Received: 5 November 2023 | Revised: 29 February 2024 | Accepted: 2 March 2024

DOI: 10.1111/aogs.14834

AOGS Acta Obstetricia et Gynecologica Scandinavica

ORIGINAL RESEARCH ARTICLE

Procalcitonin and C-reactive protein as early markers of anastomotic leakage in intestinal resections for advanced ovarian cancer (EDMOCS)

José Luis Sánchez-Iglesias[1,2] | Clara Morales-Coma[3] | Lucas Minig[4,5] | Víctor Lago[5,6] | Santiago Domingo[6] | Gemma Mancebo[7,8] | Jaime Siegrist[9] | María Soledad Fidalgo García[10] | Antoni Llueca[11,12] | Anna Serra[11,12] | Paloma Cobas Lozano[13] | Arantza Lekuona Artola[13] | Natalia R. Gómez-Hidalgo[1] | Úrsula Acosta[1] | Roser Ferrer-Costa[14] | Melissa Bradbury[1] | Assumpció Pérez-Benavente[1,2] | Antonio Gil-Moreno[1,2] | the SEGO Spain-GOG Group

[1]Department of Gynecologic Oncology, Vall d'Hebron University Hospital, Barcelona, Spain

[2]Biomedical Research Group in Gynecology, Vall d'Hebron Research Institute (VHIR), Universitat Autònoma de Barcelona, Barcelona, Spain

[3]Breast Pathology Unit, Vall d'Hebron University Hospital, Barcelona, Spain

[4]Department of Gynecologic Oncology, IMED Hospital, Valencia, Spain

[5]Department of Gynecology, CEU Cardenal Herrera University, Valencia, Spain

[6]Department of Gynecologic Oncology, La Fe University Hospital, Valencia, Spain

[7]Gynecological Cancer Multidisciplinary Unit, Hospital del Mar, Barcelona, Spain

[8]Department of Gynecology, Universitat Pompeu Fabra, Barcelona, Spain

[9]Oncologic Gynecology Unit, Department of Gynecology, La Paz University Hospital, Madrid, Spain

[10]Department of Gynecologic Oncology, Hospital Universitario Central de Asturias, Oviedo, Spain

[11]Multidisciplinary Unit of Abdominal Pelvic Oncology Surgery, Hospital General Universitario de Castellon, Castellón, Spain

[12]Department of Medicine, Universidad Jaume I, Castellón, Spain

[13]Department of Gynecologic Oncology, Hospital Universitario Donostia, OSI Donostialde, Donostia, Spain

[14]Department of Biochemistry, Vall d'Hebron University Hospital, Barcelona, Spain

Correspondence
Úrsula Acosta, Department of Gynecologic Oncology, Vall d'Hebron University Hospital, Passeig de la Vall d'Hebron 119, 08035 Barcelona, Spain.
Email: ursulaacostasanchez@gmail.com

Funding information
Fundació Institut de Recerca Hospital Universitari Vall d'Hebron

Abstract

Introduction: Serum levels of procalcitonin and C-reactive protein (CRP) have been used to predict anastomotic leakage after colorectal surgery, but information is scarce in advanced ovarian cancer (AOC) surgery with bowel resection. This study aimed to assess the predictive value of procalcitonin and CRP in detecting anastomotic leakage after AOC surgery with bowel resection. The study also aimed to determine the optimal postoperative reference values and the best day for evaluating these markers.

Abbreviations: AL, anastomotic leak; AOC, advanced ovarian cancer; AUC, area under the curve; CRP, C-reactive protein; CT, computed tomography; ERAS, enhanced recovery after surgery; ICU, intensive care unit; NPV, negative predictive value; PCT, procalcitonin; POD, postoperative day; PPV, positive predictive value; ROC, receiving operator characteristic.

Material and methods: This prospective, observational and multicentric trial included 92 patients with AOC undergoing debulking surgery with bowel resection between 2017 and 2020 in 10 reference hospitals in Spain. Procalcitonin and CRP levels were measured at baseline and on postoperative days 1–6. Receiver operating characteristic analysis was performed to evaluate the predictive value of procalcitonin and CRP at each postoperative day. Sensitivity, specificity, positive and negative predictive values were calculated.

Results: Anastomotic leakage was detected in six patients (6.5%). Procalcitonin and CRP values were consistently higher in patients with anastomotic leakage at all postoperative days. The maximum area under the curve (AUC) for procalcitonin was observed at postoperative day 1 (AUC = 0.823) with a cutoff value of 3.8 ng/mL (83.3% sensitivity, 81.3% specificity). For CRP, the maximum AUC was found at postoperative day 3 (AUC = 0.833) with a cutoff level of 30.5 mg/dL (100% sensitivity, 80.4% specificity).

Conclusions: Procalcitonin and C-reactive protein are potential biomarkers for early detection of anastomotic leakage after ovarian cancer surgery with bowel resection. Further prospective studies with a larger sample size are needed to confirm these findings.

KEYWORDS
anastomotic leakage, colorectal resection, ovarian cancer

1 | INTRODUCTION

Advanced ovarian cancer (AOC) is usually treated with a combination of cytoreductive surgery and chemotherapy.[1] Given the proximity of the rectosigmoid, bowel involvement is common.[2] Tumor implants can also affect the small intestine due to peritoneal dissemination. Consequently, it has been estimated that bowel resections, which include large bowel and small bowel resections with manual or mechanical anastomosis, are required in 20%–80% of the patients with AOC.[2,3]

When a bowel resection surgery is required in AOC, the most common procedure is modified pelvic exenteration (MPE) followed by colorectal anastomosis, which has acceptable morbidity and mortality rates.[4] A serious postoperative complication of MPE is anastomotic leak (AL). AL is defined as a defect of the intestinal wall at the anastomotic site leading to a communication between the intra- and extraluminal compartments. Mortality following AL is estimated to be between 7.3% and 16%.[4–8] Some asymptomatic patients with AL might evolve favorably with conservative management, but symptomatic patients require radiological drainage or reintervention with stoma formation. Further, these patients often require admission to an intensive care unit (ICU) due to sepsis, and prolonged hospital stay with associated high healthcare costs.[9] Additionally, AL can delay the start of adjuvant CT increasing the risk of cancer progression and recurrence.[10]

There is evidence of the utility of procalcitonin (PCT) and C-reactive protein (CRP) as early predictors of AL in patients with colorectal tumors.[11–17] Determination of PCT and CRP in the third postoperative day (POD) has been shown to provide the best results, with CRP showing a high negative predictive value (NPV) for AL.[15–17] Predicting AL in a subclinical stage may limit the consequences of the leak and accelerate the initiation of therapeutic measures. Also, these markers could help to identify patients at low risk of AL that could benefit from an early discharge in the context of the enhanced recovery after surgery (ERAS) programs. ERAS is a multidisciplinary, evidence-based pathway for the care of surgical patients that aims to improve perioperative management and outcomes. ERAS programs aim to achieve early recovery after surgery and a shorter length of hospital stay (LOS), and they have been successfully implemented in AOC surgery.[18–20]

In patients undergoing bowel resection of AOC surgery, there is emerging evidence suggesting the usefulness of PCT and CRP in predicting AL. Baseline and cutoff values of PCT and CRP in AOC

Key message

This trial involving women undergoing ovarian cancer surgery with bowel resection aimed to predict the risk of anastomotic leakage using inflammatory markers. Levels of procalcitonin and C-reactive protein were consistently higher in patients with anastomotic leakage throughout the early postoperative period.

might differ from those described in colorectal cancer surgery due to the inflammatory process associated to peritoneal carcinomatosis.[21,22] In this study we assessed the predictive value of PCT and CRP serum levels for the early detection of AL in patients undergoing debulking surgery for AOC and concomitant bowel resection (early dehiscence markers in ovarian cancer surgery [EDMOCS]). We aimed to define the optimal post-surgical reference values for PCT and CRP and determine the optimal postoperative day to evaluate these parameters in AOC patients.

2 | MATERIAL AND METHODS

This study was a prospective, observational, multicentric trial conducted at 10 major reference hospitals in Spain from June 2017 to December 2020. The management of patients was carried out according to the protocols established by each participating center, including ICU admission. This multicenter prospective observational study was endorsed by the Spanish Investigational Network Gynecologic Oncology Group (Spain-GOG) and was registered at ClinicalTrials.gov with reference number NCT03131492.

2.1 | Inclusion and exclusion criteria

Patients were included if they were aged ≥18 years and diagnosed with AOC (FIGO stages III–IV), undergoing primary debulking surgery, interval surgery, or secondary debulking surgery for recurrence. Surgery had to include a bowel resection with mechanical or manual anastomosis. Patients undergoing an emergency surgery or those who developed a surgical infection were excluded from the study. The inclusion of patients who had a protective ileostomy were minimized to less than 10% in order to avoid potential bias related to minor AL symptoms associated to this procedure, although protective ileostomies have not shown to improve the frequency of AL.

2.2 | Study procedures

The eligibility of patients for inclusion in the study was evaluated at the preoperative visit. Eligible patients underwent a preoperative baseline CRP and PCT serum determination, assessment of albumin as a nutritional status marker, and carbohydrate antigen (CA)-125 levels.

Regarding the policy of bowel resections, we contemplated a Hudson procedure if rectosigmoid involvement was superficial. When there was evidence of deeper or muscular layer involvement, we proceeded to perform a bowel resection, independently of the need of other intestinal resections, in order to achieve a complete cytoreduction.

During the postoperative period, the following variables were collected: daily registry (3 measurements per day) of clinical parameters (blood pressure, heart and respiratory rates, oxygen saturation, pain according to the visual analog scale [VAS] scale, diuresis and peristalsis) from the first postoperative day (POD) until discharge, and daily blood tests from POD 1 to 6 (red and white blood cell count, Na^+, K^+, Cl^-, glucose, urea, creatinine, coagulation markers, CRP and PCT). PCT concentration was determined by immunoassay (BRAHMS PCT reagent) with an ADVIA Centaur CP Immunoassay System (Siemens). Although the PCT samples were processed by different instruments in the participating centers, they were all calibrated to the BRAHMS standard, allowing for a combined data analysis. CRP concentration was measured by immunoturbidimetry (Olympus AU5400 equipment, Beckman Coulter). As CRP measurements could not be rigorously standardized and correlated between the different instruments used in the participating centers, only data obtained from the same instruments were pooled from two hospitals.

Sepsis is caused by a systemic inflammatory response syndrome (SIRS) secondary to infection, and, when associated with organ dysfunction, produces several life-threatening complications. The criteria for sepsis diagnosis included the presence of one or more of the following: fever >38.5°C, hypothermia <36°C, heart rate >90 bpm, tachypnea >20 breaths/min, altered mental status, significant edema (positive fluid balance), hyperglycemia (plasma glucose >120 mg/dL), leukocytosis (>12 000/μL), leukopenia (<4000/μL), and normal leukocyte count with more than 10% immature forms. When the sepsis criteria were met,[23] the following sites were evaluated for infection: the wound (examination and sample for microbiology), the lung (X-ray/computed tomography [CT]), the urinary tract (sediment/culture), and the abdomen or pelvis (CT or abdominal ultrasound).

If AL was suspected clinically, a CT-enema with water-soluble contrast (Gastrografin) was performed.[24] In some of the participating centers, a rectal examination with rectoscopy was also carried out. An elevation of CRP and/or PCT levels without a clinical suspicion for AL was not an indication to perform an imaging technique. Management of the AL depended on the colorectal surgery protocols of each participating center. All patients diagnosed with AL were excluded from the study after treatment. All intraoperative and early postoperative complications (<30 days) were reported using the Clavien–Dindo classification.[25]

Patients were followed up in the clinic one week after discharge with a physical examination and a blood test including blood count, hemostasis study and basic biochemistry, and at 30 days postoperatively just for anamnesis and physical examination.

2.3 | Statistical analyses

The sample size determination was based on data from previous published studies, which indicated that the AL rate in patients undergoing surgery for AOC with rectal-sigmoid resection was 7%. Assuming an area under the curve (AUC) >0.80 in the receiving operator characteristic (ROC) analysis, both for PCT and CRP, with a power of 95%, a total of 70 patients were required. Continuous variables are expressed as mean and standard deviations, while

categorical variables are expressed as absolute numbers and percentages. To analyze the reliability of the analytical variables (PCT, CRP) as possible diagnostic tests for the early detection of AL, ROC curves were analyzed, and the AUC was calculated for each of the variables. The sensitivity, specificity, NPV, and PPV of these parameters were assessed. Statistical significance was set at $p < 0.05$. Stata statistical software (version 16) was used for data analysis.

3 | RESULTS

A total of 92 patients out of 133 cytoreductive surgeries for AOC performed during the study period were included in the study as they met the inclusion criteria (Figure 1). The demographic and clinical characteristics are shown in Table 1. Bowel resection rate in cytoreductive surgery was 58%. A total of 55 patients (59.8%) underwent primary cytoreductive surgery. The most common type of bowel resection was rectosigmoid in 81 patients (88.0%), and seven patients (7.6%) underwent ileostomy. The ERAS protocol was applied to half of the patients (48.9%) and the median LOS was 8 days (range 4–57). A total of 41 patients (48.5%) required ICU admission.

AL was diagnosed in six patients (6.5%) between postoperative days 2 and 5. All patients with AL underwent surgical treatment. The median LOS in patients with AL was 25 days. Five of the AL occurred in patients with multiple bowel resections (rectosigmoid and ileocolic), and one patient had undergone a left hemicolectomy.

It was not possible to assess survival data because follow-up was limited to 30 days-postoperatively.

Serum levels of PCT ($N = 92$) peaked at POD 1 (Figure 2A). Higher serum levels were observed in patients who had AL at all timepoints during the postoperative period. The ROC analysis for PCT and CRP for the diagnosis of AL in the first five PODs is summarized in Table 2. The maximum AUC for PCT was observed at POD 1 (AUC = 0.823, 95% CI: 0.594–1.000) with a cutoff level at 3.8 ng/mL for predicting AL, with a sensitivity of 83.3%, a specificity of 81.3%, PPV of 25.0%, NPV of 98.5, and a false positive rate of 18.7%. The ROC curve for PCT on POD 1 for the diagnosis of AL is shown in Figure 3A.

In the analysis of CRP serum levels, only the results from two hospitals which used comparable CRP determination methodologies were considered ($N = 56$). Mean levels of CRP increased for patients with and without AL up to POD 2, and then gradually decreased for both groups (Figure 2B). However, patients with AL consistently presented higher levels of CRP compared with patients without AL. The maximum AUC for CRP was observed at POD 3 (AUC = 0.833, 95% CI: 0.727–0.939) with a cutoff level at 30.5 mg/dL for predicting AL, and a sensitivity of 100%, specificity of 80.4%, PPV of 28.6%, a NPV of 100% and a false positive rate of 19.6%. The ROC curve for CRP on POD 3 for the diagnosis of AL is shown in Figure 3B.

4 | DISCUSSION

In this study we analyzed the utility of PCT and CRP to evaluate the risk of AL after surgery for AOC and concurrent intestinal resection. The results show that both PCT and CRP levels were raised in patients with AL compared to patients without AL, suggesting that both markers could be of value for the diagnosis of this postsurgical complication. This is the first study analyzing the possible use of early inflammatory markers to detect infectious complications in the context of AOC surgery with bowel resection.

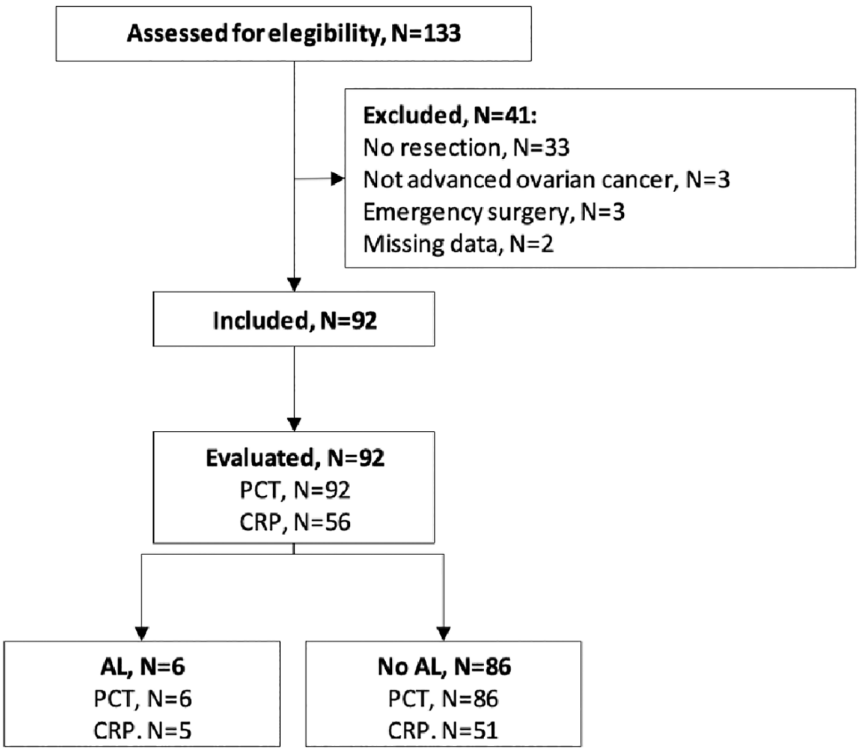

FIGURE 1 Flow chart of the study. AL, anastomotic leak; CRP, C-reactive protein; PCT, procalcitonin.

TABLE 1 Patient characteristics and surgery ($N=92$).

Variable	$N=92$
Age (years), mean (SD)	59.9 (11.7)
BMI (kg/m^2), mean (SD)	25.3 (4.21)
Smoker, *N* (%)	7 (7.6)
FIGO stage, *N* (%)	
IIIA	10 (10.9)
IIIB	8 (8.7)
IIIC	55 (59.8)
IV	19 (20.7)
Type of surgery, *N* (%)	
Primary cytoreduction	55 (59.8)
Interval	19 (20.7)
Secondary cytoreduction	18 (19.6)
Histology, *N* (%)	
Serous	77 (83.7)
Endometrioid	8 (8.7)
Clear cell	4 (4.3)
Other	3 (3.3)
CA-125, U/mL	463.8 (698.0)
Bowel resection, *N* (%)	
Rectosigmoid	81 (88.0)
Right ileocolic	12 (13.0)
Right hemicolectomy	1 (1.1)
Left hemicolectomy	2 (2.2)
Transversectomy	1 (1.1)
Small bowel resection	4 (4.3)
Appendectomy	19 (20.7)
Cytoreduction, *N* (%)	
Complete	85 (92.4)
Optimal	6 (6.5)
Suboptimal	1 (1.1)
Ileostomy, *N* (%)	7 (7.6)
ERAS protocol, *N* (%)	45 (48.9)
Anastomotic leak, *N* (%)	6 (6.5)
Blood transfusions per patient, median (SD)	2 (1.6)
ICU admissions, *N* (%)	41 (44.6)
Length of hospital stay (days), median (range)	8 (5–57)
Readmission in 30 days	7 (7.6)
Death in 30 days	1 (1.1)
Aletti complexity score, mean (range)	9 (6–14)

Abbreviations: BMI, body mass index; ERAS, enhanced recovery after surgery; FIGO, the International Federation of Gynecology and Obstetrics; ICU, intensive care unit.

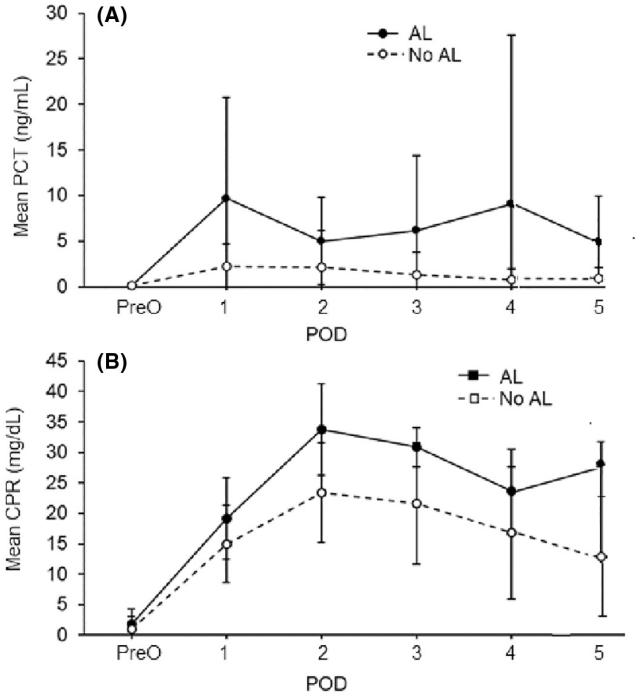

FIGURE 2 Mean procalcitonin (PCT) (A) and C-reactive protein (CRP) (B) serum concentrations in the preoperative phase and the postoperative days 1–5, for patients presenting anastomotic leak or no anastomotic leak. Bars indicate standard deviation.

PCT and CRP have been used as serum markers of infection and sepsis in cancer patients.[26,27] Recently, they have also been associated with COVID-19 severity in gynecologic cancer patients.[28] Numerous studies have shown the predictive power of PCT and CRP in the early detection of AL after colorectal surgery.[11–16] However, there is still no consensus as to the best cutoff value to consider the measurements as being positive or negative for AL, or the best POD to measure these markers. Several meta-analyses have reported that the optimal cutoff values for PCT could range from 0.17 to 68 ng/mL on PODs 3–5, and for CRP from 9.4 to 19.0 mg/dL on PODs 3–4.[11,12,29] Also, in an effort to identify the risk of AL as early as possible after surgery, a recent study reported that a NPV of 99% could be obtained at POD 3 with the combination of both markers (cutoff values of 2.5 ng/mL for PCT and 16.3 mg/dL for CRP).[15] Although our results in ovarian cancer surgery cannot be directly compared with those obtained in the context of laparoscopic surgery for colorectal cancer treatment, they suggest that the measurement of PCT and CRP could be indicative of AL even earlier in the postoperative period. Thus, in our study, we found that levels of PCT above 3.8 ng/mL on POD 1 could be indicative of AL with a NPV of 98.5%, and that a cutoff of value 30.5 mg/L for CRP at POD 3 achieved a NPV of 100% for predicting AL.

It should be noted that the measurement of CRP is strongly dependent on the technique used, and therefore comparison of results must be viewed with caution. In contrast, PCT is standardized across laboratories and the absolute values can be combined or compared. For both markers, isolated increments in measured concentrations are not enough for the diagnosis of postoperative complications, given that some patients without AL could present severe inflammatory responses associated to the disease and the surgical intervention itself. Therefore, a combination of biomarkers would be

TABLE 2 Receiver operator characteristic (ROC) analysis for the diagnosis of AL in women undergoing surgery for advanced ovarian cancer with bowel or colorectal resection.

	POD	AUC	95% CI	Cutoff value	Sensitivity	Specificity	PPV	NPV
PCT	1	0.823	0.594–1.000	3.8	83.3	81.3	25.0	98.5
	2	0.795	0.542–1.000	2.5	83.3	79.8	22.7	98.5
	3	0.805	0.510–1.000	2.3	80.0	88.2	28.6	98.7
	4	0.805	0.506–1.000	1.4	80.0	90.5	33.3	98.7
	5	0.984	0.948–1.000	2.1	100.0	95.1	42.9	100.0
CRP	1	0.671	0.375–0.967	20.0	80.0	58.3	16.7	96.6
	2	0.828	0.603–1.000	34.5	80.0	88.2	40.0	97.8
	3	0.833	0.727–0.939	30.5	100.0	80.4	28.6	100.0
	4	0.799	0.651–0.947	23.7	100.0	64.7	18.2	100.0
	5	0.905	0.821–0.989	24.9	100.0	87.8	33.3	100.0

Abbreviations: AL, anastomotic leak; AUC, area under the curve; CI, confidence interval; CRP, C-reactive protein; NPV, negative predictive value; PCT, procalcitonin; POD, postoperative day; PPV, positive predictive value.

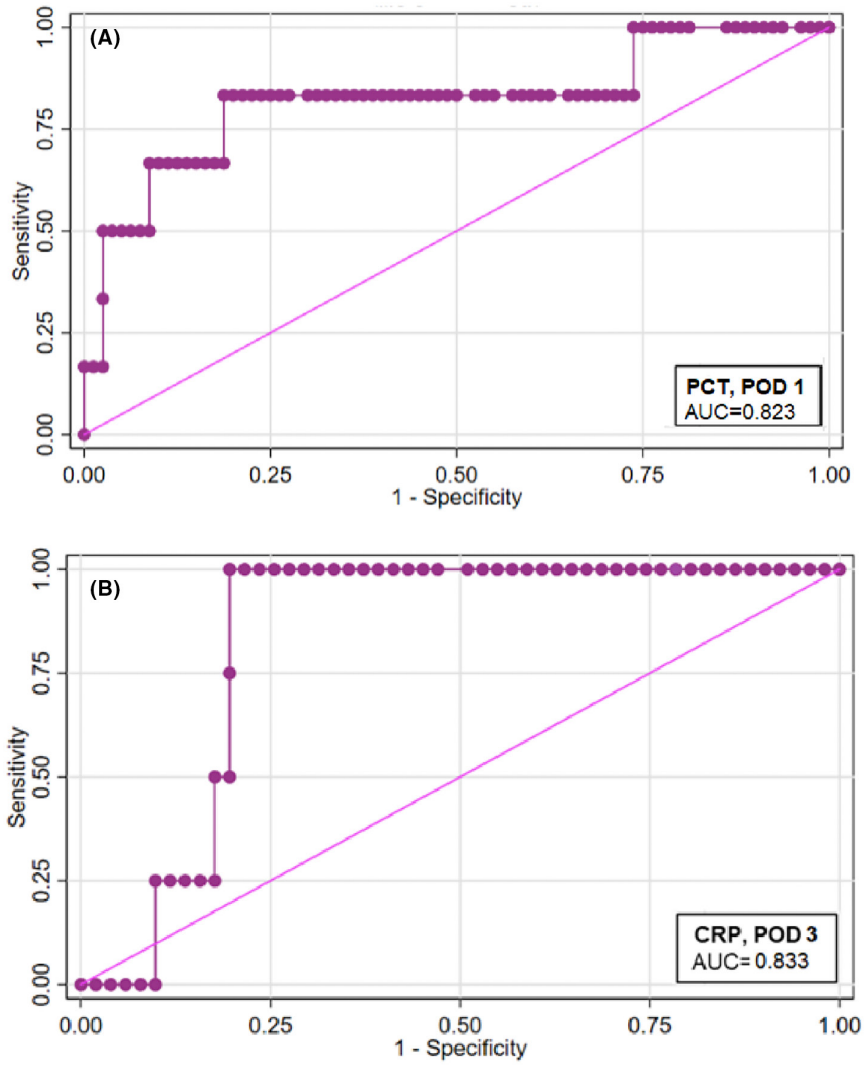

FIGURE 3 Plot of the receiving operator characteristic curve of the procalcitonin (PCT) in postoperative day (POD) 1 (A) and C-reactive protein (CRP) in POD 3 (B) for the diagnosis of anastomotic leak after surgery for advanced ovarian cancer with intestinal resection.

necessary to improve predictive accuracy. Some predictive models for complications have been described in ovarian cancer surgery and the incorporation of these biomarkers to the clinical models could improve their accuracy.[30] If an early discharge is sought, especially in the context of ERAS programs, then a high NPV of AL at an early postoperative time is necessary.[15,20]

Inflammatory processes are closely associated with cancer and increased levels of CRP and other inflammatory markers have been

associated with a subsequent increased risk of ovarian cancer.[21,31] High CRP levels in plasma have been correlated with stage and tumor size in epithelial ovarian cancer, suggesting that CRP could be valuable in the diagnosis of the disease.[32,33] Similarly, serum PCT levels are higher in cancer patients compared with noncancer patients, but these increments depend mainly on the type of cancer and the stage of the disease.[26] For these reasons, studies must be conducted to analyze PCT and CRP measurements as predictors of infectious complications after surgery in the context of each specific tumor. In this regard, the present study is the first to analyze these parameters prospectively and in multiple centers in patients with AOC in which an intestinal resection was performed during surgery.

In our study we found that only six patients developed AL (6.2%), results that are in line with those reported by others with an incidence rate of AL of 1.4%–6.8% after colorectal resection in ovarian cancer surgery.[34] Interestingly, these rates are lower than those observed in colorectal surgery for bowel tumors, from 1.2% to 15%, which again underlines the importance of studying the utility of these biomarkers specifically in surgery for AOC.[34] Unfortunately, due to the low number of AL in our study, no conclusions could be drawn about the preoperative value of these markers or the impact of different types of cytoreductive surgery (primary, interval debulking and secondary) on the results.

In addition, several authors have highlighted the utility of nomograms to estimate the risk of AL after resection of rectosigmoid colon in ovarian cancer based on clinical factors, such as diabetes, cosurgery of distal pancreatectomy, macroscopic residual tumor, and anastomotic level from the anal verge shorter than 10 cm.[35] These factors and others such as age, serum albumin level or number of bowel resections are considered on daily practice to perform a protective stoma and to prevent the consequences of AL.[5] In this regard, we believe future studies of models combining these well-known clinical variables and postoperative biomarkers such as PCT and CRP could improve the prediction of AL and help clinicians in their daily practice.

Finally, it should be noted that the use of these early postoperative biomarkers should not substitute surgical techniques used for the evaluation of the anastomosis integrity, such as methylene blue injection, sigmoidoscopic intraoperative evaluation of the anastomosis, air leak tests,[36] and indocyanine green (ICG) combined with fluorescent near-infrared imaging.[37] Also, in the postoperative setting, the usefulness of transvaginal ultrasound with serum insufflation as a minimally invasive method for detecting AL is currently being evaluated.[38]

The main strengths of this study were its novelty, as the use of PCT and CRP as markers of AL in the context of AOC had not previously been explored, and that it included more than one center. However, the study had some limitations that should be considered. The main limitation was the small number of patients that developed AL ($N = 6$, 6.2%), which, although in a proportion similar to recent publications,[34,39] considerably constrained the statistical analysis. Also, the heterogeneity of the patients included (eg, with respect to tumor stage) could have obscured differences between groups or generated an overestimation of the variation between patients, and we did not study the correlation between factors such as tumor stage or surgical complexity and PCT and CRP levels. Follow up until 30 days postoperatively did not allow long-term survival data to be assessed.

The results of this study suggest a possible preliminary algorithm for the postoperative management of patients undergoing surgery for AOC and concurrent intestinal resection. We suggest that on POD 1 all patients should be tested for PCT, and if the result is superior to 3.8 ng/mL, the test should be repeated on POD 4. If the PCT result on POD 4 is superior to 1.4 ng/mL, then a water-soluble contrast enema CT should be conducted to determine the occurrence of AL. This algorithm should be validated in future clinical trials.

5 | CONCLUSION

This study showed that PCT and CRP are potential biomarkers for AL in the context of debulking surgery for AOC and concomitant bowel resection very early after surgery. The high NPV could suggest their use in patients following ERAS programs. Future prospective studies with a higher number of patients are required to confirm our results.

AUTHOR CONTRIBUTIONS

José Luis Sánchez-Iglesias and Antonio Gil-Moreno: Conceptualization, methodology, investigation, writing—original draft, writing—review and editing. Clara Morales-Coma: Methodology, investigation, writing—review and editing. Lucas Minig, Víctor Lago, Santiago Domingo, Gemma Mancebo, Jaime Siegrist, María Soledad Fidalgo García, Antoni Llueca, Anna Serra, Paloma Cobas Lozano, Arantza Lekuona Artola, Natalia R. Gómez-Hidalgo, Úrsula Acosta, Roser Ferrer-Costa, Melissa Bradbury and Assumpció Pérez-Benavente: Investigation, writing—review and editing.

ACKNOWLEDGMENTS

Santiago Pérez-Hoyos conducted the data analysis as a member of the Vall d'Hebron Research Institute (VHIR).

FUNDING INFORMATION

The study received funding from Vall d'Hebron Research Institute (VHIR) for statistical analysis and medical writing support that was provided by Francisco López de Saro (Trialance SCCL).

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest relative to this study.

ETHICS STATEMENT

The study was approved by the Ethical and Clinical Research Committee of Vall d'Hebron University Hospital on March 9, 2017, with reference no. PR(AMI)68/2017, and at each participating

hospital, and was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). All patients provided informed consent.

ORCID

José Luis Sánchez-Iglesias https://orcid.org/0000-0002-4542-3969
Víctor Lago https://orcid.org/0000-0002-2971-1899
Antoni Llueca https://orcid.org/0000-0003-3723-8795
Úrsula Acosta https://orcid.org/0000-0001-8887-544X
Antonio Gil-Moreno https://orcid.org/0000-0003-1106-5590

REFERENCES

1. Coleridge SL, Bryant A, Kehoe S, Morrison J. Neoadjuvant chemotherapy before surgery versus surgery followed by chemotherapy for initial treatment in advanced ovarian epithelial cancer. *Cochrane Database Syst Rev*. 2021;7:CD005343.
2. Jaeger W, Ackermann S, Kessler H, Katalinic A, Lang N. The effect of bowel resection on survival in advanced epithelial ovarian cancer. *Gynecol Oncol*. 2001;83:286-291.
3. Stefanović A, Jeremić K, Kadija S, et al. Intestinal surgery in treatment of advanced ovarian cancer—review of our experience. *Eur J Gynaecol Oncol*. 2011;32:419-422.
4. Peiretti M, Bristow RE, Zapardiel I, et al. Rectosigmoid resection at the time of primary cytoreduction for advanced ovarian cancer. A multi-center analysis of surgical and oncological outcomes. *Gynecol Oncol*. 2012;126:220-223.
5. Lago V, Fotopoulou C, Chiantera V, et al. Risk factors for anastomotic leakage after colorectal resection in ovarian cancer surgery: a multi-centre study. *Gynecol Oncol*. 2019;153:549-554.
6. Mourton SM, Temple LK, Abu-Rustum NR, et al. Morbidity of rectosigmoid resection and primary anastomosis in patients undergoing primary cytoreductive surgery for advanced epithelial ovarian cancer. *Gynecol Oncol*. 2005;99:608-614.
7. Richardson DL, Mariani A, Cliby WA. Risk factors for anastomotic leak after recto-sigmoid resection for ovarian cancer. *Gynecol Oncol*. 2006;103:667-672.
8. Gruner M, Chambers LM, Yao M, et al. Anastomotic leak following interval debulking surgery with or without hyperthermic intraperitoneal chemotherapy in women with advanced epithelial ovarian cancer. *Gynecol Oncol*. 2021;162:645-651.
9. Louis M, Johnston SA, Churilov L, Ma R, Christophi C, Weinberg L. Financial burden of postoperative complications following colonic resection: a systematic review. *Medicine (Baltimore)*. 2021;100:e26546.
10. Wright JD, Herzog TJ, Neugut AI, et al. Effect of radical cytoreductive surgery on omission and delay of chemotherapy for advanced-stage ovarian cancer. *Obstet Gynecol*. 2012;120:871-881.
11. Gans SL, Atema JJ, van Dieren S, Groot Koerkamp B, Boermeester MA. Diagnostic value of C-reactive protein to rule out infectious complications after major abdominal surgery: a systematic review and meta-analysis. *Int J Colorectal Dis*. 2015;30:861-873.
12. 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;264:252-256.
13. Facy O, Paquette B, Orry D, et al. Diagnostic accuracy of inflammatory markers As early predictors of infection after elective colorectal surgery: results from the IMACORS study. *Ann Surg*. 2016;263:961-966.
14. Giaccaglia V, Salvi PF, Antonelli MS, et al. Procalcitonin reveals early dehiscence in colorectal surgery: the PREDICS study. *Ann Surg*. 2016;263:967-972.
15. Muñoz JL, Alvarez MO, Cuquerella V, et al. Procalcitonin and C-reactive protein as early markers of anastomotic leak after laparoscopic colorectal surgery within an enhanced recovery after surgery (ERAS) program. *Surg Endosc*. 2018;32:4003-4010.
16. Messias BA, Botelho RV, Saad SS, Mocchetti ER, Turke KC, Waisberg J. Serum C-reactive protein is a useful marker to exclude anastomotic leakage after colorectal surgery. *Sci Rep*. 2020;10:1687.
17. Straatman J, Harmsen AM, Cuesta MA, Berkhof J, Jansma EP, van der Peet DL. Predictive value of C-reactive protein for major complications after major abdominal surgery: a systematic review and pooled-analysis. *PLoS One*. 2015;10:e0132995.
18. Agarwal R, Rajanbabu A, Nitu PV, Goel G, Madhusudanan L, Unnikrishnan UG. A prospective study evaluating the impact of implementing the ERAS protocol on patients undergoing surgery for advanced ovarian cancer. *Int J Gynecol Cancer*. 2019;29:605-612.
19. Sánchez-Iglesias JL, Carbonell-Socias M, Pérez-Benavente MA, et al. PROFAST: a randomised trial implementing enhanced recovery after surgery for highcomplexity advanced ovarian cancer surgery. *Eur J Cancer*. 2020;136:149-158.
20. Sánchez-Iglesias JL, Gómez-Hidalgo NR, Pérez-Benavente A, et al. Importance of enhanced recovery after surgery (ERAS) protocol compliance for length of stay in ovarian cancer surgery. *Ann Surg Oncol*. 2021;28(13):8979-8986.
21. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. *Nature*. 2008;454:436-444.
22. Browning L, Patel MR, Horvath EB, Tawara K, Jorcyk CL. IL-6 and ovarian cancer: inflammatory cytokines in promotion of metastasis. *Cancer Manag Res*. 2018;10:6685-6693.
23. American College of Chest Physicians/Society of Critical Care Medicine. Consensus conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med*. 1992;20:864-874.
24. Watkins DT, Robertson CL. Water-soluble radiocontrast material in the treatment of postoperative ileus. *Am J Obstet Gynecol*. 1985;152:450-455.
25. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien–Dindo classification of surgical complications: five-year experience. *Ann Surg*. 2009;250:187-196.
26. Sbrana A, Torchio M, Comolli G, Antonuzzo A, Danova M. Italian Network for Supportive Care in Oncology (NICSO). Use of procalcitonin in clinical oncology: a literature review. *New Microbiol*. 2016;39:174-180.
27. Chaftari P, Qdaisat A, Chaftari AM, et al. Prognostic value of procalcitonin, C-reactive protein, and lactate levels in emergency evaluation of cancer patients with suspected infection. *Cancers (Basel)*. 2021;13:4087.
28. Smith M, Lara OD, O'Cearbhaill R, et al. Inflammatory markers in gynecologic oncology patients hospitalized with COVID-19 infection. *Gynecol Oncol*. 2020;159:618-622.
29. Su'a BU, Mikaere HL, Rahiri JL, Bissett IB, Hill AG. Systematic review of the role of biomarkers in diagnosing anastomotic leakage following colorectal surgery. *Br J Surg*. 2017;104:503-512.
30. Llueca A, Serra A, Maiocchi K, et al. Predictive model for major complications after extensive abdominal surgery in primary advanced ovarian cancer. *Int J Womens Health*. 2019;11:61-167.
31. Trabert B, Pinto L, Hartge P, et al. Pre-diagnostic serum levels of inflammation markers and risk of ovarian cancer in the prostate, lung, colorectal and ovarian cancer (PLCO) screening trial. *Gynecol Oncol*. 2014;135:297-304.
32. Lu Y, Huang S, Li P, et al. Prognostic evaluation of preoperative serum C-reactive protein concentration in patients with epithelial ovarian cancer. *Exp Ther Med*. 2015;9:2003-2007.
33. Yang D, Li H, Sun X, Yang S, Wang K, Liu Z. Clinical usefulness of high levels of C-reactive protein for diagnosing epithelial ovarian cancer. *Sci Rep*. 2020;10:20056.

34. Mereu L, Dalprà F, Berlanda V, et al. Anastomotic leakage after colorectal surgery in ovarian cancer: drainage, stoma utility and risk factors. *Cancer*. 2022;14:6243.
35. Kim JH, Han WH, Lee DE, et al. Anastomotic leakage after resection of the rectosigmoid colon in primary ovarian cancer. *J Ovarian Res*. 2023;29(16):85.
36. Kryzauskas M, Bausys A, Dulskas A, et al. Comprehensive testing of colorectal anastomosis: results of prospective observational cohort study. *Surg Endosc*. 2022;36:6194-6204.
37. de Nardi P, Elmore U, Maggi G, et al. Intraoperative angiography with indocyanine green to assess anastomosis perfusion in patients undergoing laparoscopic colorectal resection: results of a multicenter randomized controlled trial. *Surg Endosc*. 2020;34:53-60.
38. Lago V, Montesinos-Albert M, Segarra-Vidal B, et al. ECO-LEAK technique: early detection of colorectal anastomotic leakage by transvaginal ultrasound. *Int J Gynecol Cancer*. 2023;33(4):631-632.
39. Llueca A, Serra A, Climent MT, et al. Postoperative intestinal fistula in primary advanced ovarian cancer surgery. *Cancer Manag Res*. 2021;13:13-23.

How to cite this article: Sánchez-Iglesias JL, Morales-Coma C, Minig L, et al. Procalcitonin and C-reactive protein as early markers of anastomotic leakage in intestinal resections for advanced ovarian cancer (EDMOCS). *Acta Obstet Gynecol Scand*. 2024;103:1302-1310. doi:10.1111/aogs.14834