for a 50% drop, 96.9% of sensitivity and an NPV of 94.7%.

The CRP values that provided the highest accuracy to exclude severe complications (►**Figs. 3** and **4**) were those obtained for POD4 (AUC = 0.691) and the percentage variation between PODs 3to 4 (AUC = 0.702). Between PODs 3 to 4, a 50% drop in CRP levels had a sensitivity of 94%, with a specificity of 15.3%, and an NPV of 73.7%.

The cut-off value on POD 4 for 100% of sensitivity and NPV was of 2.83 mg/dL for both anastomotic/abdominal and

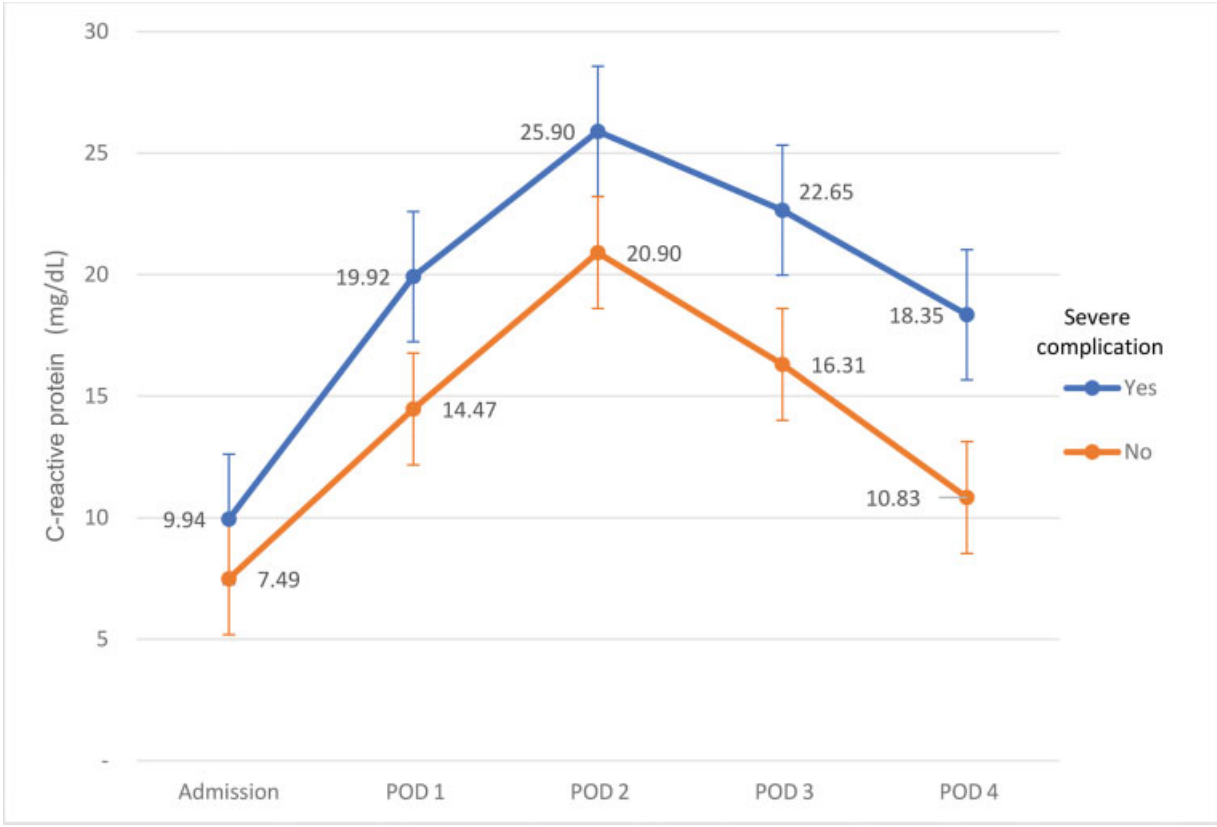
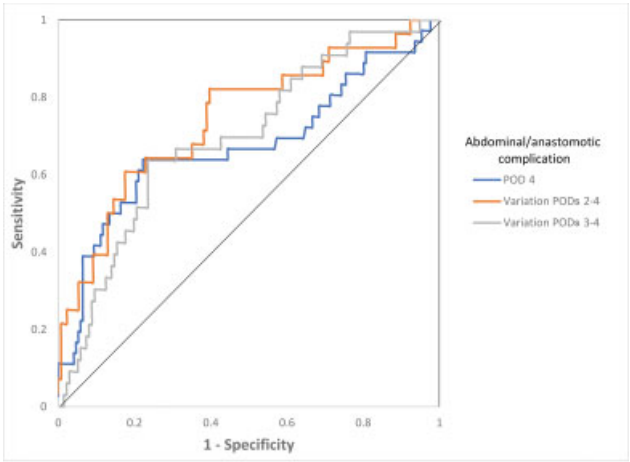
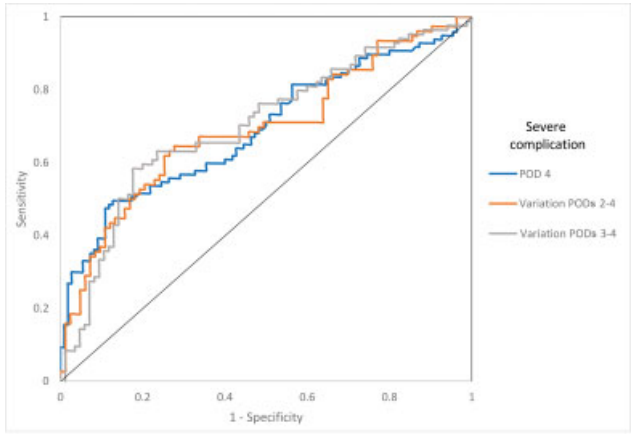


Fig. 1 Median CRP (C-reactive protein(levels (mg/dL), with standard error, in patients that had severe intra-abdominal postoperative complication and patients with mild or no complications between the preoperative period and the fourth postoperative day (POD 4).



CRP	n	AUC
Preoperative period	266	0.48250
POD 1	203	0.60920
POD 2	205	0.56864
POD 3	198	0.64474
POD 4	200	0.67381
Variation PODs 0-2	205	0.51790
Variation PODs 2-4	159	0.74400
Variation PODs 2-3	168	0.67015
Variation PODs 2-4	169	0.69474

Fig. 2 Receiver operating characteristic curve for the accuracy of C-reactive protein (CRP) between admission and the fourth postoperative day (POD 4), and the percentage variation between these dosages in the diagnosis of complications of anastomosis/ostomy and the abdominal cavity. Abbreviation: AUC, area under the curve.



CRP	n	AUC
Preoperative period	266	0.56903
POD 1	203	0.62682
POD 2	205	0.62404
POD 3	198	0.67885
POD 4	200	0.69114
Variation PODs 0-2	205	0.47926
Variation PODs 2-4	159	0.63580
Variation PODs 2-3	168	0.63580
Variation PODs 2-4	169	0.70238

Fig. 4 Receiver operating characteristic curve for the accuracy of C-reactive protein (CRP) between admission and the fourth postoperative day (POD 4) and the percentage variation between these dosages in the diagnosis of severe complications. Abbreviation: AUC, area under the curve.

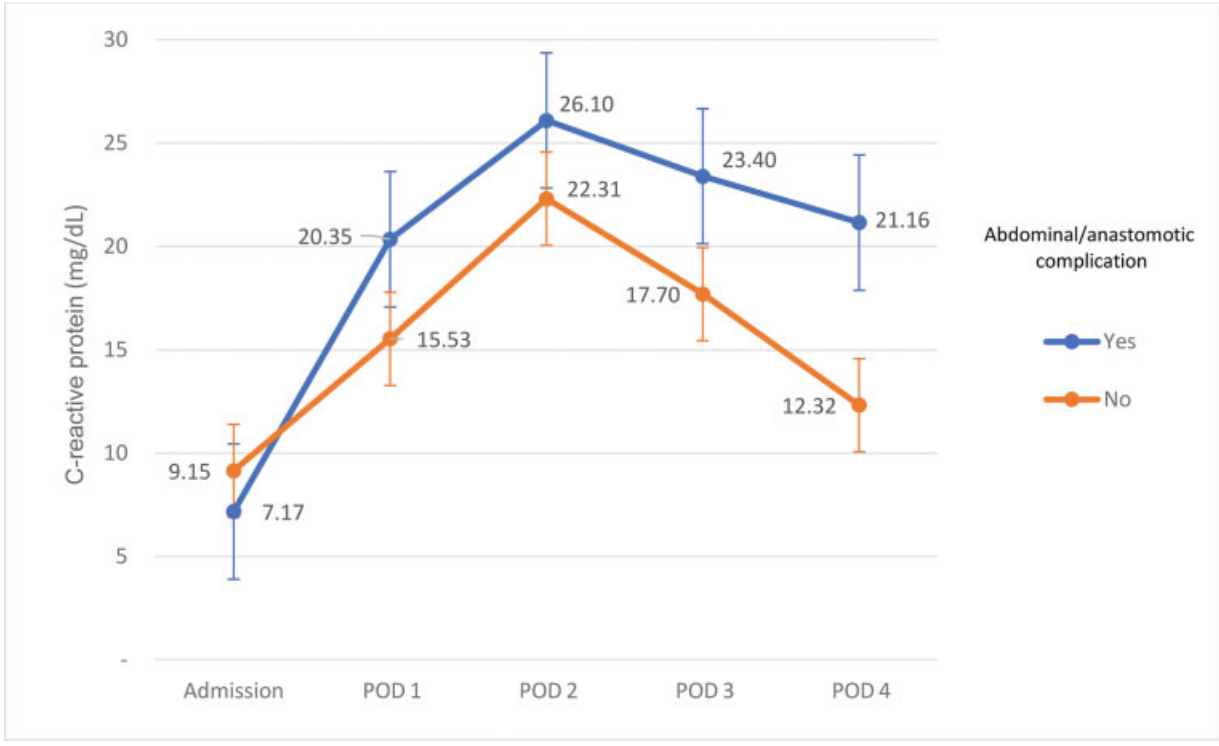


Fig. 3 Median CRP (C-reactive protein) levels (mg/dL), with standard error, in patients that had intra-abdominal postoperative complication and patients with no intra-abdominal complications between the preoperative and the fourth postoperative day (POD 4).

severe complications. We determined a CRP of 7.48 mg/dL considering sensitivities of 91.7% for abdominal complications, and of 89.7% for severe complications, with NPVs of 91.7% and 73% respectively.

Discussion

In the present study, we were able to propose a useful cut-off value on POD 4, and associate a CRP drop compatible with its short half-life to the absence of severe and anastomotic/abdominal complications. When comparing all values in the ROC curve, the CRP on POD4 showed a higher AUC. When we individualized their cut-off values, however, the levels evidenced for maximum sensitivity and NPV were of 2.83 mg/dL, a very low and infrequent finding. Only four patients in the sample met this criterion, all with Clavien-Dindo II complications and no infection. However, following the rationale for the 19-hour half-life of CRP, we found that a 51% CRP drop between PODs 2 and 3 and a 46% drop between PODs 3 and 4 showed 100% of sensitivity and NPV for anastomotic leak and abdominal cavity abscess. We have not heard of another study so far using the percentage variation of CRP between PODs of colorectal operations, be them elective or urgent, to predict complications, or as a criterion for hospital discharge.

The use of inflammatory markers, especially CRP, has enabled safe early hospital discharge for patients undergoing elective colorectal procedures with a lower chance of readmission,[13] and the diagnosis of complications before their first clinical manifestation.[2,14] Thus, reductions in the severity of complications, length of hospital stay, and mortality are expected.[15]

The serum values of CRP tend to be low in healthy individuals.[15,16] Due to the metabolic response to surgical trauma, the release of inflammatory cytokines promotes the elevation of CRP levels up to POD The trend towards a complication-free course is a peak in serum CRP on POD 2 followed by a continuous drop on subsequent days. The higher levels of preoperative CRP in emergency surgery patients used to be a criterion to exclude this population from studies on inflammatory markers in the PO period. However, Straatman et al.[8] demonstrated that, despite that variation, the CRP levels stabilized starting on POD 3, as in elective cases.

Patients with poor outcomes are more likely to have high CRP levels even in the first 24 PO hours, and a drop in this indicator was associated with a lower complication rate.[15,17,18] This finding has been corroborated by most studies since the beginning of the use of CRP in the PO of surgical procedures in general,[19,20] and, more recently, specifically in the case of colorectal resections.[8] We observed the same high CRP levels in the preoperative period or on POD 1 (►**Fig. 5**), but the values were not useful for closer follow-up, for lowering the threshold for intervention, or for making

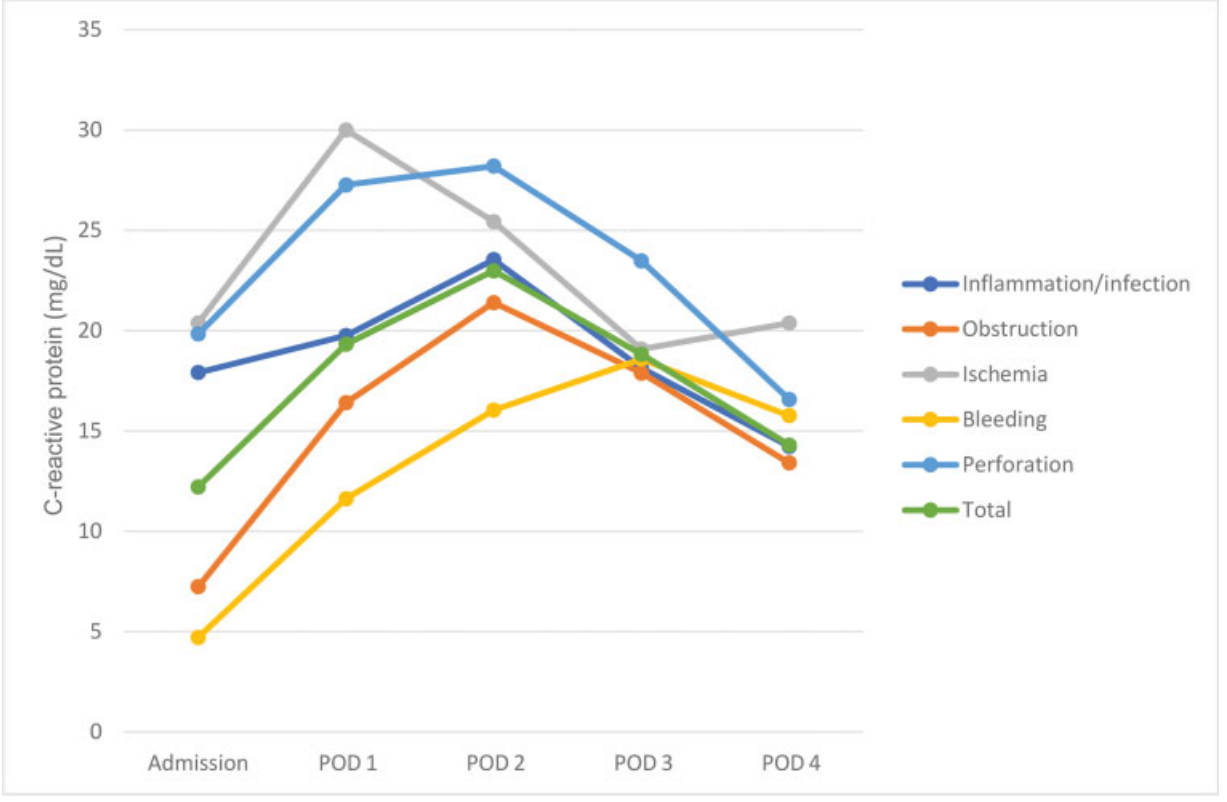


Fig. 5 Evolution of the mean dosages of C-reactive protein according to the surgical indication between the preoperative period and the fourth postoperative day (POD 4).

radiology-based tests mandatory in the initial PO for early diagnosis of severe or anastomotic complications.

The study groups were thus stratified considering the different characteristics of indication for urgent surgery of patients with neoplastic and non-neoplastic ("benign") disease, as well as the greater possibility of prevention of cases of advanced tumors. Our service is in the only hospital of a health insurance company for $\sim$ 1.5 million public servants and their dependents in the state of São Paulo, most of them elderly. This survey of the total neoplastic emergencies composes a study recognizing our patterns for establishing prevention plans. Our sample had a higher frequency of obstruction for neoplasms (124 of 176; 70.5%), while non-neoplastic indications included mostly (86 of 132; 65,1%) etiologies with higher tissue and inflammation such as acute diverticulitis with peritonitis and acute colonic ischemia.

The higher incidence of death among patients without neoplasia might be due to the inclusion in this group of diseases of vascular and perforative etiology, with mortality rates of 61.5% and 40.7% respectively. Despite its rate, mortality in the present study was equivalent to the mortality reported in the literature: 26 to 81% for acute mesenteric ischemia,[21] and 30 to 70% for perforations.[22]

Preoperative CRP values may vary even in elective patients, as well as the inflammatory PO response of each individual due to differences in immune response associated with age, gender, race, and nutrition status.[10] It seems more reliable to use the variation than an isolated value. Since CRP has a 19-hour half-life, when there is no stimulus for its production, there is a significant drop in levels from one day to the next.[23]

The present study is limited by its retrospective design. Moreover, we did not consider the comorbidities of patients and preoperative clinical conditions or demographic data, as in most publications.

We suggest daily CRP tests from POD 2 onwards for the use of its gradient as a criterion for hospital discharge on PODs 3 or 4 of colorectal surgical procedures as a matter of urgency.

Conclusion

The levels of CRP can be used for the exclusion of severe complications and as a criterion for hospital discharge on POD 4 of emergency colorectal surgery.

Conflict of Interests

The authors have no conflict of interests to declare.

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