

## CLINICAL ARTICLE

## Gynecology

# C-reactive protein “at first sight”: Standard postoperative trend in gynecological surgery and a comparative analysis with white blood cell levels

Carlo De Cicco Nardone<sup>1</sup> | Cristiana De Luca<sup>1</sup>  | Francesco Plotti<sup>1</sup> | Silvia Fabris<sup>2</sup> | Gianmarco Rossini<sup>1</sup> | Roberto Montera<sup>1</sup> | Daniela Luvero<sup>1</sup> | Roberto Angioli<sup>1</sup> | Corrado Terranova<sup>1</sup>

<sup>1</sup>Gynecology and Obstetrics, Campus Bio Medico University, Rome, Italy

<sup>2</sup>Unit of Medical Statistics and Molecular Epidemiology, Campus Bio Medico University, Rome, Italy

## Correspondence

Cristiana De Luca, Gynecologist, Campus Bio Medico, 00128 Rome, Italy.  
Email: [cristianadeluca19@gmail.com](mailto:cristianadeluca19@gmail.com)

## Abstract

**Objective:** There is a lack of information about the normal trend of C-reactive protein (CRP) blood levels in the postoperative days after gynecological benign surgery. We investigated the impact of different surgical techniques on CRP trend. We performed a comparative analysis between a CRP and white blood cell (WBC) trend in postoperative monitoring.

**Methods:** We studied 207 surgical patients for benign gynecological pathology. We analyzed CRP and WBC levels after surgery in the total number of women and separately by approaches.

**Results:** CRP mean log scores showed a typical behavior. Moreover, results from chi-square test underline that the proportion of women with this result is independent from the type of surgery they underwent. Log score mean values of CPR differed between all groups and between times. No difference in the mean number of white cells between the second and the third day was found, as observed for CRP.

**Conclusions:** Our study shows a trend reference model in postoperative monitoring of patients with benign gynecological surgery. The comparative analysis between the CRP and WBC trend in the postoperative days provided us data demonstrating the superiority of CRP in postsurgical patient outcomes monitoring.

## KEYWORDS

C-reactive protein, gynecological benign surgery, postoperative complications, white blood cells

## 1 | INTRODUCTION

C-reactive protein (CRP) is recognized as an acute-phase protein. Serial monitoring of CRP has diagnostic value in the early identification of postoperative complications such as anastomotic dehiscence

and ureteral damage after intestinal resection. CRP blood concentration significantly increases during the postoperative period.<sup>1,2</sup> There is no significant difference between the CRP serum levels in patients with endometriosis and those in infertile women without endometriosis.<sup>3</sup>

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial](https://creativecommons.org/licenses/by-nc/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2022 The Authors. *International Journal of Gynecology & Obstetrics* published by John Wiley & Sons Ltd on behalf of International Federation of Gynecology and Obstetrics.

The lack of information about the normal trend of CRP blood levels in the postoperative days and the impact of postoperative complications on this trend led us to investigate CRP values in patients undergoing surgery. As white blood cell (WBC) level is universally used in clinical practice, our aim was first to assess whether a CRP and WBC standard postoperative trend could be found in benign gynecology. We then wanted to compare WBC and CRP levels' reliability in the evaluation and monitoring of patients who underwent gynecological surgery with the aim to recognize early any curve deviation as a suspected complication onset.

Our study produced a reference model with a normal trend that allows monitoring of the postoperative course in patients undergoing surgery. It could provide a useful tool for early identification of the onset of complications before symptoms arise. A surgical patient with an uncomplicated postoperative course will present with CRP values with a typical curve. On the contrary, patients who develop postsurgical complications will present with a CRP trend that deviates from our reference curve.

The secondary outcome was to analyze data of the patients divided according to the surgical approach received, in order to show the impact that the different surgical techniques have on the CRP trend and to create specific reference curves for every single approach.

## 2 | MATERIALS AND METHODS

This was a monocentric study performed in the Gynecology Department of the Campus Bio Medico University Hospital of Rome. Between October 2016 and October 2018, we retrospectively recruited consecutive patients through selection from the data storage system provided in our hospital (MEDArchiver).

Women who met the following criteria were included: age 18–75 years, body mass index 18–35, benign gynecological pathology, gynecological surgery, three or more postoperative days before discharge, three or more postoperative days of CRP daily dosage, and no other known conditions of higher preoperative CRP levels. Women who met the following criteria were not included: preexisting coagulation, cardiac or respiratory pathology, anesthesiological criteria (3/4), ongoing pelvic inflammation, neurological or cognitive dysfunctions, active or previous neoplastic pathology, and known conditions of higher preoperative CRP levels.

We computed an explanatory analysis about CRP and white cells measured during the 3 days after surgery. We transformed those values into their logarithmic scale and we studied mean and median values in order to understand whether there could be a time trend. The descriptive analysis had been performed on the total number of women and separately by approaches. Once we recognized a potential trend, we compared the proportion of women reporting this behavior among the different types of surgery by chi-square test, with a 95% significance level and within every group and in the total number of patients using the one-sample proportions test, with the same confidence level. We then studied white cell values in terms of

exceeding or not the 10000 threshold (9.21 on its log score), capturing the typical behavior to then compare the proportion of women who followed it or not. This had been done in the total number of patients and by approaches; to do this, we used chi-square test and one-sample proportions test with a 95% significance level. Finally, we compared log values in terms of times and approaches running repeated-measures ANOVA test. Where needed, we implemented a pairwise comparison *t* test. Both ANOVA and *t* test results had been evaluated with a 95% significance level.

The Campus Bio Medico University's local ethics committee approved the study. All participants gave written informed consent, because in our hospital all patients sign informed consent about the possibility that their data could be used for scientific aims.

## 3 | RESULTS

Among the 553 women who had undergone surgery, we selected 207 patients who reported all CRP values between the first and the third days after surgery (Table 1).

CRP mean log scores, together with median values (Figure 1), show a typical behavior on the total number of women and for each type of surgery separately: more specifically the 80.19% of patients showed CRP values increasing on the second day and decreasing on the third day, as do the mean log values. In particular, 76.1%, 84.9%, and 73.3% of women among the laparoscopic, laparotomic, and vaginal groups, respectively, reported this trend on their log score. The one-sample tests highlight that within any surgery group and in the total number of patients, the proportion of women who follow the trend is not statistically equal to the proportion of women who do not ( $P < 0.05$ ). Moreover, the results from chi-square test underline that the proportion of women who report this behavior is independent from the type of surgery they underwent ( $P = 0.208$ ).

Considering that the 201 patients who reported white cell values completed information recorded on the first 3 days after surgery, we observed mean and standard deviation (SD) log values as specified in Table 2.

On the one hand, as shown in Table 2 and the box plot in Figure 2, we were able to identify a decreasing trend in 80% of patients, more specifically in the 68%, 86%, and 83% of women who underwent laparoscopic, laparotomic and vaginal approaches, respectively. The one-sample tests confirm that the proportion of patients reporting this behavior is different from those who do not show this trend ( $P < 0.01$ ). On the other hand, the chi-square *P* value underlines that the proportion of patients who follow this trend is not statistically independent from the type of surgery ( $P = 0.016$ ). In terms of exceeding the 9.21 threshold, mean log values reported in Table 2 are greater than the threshold on the first day only. Analyzing the proportion of patients reporting a WBC count greater than 10000 on the first day and lower on the second and the third days, the 50% does show this behavior; in fact, the one-sample test for proportions report a  $P = 1$ , demonstrating, with 95% significance, that the two

TABLE 1 Number of patients undergoing surgery by CRP mean log score values and SDs

Type of surgery	No. of patients	First day CRP, mean (SD)	Second day CRP, mean (SD)	Third day CRP, mean (SD)
Laparoscopic	71	2.72 (1)	3.38 (1.1)	3.03 (1.1)
Laparotomic	106	3.74 (0.7)	4.34 (0.5)	3.90 (0.6)
Vaginal	30	2.92 (0.6)	3.58 (0.7)	3.49 (0.7)
All patients	207	3.27 (1)	3.90 (0.9)	3.54 (0.9)

Abbreviations: CRP, C-reactive protein; SD, standard deviation.

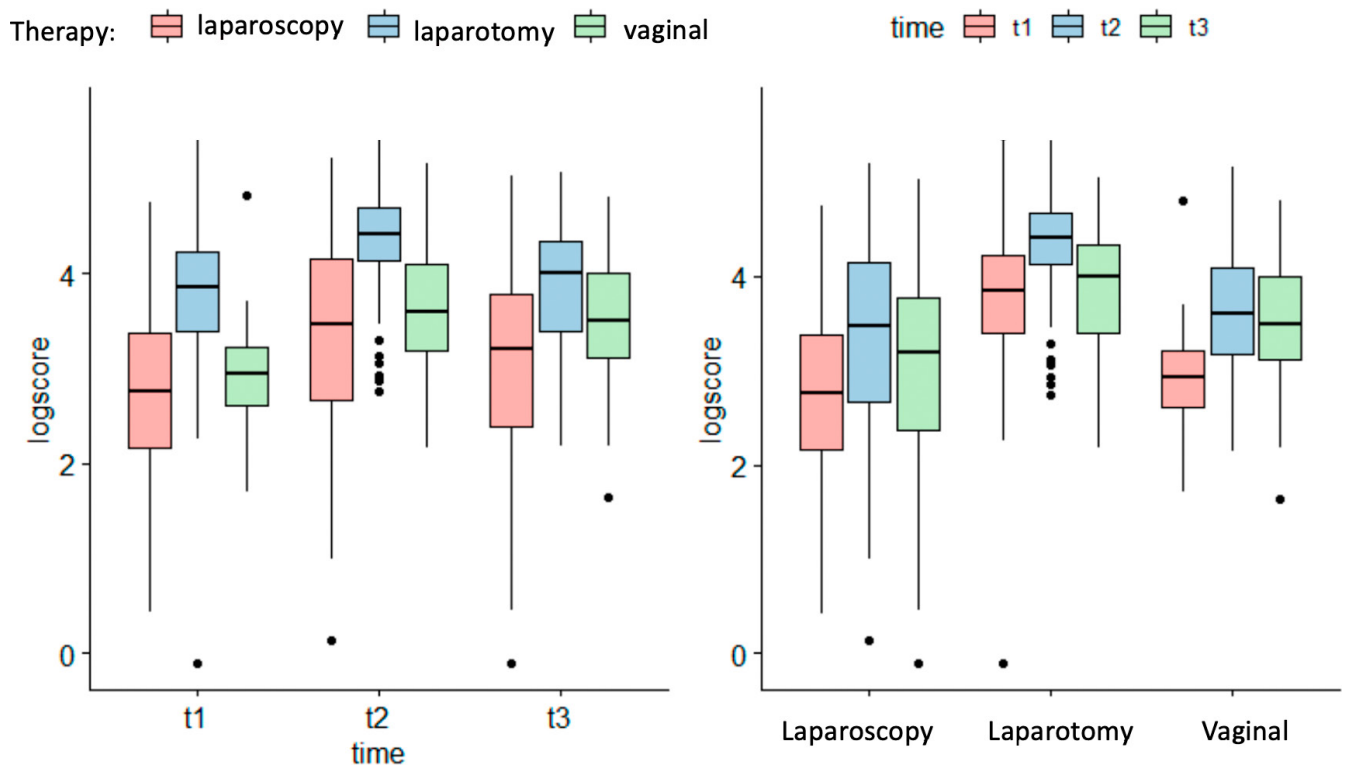


FIGURE 1 Pairwise comparison between times and groups.

TABLE 2 Number of patients undergoing surgery by WBC mean log score values and SDs

Type of surgery	No. of patients	First day WBCs, mean (SD)	Second day WBCs, mean (SD)	Third day WBCs, mean (SD)
Laparoscopic	70	9.29 (0.2)	8.91 (0.3)	8.76 (0.3)
Laparotomic	102	9.42 (0.3)	9.09 (0.2)	8.87 (0.3)
Vaginal	29	9.38 (0.2)	9.14 (0.3)	8.95 (0.3)
All patients	201	9.27 (0.2)	9.03 (0.3)	8.84 (0.3)

Abbreviations: SD, standard deviation; WBCs, white blood cells.

proportions did not differ. The same result had been found within surgery groups, in particular the 51% of women who underwent laparoscopic surgery, the 53% of those who underwent laparotomic surgery, and the 34% of those who underwent vaginal surgery, following the trend, respectively ( $P = 0.905, 0.62, \text{ and } 0.137$ ). There appears to be no dependence between reporting the highlighted behavior and the type of surgery ( $P = 0.202$ ).

Finally, results from repeated-measures ANOVA demonstrate that both CRP and white cells differ between groups (both  $P < 0.001$ ) and within groups in terms of time (both  $P < 0.001$ ). On the contrary, there was no significant interaction between time and surgery approaches ( $P = 0.519 \text{ and } 0.312$ ). Results from pairwise  $t$  test are shown together with respective significance level in Figures 1 and 2. Figure 1 reports that log score mean values of CRP differ between all groups and all

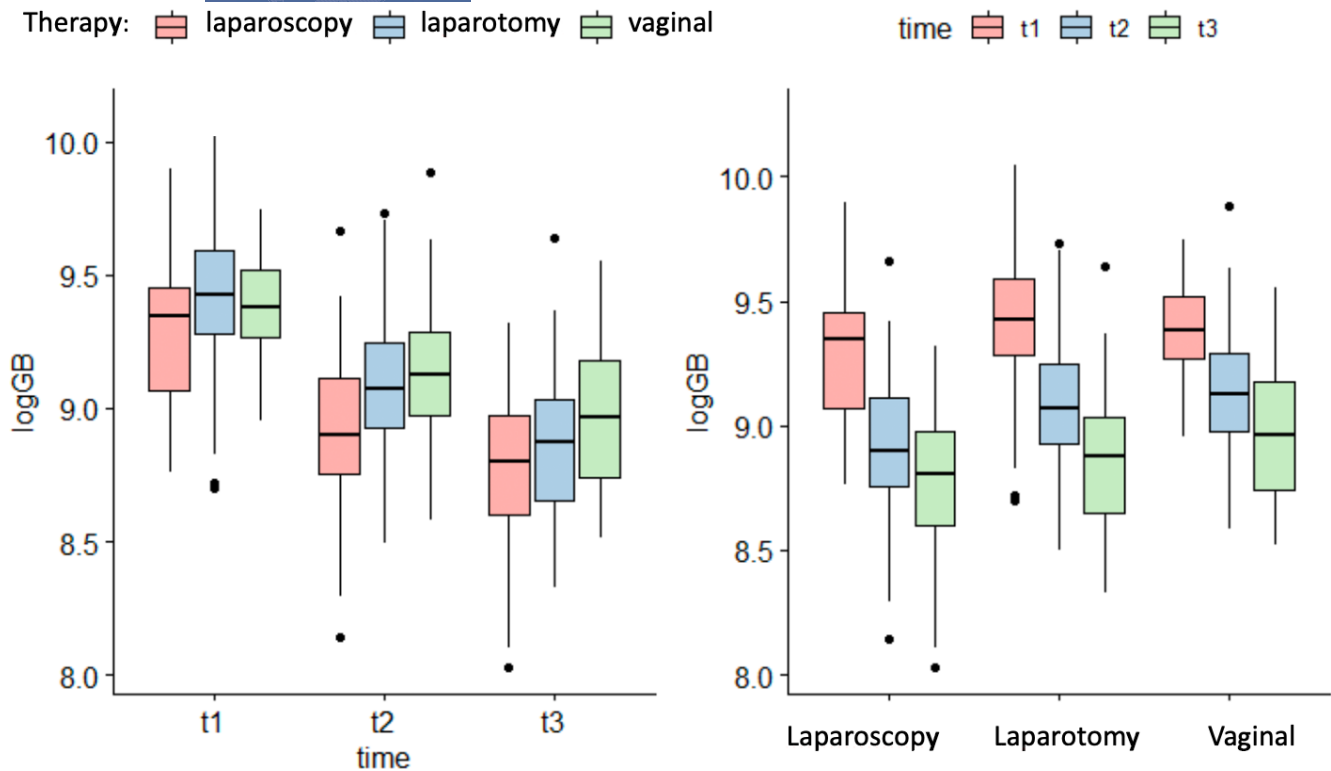


FIGURE 2 White cell pairwise comparison between times and groups. WBC, white blood cells.

times. Figure 2 shows no difference in the mean number of white cells between the second and third days, as observed for CRP, and there was no statistical equality between the surgery groups.

#### 4 | DISCUSSION

CRP is an alpha globulin secreted by the liver. CRP is part of the acute-phase proteins. CRP has numerous triggers such as harmful agents, pathogenic microorganisms, infections, acute articular rheumatism, Crohn disease, traumas, burns, and following surgical procedures. It has no circadian rhythm. It can be accurately determined on both fresh and frozen samples without requiring special sample collection procedures. CRP is part of a defense mechanism and contributes to nonspecific immunity with the activation of the complement cascade and acceleration of monocytes-macrophages phagocytosis.

In deep endometriosis surgical patients, CRP serial monitoring has a diagnostic value in the early identification of anastomotic dehiscence or ureteral damage after bowel resection. CRP blood level is significantly increased during the postoperative period.<sup>1,2</sup>

A retrospective randomized study has shown higher CRP levels in patients after abdominal hysterectomy than in those undergoing laparoscopic and vaginal hysterectomy.<sup>4</sup>

Surgery leads to a cytokine pattern promoting increased CRP.<sup>5,6</sup> A recent study argues that perioperative CRP dosage should only be performed if there is a clear clinical indication.<sup>5</sup>

CRP can predict postsurgical complications with a predictive value of 30.5%, while a reduction in the postoperative peak of the

CRP can anticipate an uncomplicated course with a predictive value of 92.1%.<sup>1</sup> CRP has also been studied in bariatric surgery with the aim of evaluating its predictive value of postsurgical complications, even if the ability of this marker to accurately predict such events has not been determined.<sup>7</sup>

CRP was considered a useful test with negative predictive value to suspect the early dehiscence of anastomoses in patients undergoing colorectal resections.<sup>8-10</sup> It has been shown that its postoperative values are predictive of complications of the anastomosis in minimally invasive esophageal surgery.<sup>11</sup> Regarding gynecology surgery, a study published in 2016<sup>1</sup> focused on the evaluation of the serum levels of various inflammatory biomarkers, including CRP, in patients undergoing hysterectomy. CRP concentration is significantly increased during the postoperative period.<sup>12</sup> Postoperative CRP levels have been observed to be significantly higher in patients undergoing abdominal hysterectomy than in those undergoing laparoscopic and vaginal hysterectomy.<sup>2</sup>

The extent of tissue damage caused by abdominal hysterectomy and laparoscopic hysterectomy causes an increase in CRP, confirming that surgery is a significant cause of tissue stress.<sup>13</sup> Studies have confirmed the negative predictive value of serum CRP concentration on day 4 after surgery to exclude a postoperative infection.<sup>6,14</sup> In this landscape, our study analyzed CRP values in the postoperative days in patients undergoing surgery for therapeutic purposes for benign gynecological pathologies to identify a standard trend and define a reference model useful in clinical practice and eventually distinguish specific curves for each surgical approach: laparotomy, laparoscopic, and vaginal.

CRP typically undergoes an increase on the first postoperative day and reaches its peak on the second day, after which, in the absence of complications, the degrowing phase begins. Therefore, to make this standard trend evident, it was necessary to obtain the CRP values for at least the 3 days following surgery.

As shown in Figure 3, the trend of CRP in the four postoperative days of all patients enrolled in the study was observed overall, without distinction by approach. Figure 3 makes it evident that during the first day the CRP increased rapidly, reaching the maximum value on the second day (peak). After reaching the peak, the value begins a phase of slow decrease, gradually tending to stabilize in the basal levels of the individual in the following days. Once divided by surgical approach, the data in Figures 4–6 show the same kind of trend; however, the peak values on the second day are drastically lower following the vaginal approach (Figure 6), compared with both the laparotomy and laparoscopic approaches, which also show lower values than the laparotomy approach.

The average values for each day are lower than for the laparotomic approach, both for the vaginal and laparoscopic approaches (Figure 7). These differences, in patients who did not develop complications, can be explained by the differences between the various surgical approaches. The laparotomic approach involves an incision of the skin, subcutaneous tissue, and muscle-fascial layer before entering the abdominal cavity. Both the incision process of the abdominal wall and the exposure to the ambient air of the viscera and peritoneal membrane, as well as their manipulation, triggers an inflammatory process with the release of cascade factors such as cytokines and CRP.

For the laparoscopic approach, a large incision is not made in order to access the abdominal cavity but rather small cuts for trocars. However, CO<sub>2</sub> insufflation is responsible for relative hypoxic stress in the tissues, which perceive hypercapnia and trigger the release of inflammation factors. The vaginal approach is the least traumatic for a small surgical incision and no CO<sub>2</sub> is used.

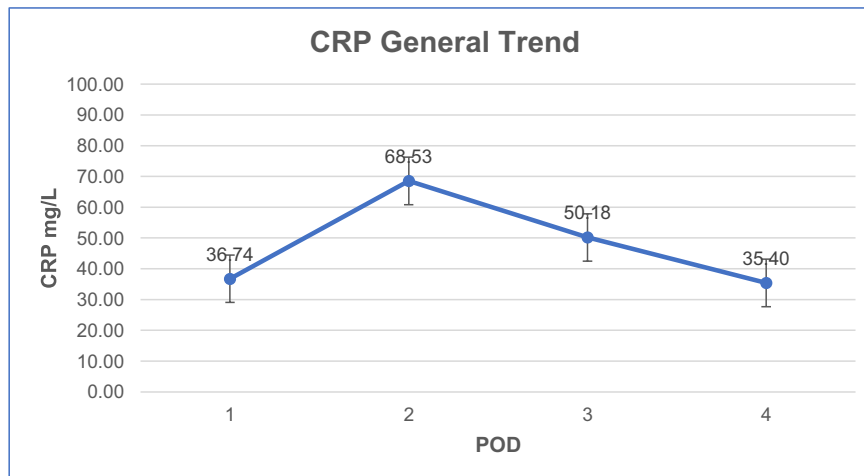


FIGURE 3 Total patients. CRP, C-reactive protein; POD, postoperative day.

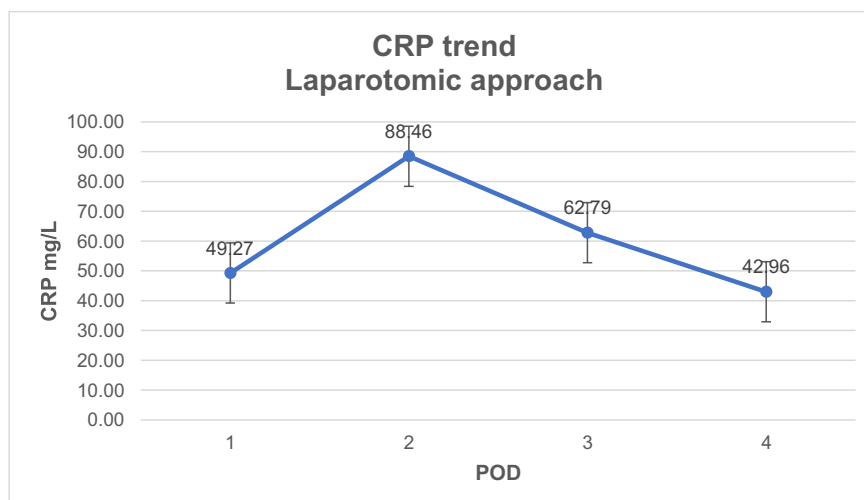


FIGURE 4 Laparotomic approach. CRP, C-reactive protein; POD, postoperative day.

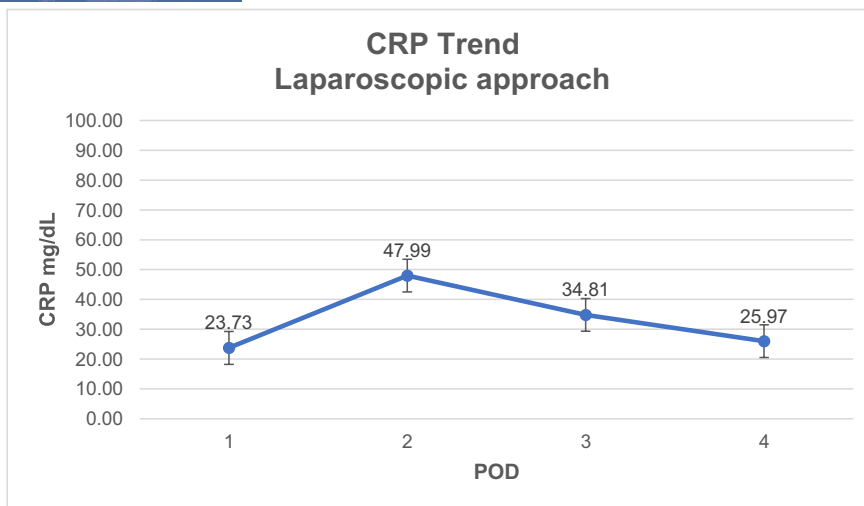


FIGURE 5 Laparoscopic approach. CRP, C-reactive protein; POD, postoperative day.

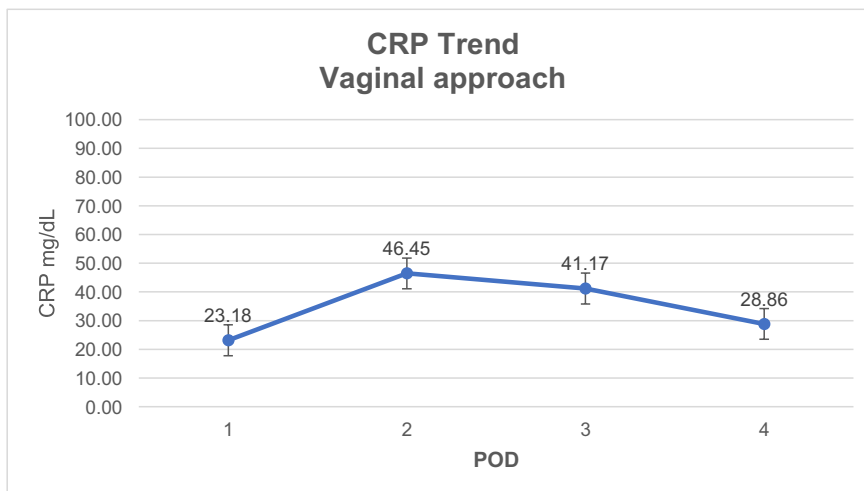


FIGURE 6 Vaginal approach. CRP, C-reactive protein; POD, postoperative day.

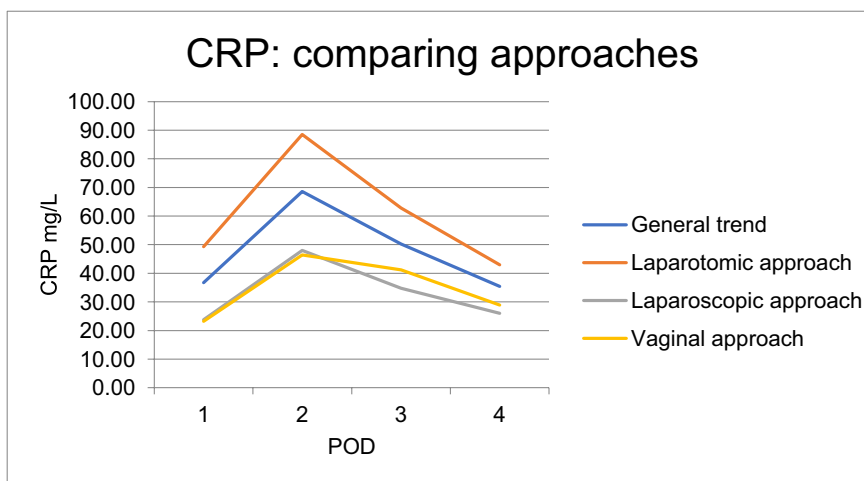


FIGURE 7 Comparing approaches. CRP, C-reactive protein; POD, postoperative day.

Our study has limitations worth noting. The small number of patients, the heterogeneous pool of patients, and the lack of a randomization did not allow us to obtain any clear evidence. The comparative analysis between CRP trend and WBC trend in the postoperative days provided us data demonstrating the superiority of CRP over WBC in postsurgical patient outcomes monitoring, but further research is needed to confirm and validate our results.

In conclusion, the analysis of patients undergoing gynecological surgery for benign pathologies without developing postoperative complications provided us a trend reference curve of CRP levels. The comparative analysis between CRP trend and WBC trend in the postoperative days presents us with data demonstrating the superiority of CRP over WBC in postsurgical patient outcomes monitoring. This could represent the basis for further studies on the postoperative inflammatory response in various conditions including different intraoperative and postoperative complications. The division of the values by approach has provided further evidence of the greater inflammatory response in case of laparotomy procedures. Comparing all of the approaches, the vaginal method determines CRP values lower than all of the others in the first two postoperative days, but its phase of decreasing in the third day is less steep than that seen with laparoscopy. However, we cannot exclude that this curve shape depends on the small number of recruited patients undergoing vaginal surgery. Perhaps an expanded sample could detail the expected trend.

#### AUTHOR CONTRIBUTIONS

Study design and planning: Carlo De Cicco Nardone, Cristiana De Luca, Francesco Plotti, Roberto Angioli, Corrado Terranova, Roberto Montera, Daniela Luvero, and Gianmarco Rossini; data curation: Carlo De Cicco Nardone, Cristiana De Luca, Silvia Fabris, Corrado Terranova, Roberto Montera, Daniela Luvero, and Gianmarco Rossini; formal analysis: Cristiana De Luca, Silvia Fabris; resources: Roberto Angioli; writing – original draft: Carlo De Cicco Nardone and Cristiana De Luca; and writing – review and editing: Carlo De Cicco Nardone and Cristiana De Luca, Francesco Plotti, and Roberto Angioli.

#### ACKNOWLEDGMENTS

We thank all of our patients for contributing to our work. We thank Campus Bio Medico University and all colleagues who helped with our investigation.

#### CONFLICT OF INTEREST

The authors have no conflicts of interest to declare. All co-authors have reviewed and agree with the contents of the article. There are no financial interests to report.

#### DATA AVAILABILITY STATEMENT

Research data are not shared.

#### ORCID

Cristiana De Luca  <https://orcid.org/0000-0002-9465-4149>

#### REFERENCES

1. Riiskjær M, Forman A, Kesmodel US, Andersen LM, Ljungmann K, Seyer-Hansen M. Diagnostic value of serial measurement of C-reactive protein in the detection of a surgical complication after laparoscopic bowel resection for endometriosis. *Gynecol Obstet Invest.* 2016;82:410-416.
2. Pilka R, Marek R. Systemic inflammatory response after open, laparoscopic and robotic surgery in endometrial cancer patients. *Anticancer Res.* 2016;36(6):2909-2922.
3. Kianpour M, Nematbakhsh M, Ahmadi SM. C-reactive protein of serum and peritoneal fluid in endometriosis. *Iran J Nurs Midwifery Res.* 2012;17(2 suppl 1):S115-S119.
4. Aka N, Kose G, Gonenc I, Api M. Tissue trauma after vaginal hysterectomy and colporrhaphy versus abdominal hysterectomy: a randomised controlled study. *Aust N Z J Obstet Gynaecol.* 2004;44:328-331.
5. Cole DS, Watts A, Scott-Coombes D, Avades T. Clinical utility of peri-operative C-reactive protein testing in general surgery. *Ann R Coll Surg Engl.* 2008;90(4):317-321. doi:10.1308/003588408X285865
6. Adamina M, Steffen T, Tarantino I, Beutner U, Schmied BM, Warschkow R. Meta-analysis of the predictive value of C-reactive protein for infectious complications in abdominal surgery. *Br J Surg.* 2015;102:5908.
7. Gruys E, Toussaint MJ, Niewold TA, Koopmans SJ. Acute phase reaction and acute phase proteins. *J Zhejiang Univ Sci B.* 2005;6(11):1045-1056. doi:10.1631/jzus.2005.B1045
8. Villard MA, Helm MC, Kindel TL, Goldblatt MI, Gould JC, Higgins RM. C-reactive protein as a predictor of post-operative complications in bariatric surgery patients. *Surg Endosc.* 2018. doi:10.1007/s00464-018-6534-0. [Epub ahead of print].
9. Lagoutte N, Facy O, Ravoire A, et al. C-reactive protein and procalcitonin for the early detection of anastomotic leakage after elective colorectal surgery: pilot study in 100 patients. *J Visc Surg.* 2012;149(5):e345-e349. doi:10.1016/j.jviscsurg.2012.09.003
10. Cousin F, Ortega-Deballon P, Bourredjem A, Doussot A, Giaccaglia V, Fournel I. Diagnostic accuracy of procalcitonin and C-reactive protein for the early diagnosis of intra-abdominal infection after elective colorectal surgery: a meta-analysis. *Ann Surg.* 2016;264(2):252-256. doi:10.1097/SLA.0000000000001545
11. Prochazka V, Marek F, Kunovsky L, et al. C-reactive protein as predictor of anastomotic complications after minimally invasive oesophagectomy. *J Minim Access Surg.* 2019;15(1):46-50. doi:10.4103/jmas.JMAS\_254\_17
12. Holub Z, Jabor A, Kliment L, Sprongl L. Inflammatory responses after laparoscopic uterine myomectomy compared to open surgery in current clinical practice. *Saudi Med J.* 2006;27:1693-1697.
13. Atabekoglu C, Sönmezer M. Tissue trauma in abdominal and laparoscopic-assisted vaginal hysterectomy. *J Am Assoc Gynecol Laparosc.* 2004;11(4):467-472.
14. Suarez-de-la-Rica A, Maseda E, Anillo V, et al. Biomarkers (procalcitonin, C reactive protein, and lactate) as predictors of mortality in surgical patients with complicated intra-abdominal infection. *Surg Infect (Larchmt).* 2015;16(3):346-351. doi:10.1089/sur.2014.178

**How to cite this article:** De Cicco Nardone C, De Luca C, Plotti F, et al. C-reactive protein "at first sight": Standard postoperative trend in gynecological surgery and a comparative analysis with white blood cell levels. *Int J Gynecol Obstet.* 2023;160:237-243. doi:10.1002/ijgo.14314