

# The Role of Serum Interleukin-6 Levels in Prognosticating Postoperative Complications After Cytoreductive Surgery for Ovarian Cancers: A Prospective Observational Study

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## Abstract

**Background:** Interleukin-6 (IL-6), a pro-inflammatory cytokine, has been associated with adverse prognosis in ovarian cancer. Cytoreductive surgery for ovarian cancer has a higher risk of postoperative surgical complications (POCs). We aimed to find out if serum IL-6 is elevated preoperatively in patients undergoing cytoreductive surgery for ovarian cancer and if it can predict POCs. We also compared its trend with serum C-reactive protein (CRP) in the early postoperative period.

**Materials and Methods:** Fifty-one patients between 18–75 years, posted for elective ovarian cytoreductive surgery at a tertiary cancer hospital were included after taking informed consent. Serum IL-6 and CRP were done the day before surgery and repeated 24 and 72 hours post-surgery. All parameters that affect POCs were captured. POCs were graded using the Clavein Dindo classification. We recorded the length of the intensive care unit (ICU), hospital stay, and 30-day mortality. Appropriate statistical tests were used and p value <0.05 was considered significant.

**Results:** Out of 51 enrolled patients, 46 were included for data analysis after exclusions. The mean age of patients in this study was 49.76 +/- 12.42 years with a mean surgical duration of 302.39 +/- 127.04 minutes and mean blood loss of 332.6 +/- 274.71 mL. The incidence of POCs in our study was 21.7% (10/46 patients). Preoperative IL-6 was raised and was able to predict POCs with 70% sensitivity and 86% specificity at a cutoff value of 23.56 pg./mL ( $R^2 = 0.71$ ; AUC = 0.79). In patients who developed POCs, IL-6 values (1196.7 +/- 1461.4 pg./mL) peaked at 24 hours whereas CRP values (360 +/- 430.1 mg/L) peaked at 72 hours; thus, allowing early prognostication with IL-6. The cut-off value of serum IL-6 at 24 hours to predict POCs is 480 pg./mL ( $R^2 = 0.50$ ; AUC = 0.79) with 80% sensitivity and 89% specificity. Two patients died - on postoperative days 5 and 28 respectively.

**Conclusion:** Preoperative IL-6 is raised in patients with ovarian cancer posted for cytoreductive surgery. A cut-off value of 23.56 pg./mL preoperatively and 480 pg./mL at 24 hours after surgery could predict postoperative surgical complications.

**Keywords:** C-reactive protein, Interleukin-6, Ovarian cancer, Postoperative surgical complications

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## Introduction

Interleukin-6 (IL-6) is an acute-phase cytokine, with a pro-inflammatory character. Raised serum IL-6 levels have been associated with acute and chronic inflammatory conditions including cancer (1). An elevated serum IL-6 level has been associated with an adverse prognosis in patients with different types of cancers, including ovarian cancer. In ovarian cancer, IL-6 activation has been shown to promote tumor cell growth and metastasis (2). The IL-6/IL-6 receptor pathway has also gained interest as a therapeutic target in ovarian cancer (3). But there is limited literature on the perioperative role of IL-6 in patients with ovarian cancer undergoing cytoreductive surgery. Cytoreductive surgery for ovarian cancer is associated with a higher incidence of 30-day postoperative morbidity (up to 34%) (4). This can significantly affect the hospital stay, cost, and psychological well-being of the patient. Any preoperative parameter that can help risk stratify these patients would be helpful for the clinician as well as the family in taking a prudent decision. There is limited literature evaluating the perioperative changes in the serum IL-6 levels during cytoreductive surgery for ovarian cancer and its relation to postoperative surgical complications (POCs). Our primary aim was to find out if serum IL-6 is elevated preoperatively in patients undergoing cytoreductive surgery for ovarian cancer. Our secondary aim was to see if preoperative serum IL-6 can predict POCs and compare it with C-reactive protein (CRP).

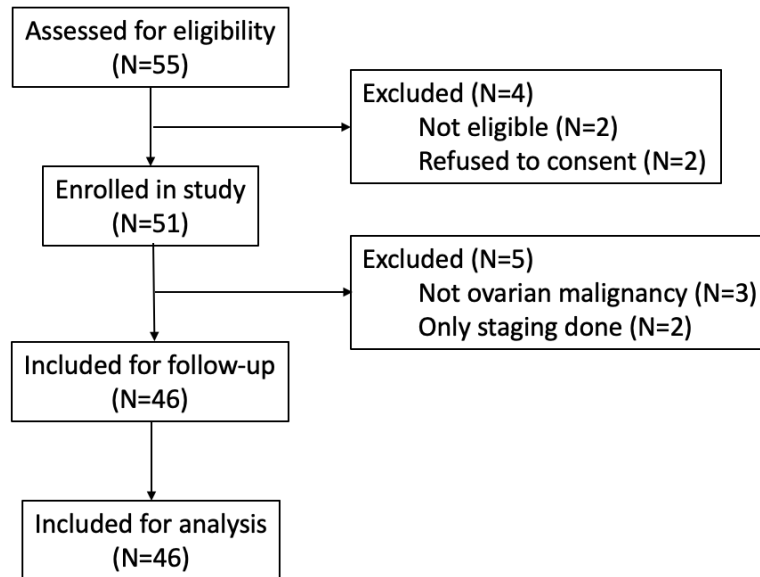
## Methods

This prospective observational study was performed in our tertiary cancer care hospital by the declaration of Helsinki. The study was approved by the institutional ethics committee (IEC/2017/27) and CTRI registration (CTRI/2018/04/013162) was done. Fifty-one patients between 18–75 years and undergoing elective cytoreductive surgery between March 2017 to February 2018 for ovarian cancer were enrolled. Patients were excluded if the ovarian mass was benign on an intraoperative frozen section or cytoreductive surgery not done given extensive disease. A written informed consent was taken. A pre-anesthetic

evaluation was done as per institutional protocol and baseline parameters like demographics, ASA class, ECOG status, and comorbidities were noted. Preoperative investigations included complete blood count, prothrombin time, fasting blood glucose, serum creatinine, serum albumin, and viral screening at the minimum. Further investigations based on the patient's comorbidities were done as deemed necessary and medical conditions were optimized before surgery. Pre-operatively IL-6 & CRP were measured on the day before surgery and were repeated at 24 hours and 72 hours after surgery. IL-6 was measured by electrochemiluminescence immunoassay technique (Elecsys & Cobas e-analyzer). CRP was done by slide agglutination technique. The normal values were IL-6 < 7 pg/mL and CRP < 6 mg/mL. Simultaneous measurement of total leucocyte count (TLC) was available and captured. Preoperative tumor markers like CA-125, CEA, AFP & beta HCG (as appropriate) were also captured.

All patients underwent cytoreductive surgery under general anesthesia along with epidural analgesia as per the institutional protocol. Cytoreductive surgery included - total abdominal hysterectomy, bilateral salpingo-oophorectomy, peritonectomy, and omentectomy. Additional procedures like locoregional lymph node dissection, appendectomy, cholecystectomy, splenectomy, bowel resection, and anastomosis were performed when deemed necessary. Vital signs monitoring was done and maintained within 30% of the baseline. Intraoperative fluids were administered based on the extent of surgery and blood loss. Vasopressor medications were started to maintain blood pressure if needed. A blood transfusion was given to target intraoperative hemoglobin above 8 gm/dL. Parameters that can affect POCs like the duration of surgery, blood loss, need for vasopressors, and transfusions were noted. The surgical staging was done according to the International Federation of Gynecologists and Obstetricians (FIGO) guidelines, postoperative tumor grade and histology were noted. All patients were transferred postoperatively to the surgical intensive care unit (SICU). The treatment and care in the SICU were based on the existing protocols and the discretion of the treating doctors.

The postoperative course was monitored for complications, length of ICU, hospital stay, and 30-day



**Figure 1.** Patient study flow diagram.

mortality. All POCs were recorded as per the Clavien-Dindo classification of surgical complications (5) and analyzed as shown in Appendix 1. Clavien Dindo classes 1 and 2 were considered as no complications (MOD CD class 0) and classes 3 and above were considered as the presence of complications (MOD CD class 1). Patients were moved out of ICU when hemodynamically stable and had no oxygen requirement. Patients were discharged from the hospital when able to tolerate orals, ambulate, low drain output, was afebrile, and had acceptable pain control. All patients were followed up till postoperative day 30 for morbidity and mortality.

Data were analyzed and continuous variables are presented as mean  $\pm$  standard deviation whereas categorical data as ratios or percentages. A  $p$ -value  $< 0.05$  was considered statistically significant. Linear mixed models were used to look at changes in TLC, CRP, and IL-6 over time. The model included fixed effects for the MOD CD class, time, and the MOD CD Class with time interaction. In this, time was modeled as categorical, and a random subject effect was included. Tukey's method corrected for multiple comparisons between pairwise comparisons. SAS software version 9.4 was used for data analysis (SAS Institute Inc., Cary, NC).

## Results

Figure 1 depicts the patient study flow diagram for this observational study. Of the 55 consecutive patients assessed for eligibility, 2 patients did not match the inclusion criteria and 2 patients refused consent. 51 patients were enrolled and underwent surgery and 5 patients were excluded at the end of surgery. 3 were excluded as the intraoperative frozen section did not confirm an ovarian malignancy and two patients underwent only diagnostic laparoscopy and staging given extensive disease. Hence, data from 46 patients were analyzed in this study cohort. Table 1 depicts the demographic details of the patients included. The mean age of patients in this study was  $49.76 \pm 12.42$  years with a mean surgical duration of  $302.39 \pm 127.04$  minutes and mean blood loss of  $332.6 \pm 274.71$  mL. The mean preoperative serum IL-6 value in our patient cohort was raised ( $24.97 \pm 50.43$  pg/mL). The incidence of POCs (MOD CD class 1) in our study was 21.7% (10/46 patients). Figure 2a depicts the ROC curve of preoperative IL-6 values for predicting patients who developed POCs. It has an  $R^2$  value of 0.7

**Table 1:** Patient demographics and characteristics (n=46).

Patient characteristics	Mean (+/- SD) or n
Age (years)	49.76 (+/- 12.42)
ASA class I/II/III (n)	0/44/2
ECOG performance status 0/1/2/3 (n)	1/37/7/1
Comorbidities – HTN, DM, CAD, Asthma, Hypothyroid (n)	9/5/3/2/4
Preoperative chemotherapy Y/N (n)	32/14
Preoperative haemoglobin (gm/dL)	11.23 (+/- 1.29)
Preoperative serum albumin (mg/dL)	3.97 (+/- 0.44)
Preoperative serum creatinine (mg/dL)	0.62 (+/- 0.14)
Preoperative IL-6 (pg./mL)	24.97 (+/- 50.43)
Surgical stage FIGO I/II/III/IV (n)	9/2/33/2
Duration of surgery (mins)	302.39 (+/- 127.04)
Blood loss (mL)	332.6 (+/- 274.71)
Clavien Dindo class at discharge 1/2/3/4/5 (n)	24/12/7/2/1
MOD CD class 0/1 (n)	36/10
ICU stay (hours)	96 (+/- 101.42)
Hospital stay (days)	9.56 (+/- 6.38)
30-day mortality Alive/dead (n)	44/2

SD: Standard deviation; n: Number of patients; ASA: American Society of Anaesthesiologists; ECOG: Eastern Cooperative Oncology Group; HTN: Hypertension; DM: Diabetes mellitus; CAD: Coronary artery disease; FIGO: International Federation of Gynaecology and Obstetrics; MOD CD class: Modified Clavien Dindo class; ICU: Intensive care unit.

**Table 2:** Trends of TLC, CRP and IL-6 values at baseline, after 24 and 72 hours.

Parameter	MOD CD Class 0			MOD CD Class 1		
	Preoperative	After 24 hours	After 72 hours	Preoperative	After 24 hours	After 72 hours
TLC count/ micro	6725 (1712.6)	9761.1 (2715.3)	7616.1 (2996.5)	8852 (3908.4)	10510 (4155.4)	10350 (5098)
CRP mg/L	16.5 (29.6)	214.7 (248.8)	192.7* (122)	50.4 (58.2)	201.6 (105.6)	360* (430.1)
IL-6 pg./mL	16.4 (21.4)	181.7* (143.6)	66.7* (185.1)	55.9 (97.9)	1196.7* (1461.4)	673.7* (1529.1)

\* p<0.001

TLC: Total leucocyte count; CRP: C reactive protein; IL-6: Interleukin 6; MOD CD class: Modified Clavien Dindo class; SD: Standard deviation.

and the preoperative IL-6 cut-off value of 23.56 pg./mL gave 70% sensitivity and 86% specificity in predicting POCs.

Table 2 depicts the trends of TLC, CRP, and IL-6 values i.e., baseline (preoperatively), 24 and 72 hours postoperatively in all patients, tabulated according to the presence/absence of POCs. The IL-6 values in both MOD class 0 and 1 peak at 24 hours and the difference in the values between groups were highly significant both at 24 and 72 hours (p<0.001). The values of CRP peak at 72 hours but the difference between groups is significant only at 72 hours (p<0.001) and not at 24 hours. The TLC variation amongst groups over time

was not statistically significant. This trend is also depicted in a graph in Fig 3. Tables 3a and 3b further elaborate on the relationship of these three parameters over time and between the groups using a linear mixed model. CRP was analyzed after square root transformation and IL-6 after natural log transformation. No transformation was necessary for TLC. No significant interactions were observed between time and MOD CD class. All three tests differ significantly between MOD CD class, but a highly significant difference is noted in the IL-6 trend [TLC (p=0.024), CRP (p=0.045), and IL-6 (p<0.0001)] which peaks at 24 hours. Thus, serum IL-6 value at 24

**Table 3a:** Repeated measures of analysis of TLC, CRP and IL-6 at baseline, 24 hours and 72 hours in patients with MOD CD class 0 and 1.

Time	MOD CD Class	TLC		Sqrt (CRP)		Ln (IL-6)	
		Estimate	Standard Error	Estimate	Standard Error	Estimate	Standard Error
0	0	6725.00	510.75	2.2152	0.8433	2.2646	0.1735
0	1	8852.00	969.08	5.6266	1.6000	3.3226	0.3291
24	0	9759.76	517.10	13.3592	0.8666	4.8486	0.1785
24	1	10510	969.08	13.7868	1.6000	6.3776	0.3291
72	0	7504.17	536.59	13.1516	0.9185	3.5407	0.1899
72	1	10350	969.08	17.0131	1.6000	5.2514	0.3291
Time p-value		0.0015		<0.0001		<0.0001	
MOD CD class p-value		0.024		0.045		<0.0001	
Interaction p-value		0.24		0.27		0.42	

TLC: Total leucocyte count; CRP: C reactive protein; IL-6: Interleukin 6; MOD CD class: Modified Clavein Dindo class; Sqrt: Square root; Ln: Logarithmic.

**Table 3b:** Pairwise p-values between time points.

time	_time	TLC		CRP		IL-6	
		p-value	Adj P	p-value	Adj P	p-value	Adj P
0	24	0.0003	0.0009	<.0001	<.0001	<.0001	<.0001
0	72	0.0737	0.1722	<.0001	<.0001	<.0001	<.0001
24	72	0.0584	0.1396	0.1928	0.3919	<.0001	<.0001

TLC: Total leucocyte count; CRP: C reactive protein; IL-6: Interleukin 6.

hours seems to be the best predictor of POCs. Figure 2b depicts the ROC curve of serum IL-6 values at 24 hours for predicting patients who developed POCs. It has an  $R^2$  value of 0.5 and the IL-6 cut-off value of 480 pg./mL gave 80% sensitivity and 89% specificity in predicting POCs.

One patient died on postoperative day 4 due to severe sepsis. The preoperative IL-6 value of this patient was 41.37 pg./mL and the value at 24, as well as the 72-hour value, was >5000 pg./mL (more than the upper limit of detection for the kit). One patient died on day 28 due to breathing difficulty at home. The cause of death could not be confirmed in this patient. This patient had IL-6 values of 8.59 pg./mL, 348.2 pg./mL, and 30.32 pg./mL at preoperative, at 24 and 72 hours respectively. This suggests that IL-6 values may have a role in predicting only the early POCs.

## Discussion

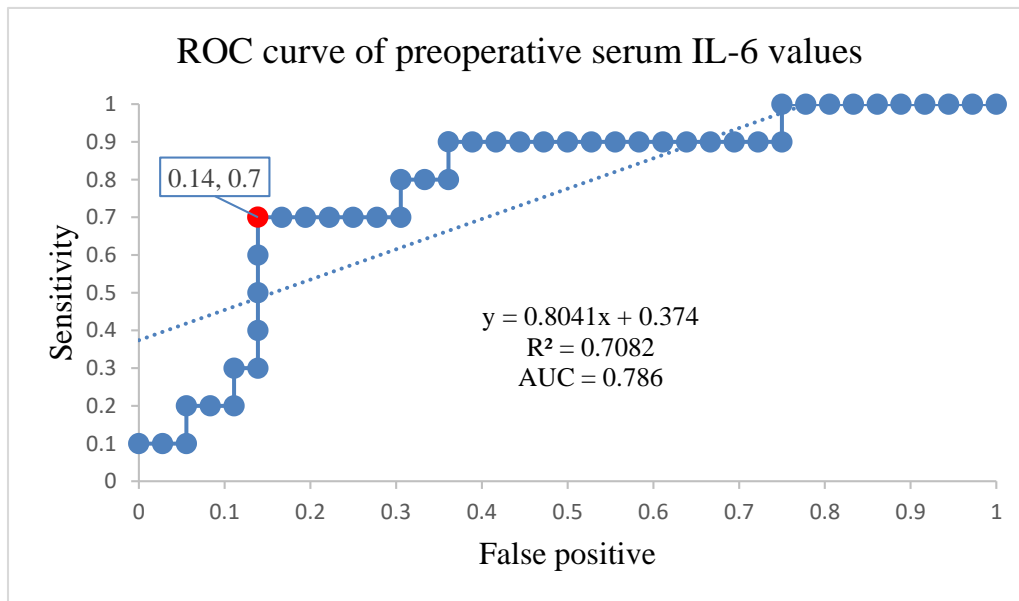
IL-6 is a proinflammatory cytokine produced predominantly by monocytes and macrophages. The serum IL-6 values in normal healthy humans seem to be variable across studies, with a recent study giving a pooled estimate of 5.18 pg./mL [95% CI 4.63, 5.74] (6). We found the baseline serum IL-6 levels raised

(24.97 +/- 50.43 pg./mL) in patients with ovarian cancer undergoing cytoreductive surgery. FIGO staging can affect the baseline serum IL-6 levels; with values near normal in FIGO stages 1 and 2 and higher in stages 3 and 4 (7). This could be the reason for the wider variance in preoperative serum IL-6 values observed in our study. Only 24% (11 out of 46) of the patients were in FIGO 1 and 2 stages.

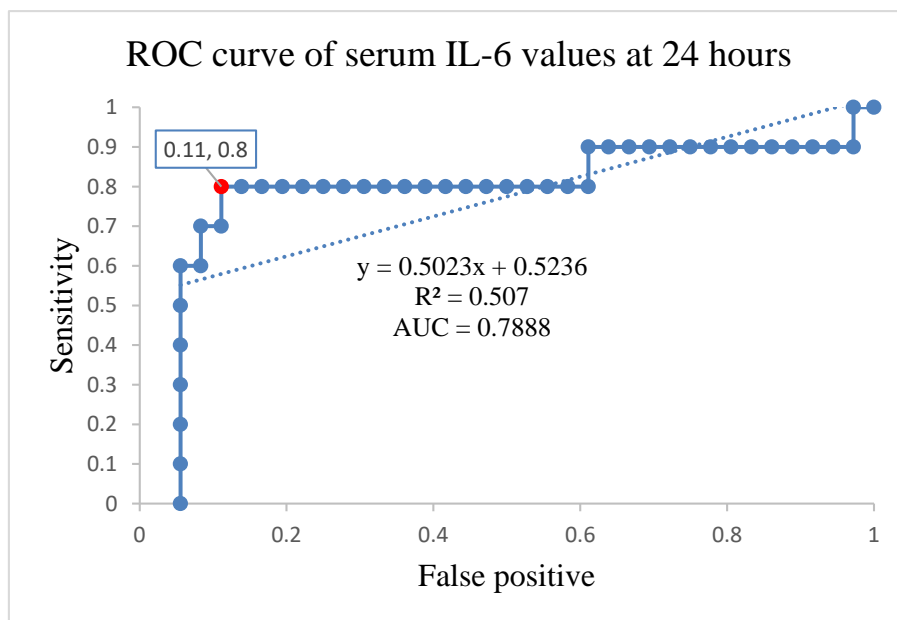
A recent meta-analysis has shown an association between elevated CRP levels with subsequent risk of ovarian cancer (8). But the role played by these acute phase reactants (IL-6 and CRP) in the perioperative period of ovarian cytoreductive surgery is unknown. The acute phase reactants like CRP and IL-6 increase postoperatively in response to the surgical insult. Watt et al., in a systemic review, demonstrated IL-6 to peak at 18-24 hours whereas CRP at 48-72 hours after an operative insult (9). The postoperative peak levels have been shown to correlate with the magnitude of the surgical procedure, but they have not studied its correlation with POCs. In the postoperative period, IL-6 has been studied earlier in patients undergoing colorectal surgery, esophagectomy, and gastric surgery, but not in ovarian cytoreductive surgery. In colorectal surgery, the increased peritoneal IL-6 levels were significantly associated with colorectal anastomotic leaks as evident

in the meta-analysis by Sparreboom et al (10). The association of raised serum IL-6 levels postoperatively is predictive of postoperative pneumonia following esophagectomy (11). Similarly, in gastric cancer surgery, postoperative day 1 level of serum IL-6 is an independent predictor of POCs (12). Klaschik et al. observed that a postoperative rise in IL-6 after

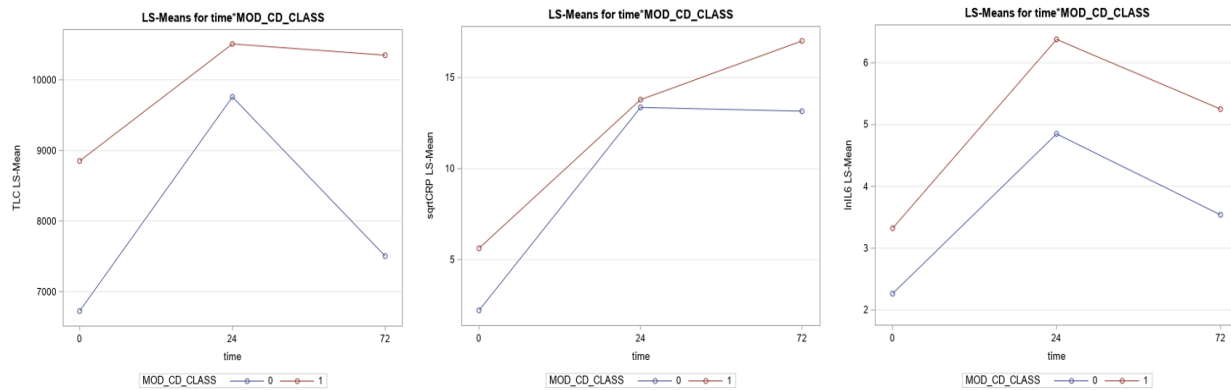
cytoreductive surgery for ovarian carcinoma induces a serum profile promoting vascular leakage, leading to hemodynamic alterations and increased fluid requirements (13). These predispose the patient to increased POCs, though the group had not specifically looked at these outcomes. Our study demonstrates the role of preoperative serum IL-6 as well as the peak rise at 24



**Figure 2a.** ROC Curve for cutoff value of preoperative serum IL-6 = 23.56 pg./mL; ROC: Receiver operating curve; AUC: Area under curve.



**Figure 2b.** ROC Curve for a cutoff value of serum IL-6 at 24 hours = 480 pg./mL. ROC: Receiver operating curve; AUC: Area under curve.



**Figure 3.** Graphical representation of change in TLC, CRP and IL-6 values over time in patients with MOD CD class 0 and 1; TLC: Total leucocyte count; CRP: C reactive protein; IL-6: Interleukin 6; MOD CD class: Modified Clavein Dindo class.

hours after surgery, in predicting POCs after cytoreductive surgery for ovarian cancers.

In patients who developed postoperative surgical complications, the difference in CRP values was statistically significant at 72 hours but not at 24 hours. Published literature has attributed this to the slower rise and fall in CRP levels compared to IL-6 (9). In a systematic review and pooled analysis of 1427 patients by Straatman et al., a CRP cut-off of 215 mg/L on the third postoperative day served as a predictor of POCs after major gastrointestinal surgical procedures.

A mean third postoperative day CRP value of 360 mg/L in our study could be reflective of the greater extent of resection in cytoreductive surgery for ovarian cancers (14). The time lag in CRP elevation was also noted in our study, hence IL-6 as a biomarker may be superior to CRP in the early detection of POCs after cytoreductive surgery for ovarian cancers. The limitation of this study is the small sample size. A larger patient sample can further authenticate the relationship between preoperative IL-6 and POCs. Some studies have shown peritoneal fluid IL-6 values to be more reliable in differentiating malignant from benign ovarian tumors as well as in identifying anastomotic leaks after gastrointestinal surgical procedures.

We could have additionally tested for peritoneal fluid IL-6 values and their association with POCs.

Since CRP peaks at 48 – 72 hours, repeating CRP on the fourth postoperative day could have possibly shown an association with POCs. This was not done in our study as we intended to look for a biomarker that could help in the early identification of POCs.

## Conclusion

This study adds to our understanding of the role of serum IL-6 perioperatively in prognosticating patients with ovarian cancers undergoing cytoreductive surgery. A preoperative serum IL-6 cut-off value of 24 pg./mL and a 24-hour cut-off value of 480 pg./mL can help predict POCs with good sensitivity and specificity. This can help clinicians take timely prudent decisions in the perioperative care of these patients.

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## Conflicts of Interest

The authors declare that they have no conflict of interest.

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**Appendix 1.** Clavien-Dindo classification of surgical complications.

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Class 1	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions (Antiemetics, antipyretics, analgesics, diuretics, electrolytes and physiotherapy allowed)
Class 2	Requiring pharmacological treatment with drugs other than such allowed for Grade 1 (Blood transfusion and parenteral nutrition included)
Class 3	Requiring surgical, endoscopic and radiological interventions
Class 4	Life-threatening complication (single or multiorgan) requiring ICU management
Class 5	Death

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Clavien Dindo class 1 and 2 were considered as no complications (MOD CD class 0) and class 3 and above were considered as presence of complications (MOD CD class 1)