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The utility of fibrinogen level as a predictor of complications after laparoscopic gynecologic surgery: a prospective observational study

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Abstract

Background: Complications after laparoscopic gynecological surgery may increase patients' morbidity and mortality; therefore, their timely diagnosis and early treatment would help clinicians to avoid life-threatening situations. We aimed to evaluate the predictive role of fibrinogen for diagnosing complications after laparoscopic gynecologic surgery for benign and malignant conditions.

Patients and methods: All patients who underwent elective laparoscopic gynecologic surgery between June 2013 and December 2017 at the Department of Gynecologic Oncology, Azienda Ospedaliera Brotzu, Cagliari, were prospectively included. Post-operative complications were assessed and graded according to the Clavien-Dindo classification. Fibrinogen and white blood cell level were determined preoperatively, on the first post-operative day and at the appearance of symptoms indicative of an irregular post-operative course or at the time of re-hospitalization for persistent symptoms. The postoperative changes (calculated from the first postoperative day) were correlated with the occurrence and severity of complications and their predictive role was assessed.

Results: We enrolled 1016 patients: 36% underwent surgery for benign pathologies (mainly voluminous fibromatous uteri and severe deep endometriosis) and 64% for gynecologic malignancies. The overall complication rate was of 3.45%, the rate of major postoperative complications was 2.85%. A postoperative fibrinogen increase ≥ 20% had a high diagnostic accuracy to identify postoperative complications early (AUC 0.931, sensitivity 89%, and specificity 99%). The magnitude of postoperative fibrinogen change was associated with complication severity.

Conclusions: Our findings demonstrated that fibrinogen increase can enable the early detection of postoperative complications after laparoscopic gynecological surgery. Further prospective and multi-center studies are warranted to confirm these results.

Keywords: Laparoscopic surgery, Fibrinogen, Postoperative complications, Inflammation, Gynecological surgery

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Background

The current data available in the literature demonstrate many direct benefits of laparoscopic surgery for gynecologic pathologies when compared to open surgery [1–3]. The known rate of intraoperative and postoperative major complications during gynecologic laparoscopic surgery was 0.7–4% after surgery for benign pathologies [4–6] and 4–21% after surgery for malignant diseases [7–9]. Complications can be identified during laparoscopic surgery, or can develop immediately after, and even considerably after discharge; they lead to extended recovery periods, re-hospitalization, and increased costs. If not diagnosed in time, these complications can cause high morbidity or even mortality; therefore, finding safe methods capable of detecting complications early is important.

Normally, surgery causes trauma to the body, activating the coagulatory and immune responses; complications greatly increases the activity of these systems. These two processes have mostly been studied as functioning independently of each other; however, numerous researches have determined several checkpoints that affect both the hemostatic and the immune response/inflammatory cascades. In fact, coagulation and inflammation are activated by the same types of injuries, usually with a precise temporal correlation. During surgery, when tissues are damaged, macrophages are activated and various monokines are released, mainly tumor necrosis factor α (TNF-α), interleukin 6 (IL-6), and IL-1β [10], which in turn promote acute-phase protein synthesis in the liver [11, 12]. C-reactive protein, serum amyloid A, haptoglobin, hepcidin, α1-antitrypsin, α1-acid glycoprotein, and fibrinogen are the main acute-phase reactants [13]. In case of complications, the organ damage is greater resulting in increased serum levels of such inflammation markers. These increases may be sufficiently sensitive to allow early diagnosis of the same complications.

Among these proteins, fibrinogen, in particular, could be an accurate indicator of an adverse post-operative course, including surgical and non-surgical complications. In fact, as a coagulation factor, it plays important biological roles not only in hemostasis but also in tissue repair and inflammatory responses in several pathologic conditions [14]. Therefore, the circulating levels of fibrinogen may increase several-fold after the operative trauma, and these levels are greater the more intense the inflammatory response [15]. To date, the ability of fibrinogen to predict postoperative surgical complication has been shown only retrospectively and in small and very selected populations [16].

The aim of this research was to evaluate prospectively the predictive properties of fibrinogen for diagnosing complications after laparoscopic gynecologic surgery for benign and malignant conditions. Timely diagnosis and early treatment of these complications will help clinicians to avoid life-threatening situations.

Patients and methods

We enrolled prospectively 1016 patients who underwent elective laparoscopic gynecologic surgery between June 2013 and December 2017 at the Department of Gynecologic Oncology, A. Businco Hospital, Azienda Ospedaliera Brotzu, Cagliari. This study was undertaken with the approval of the Local Institutional Ethics Committee. Enrolled patients gave written informed consent for the surgical procedures and for study participation.

Post-operative complications were defined as those occurring post-operatively up to 8 weeks after surgery. The complications were graded according to the Clavien-Dindo classification, based on the severity and intervention required [17, 18]. Severity grading increases from one to five: complications of grade III or more were defined as major complications because they required surgical, endoscopic, or radiologic intervention [18]. In cases wherein more than one complication occurred, the highest-grade complication was used for analysis.

The complications were assessed prospectively. The detection and classification of complications were made by physicians blinded to the laboratory results (i.e., fibrinogen and WBC levels).

We included and graded the following post-operative complications categories: -) infection confirmed by culture or fever (body temperature > 38.0 °C) after 48 h post op requiring antibiotics; –) vascular injury; –) hemorrage: primary hemorrage (i.e., hemorrhage within 24 h from surgery) and secondary hemorrage (haemorrage after 24 h form surgery); –) intestinal complications including intestinal injuries, and peritonitis (postoperative ileus requiring NG tube/total parental nutrition, bowel obstruction, bowel perforation, others such as constipation, diarrhea, fecal incontinence/urgency; –) anastomotic leak of small or large bowel; –) urologic complications such as bladder and ureteral injuries, urinary obstruction, incontinence/urge; –) vaginal vault complications such as infection, bleeding, and vaginal cuff dehiscence; –) fistula (enterocutaneous, enterovaginal, vesicovaginal, ureterovaginal, others); –) wound complications: infection and wound breakdown (deep or superficial); –) pelvic or abdominal abscess/hematoma; –) surgical hernia; –) lymphocyst/lymphoedema; –) thromboembolic disorders (deep venous thrombosis and pulmonary embolia); –) cardiac complications (i.e., atrial fibrillation, myocardial infarction, cardiac failure, and other cardiac problems); –) respiratory complications (i.e., pulmonary oedema, pneumothorax, atelectasia, pleural effusion, and other respiratory problems excluding pneumonia); –) neurological complications: nerve injury with associated neuropathic pain/paraesthesia/nerve palsy;

–) psychiatric complications (postoperative delirium, psychosis, depression, and other).

To detect the occurrence of complications, a daily clinical assessment was performed postoperatively and additional examinations (i.e., contrast-enhanced computed tomography or magnetic resonance, exploratory laparoscopy) were performed as indicated clinically. After discharge, the patients were checked by phone call every 2 days and visited after 1 week and then every 4 weeks, or sooner in the presence of symptoms, for 2 months after surgery.

The descriptive analysis of the enrolled population also included some demographic and anthropometric data (age, body mass index), parity, indication to surgery, previous abdominal surgery, as well as operative data (i.e., operative time, blood loss, length of hospital stay, time taken to achieve well-being).

Assessment of circulating levels of fibrinogen and inflammatory parameters

Fibrinogen level was determined along with the other coagulation parameters (prothrombin, partial thromboplastin time, d-dimer) preoperatively, on the first postoperative day and at the appearance of symptoms indicative of an irregular post-operative course or at the time of re-hospitalization for persistent symptoms such as pain and/or bleeding. Additionally, white blood cell (WBC) count was assessed at the same time intervals. The changes (% variation) of fibrinogen and WBC between first POD value and the value determined at the appearance of symptoms indicative of an irregular postoperative course or at the time of re-hospitalization for persistent symptoms was considered an independent variable to predict the occurrence of complication (dependent variable).

As additional parameters evaluated at the time of suspicion of postoperative complications (on the basis of fibrinogen values), we also tested the C-reactive protein (CRP) and the IL-6 levels.

For the analysis, blood samples were obtained and placed in tubes containing sodium citrate for the fibrinogen assay. Plasma was separated with centrifugation at 4 °C within 15 min. Plasma fibrinogen levels were assessed with the routine method described by Clauss (normal range 200–400 mg/dL) [19]. The WBC count was analyzed via an automatic hematological blood analyzer (Coulter Gen-S; Beckman Coulter, Fullerton, CA). Serum concentrations of CRP (mg/L) were measured by nephelometry using an autoanalyzer with a lower detectable limit of 1 mg/dL. Serum IL-6 levels were assessed with an enzyme-linked immunosorbent assay (ELISA) using a commercially available kit (DRG Instruments GmbH, Marburg, Germany). All the assays were performed at the clinical laboratory at the Businco Hospital, Cagliari, Italy, according to the manufacturer's protocol. The laboratory personnel were blinded to the clinical information.

Perioperative management

Laparoscopic gynecologic surgeries followed a standardized procedure and were performed by the same qualified/experienced principal surgeon with a minimal caseload of 50 operations/years and by a small selected team throughout the study duration. All major surgical procedures performed at the Gynecologic Oncology Department at the Businco Hospital were included in the study. The procedure included surgery for benign conditions such as ovarian cysts with a pre-operative suspicion of cancer or fibromatous uteri and malignancies (ovarian, endometrial, cervical cancers, and uterine sarcoma); cases with a complex surgical history that were referred to the gynecologic oncology team (i.e., deep endometriosis); and risk-reducing surgery. Minor diagnostic procedures were excluded. In cases of malignant gynecological tumors, the extent of surgery was determined in each case by the surgeons, who aimed to achieve a radical resection according to specific cancer treatment guidelines. All patients received preoperative antibiotic prophylaxis (2000 mg ceftriaxone intravenously) 30 to 60 min before surgery. Anticoagulation was achieved with low-molecular-weight heparin administered at a prophylactic dose (adjusted for body weight and thromboembolic risk according to clinical history) starting from the day of surgery in all patients.

Statistical analysis

Categorical data were reported as a number (and percentage) of patients. To define the distribution, continuous variables were explored for skewness and kurtosis. Normally distributed continuous variables were reported as the mean ± standard deviation and non-normally distributed continuous variables were reported as the median with a range of minimum and maximum values. Comparisons of means were performed with Student's t test for quantitative variables following normal distribution and the Mann-Whitney method for non-normal distributions. Comparison of qualitative variables was performed with the chi-square test. Correlation analysis was performed by Pearson's correlation methods for variables following the normal distribution.

In order to assess the predictive role of routine laboratory parameters (% change of fibrinogen and WBC) to detect the onset of postoperative complications (primary aim of the study), we used the receiver operating characteristic (ROC) curve analysis and the respective areas under the curve (AUC) to check the sensitivity and specificity of the continuous variable (% change of Fbg and WBC). The AUC of ROC analyses using Fbg and WBC changes

showed higher than 0.60, and so ROC analyses were used to determine the appropriate threshold value of these two variables. Then, the identified thresholds were used to perform the univariate regression analysis in order to identify the association between laboratory variables (independent variables) and the presence of post-operative complications (outcome dependent variable). Factors significant in the univariate analysis entered the multivariate logistic regression analyses, running a stepwise elimination model (variable entered if $p < 0.05$, variable removed if $p > 0.1$). Odds ratios and confidence intervals were determined. A 2-sided p value < 0.05 was considered significant. All statistical analyses were performed using SPSS version 17.0 (SPSS Inc., Chicago, IL).

Results

Patient variables and clinical data

Between June 2013 and December 2017, 1016 (240 per year) consecutive patients underwent laparoscopic surgery. The relevant anthropometric characteristics of all patients are summarized in Table 1. Of the analyzed procedures, 36% were for benign pathologies (mainly for voluminous fibromatous uteri and severe deep endometriosis) and 64% for gynecologic malignancies (ovarian, endometrial and cervical cancer, and sarcoma). Among the latter, 48% were for ovarian cancer, 40% for endometrial cancer, 11% for cervical cancer, and 1% for sarcoma.

There was a total of 35 postoperative complications, resulting in an overall complication rate of 3.45%: these included 29 (2.85%) major postoperative complications (grade III or greater according to the Clavien-Dindo classification). The frequency of each type of complication is summarized in Table 2. Among major (grade ≥ III) post-operative complications, the following were seen: 1 small bowel obstruction in a patient with ovarian cancer; 3 bowel perforations, 1 in a patient with ovarian cancer and 2 in patients with endometriosis; 1 anastomotic leak of the large bowel in a patient with deep endometriosis; 2 anastomotic leak in patients with ovarian cancer, both resolved laparoscopically (both stoma were reversed after 2 months); 1 anastomotic leak in a patient with cervical cancer; 5 ureteral injuries, 1 in a patient with a large myoma and a previous cesarean section, 1 in a patient with endometriosis, 1 in a patient with advanced cervix cancer after chemoradiotherapy, and 2 in patients with advanced ovarian cancer; 1 bladder injury diagnosed 20 days after surgery in a patient with advanced ovarian cancer (stage IIIC); 8 vaginal cuff dehiscence; 2 cases of hemoperitoneum; 3 trocar site

Table 1 Baseline patient characteristics

	No.	%
Patients enrolled	1016	
Age, years: mean ± SD (range)	60 ± 5 (18–75)	
BMI, mean ± SD	24.6 ± 8	
Mean Parity (range)	2 (0–3)	
Nulliparous,	457	45.3
Indications		
Benign pathology	365	35.9
Gynecologic malignancy	651	64.1
Ovarian cancer	314	30.9
Endometrial cancer	260	25.6
Cervical cancer	72	7.1
Sarcoma	5	0.5
Previous surgery, no. (%)		
Cesarean section	140	13.8
Abdominal-pelvic	548	53.9

Abbreviations: *BMI* body mass index

Table 2 Postoperative complications by grade

Hospital and patient-reported postoperative complications: grade II–V (no. of surgery = 1016)

Complication category	Total	Clavien and Dindo grade II–V				
		Grade II	Grade IIIa	Grade IIIb	Grade IVa	Grade V
Infection	2			2		
Hemorrhage						
Primary hemorrhage	0					
Secondary hemorrhage	2			2		
Intestinal complications	5	1		4		
Ileus	1	1				
Bowel obstruction	1			1		
Bowel perforation	3			3		
Anastomotic leak	1			1		
Urological complications	4			4		
Vaginal vault complications	8		2	6		
Fistula	0					
Wound complication	0					
Abscess/hematoma	1	1				
Hernia	2		1	1		
Thromboembolic disorders	0	0				
Cardiac	1	1				
Respiratory	1	1				
Neurological	2	2				
Psychiatric	0					
Total	35	6	3	20	0	0

hernia, including 1 case of tumor recurrence within the trocar site; 2 intra-abdominal infections (peritonitis), 1 in a patient with advanced borderline ovarian cancer, that required re-intervention and intra-abdominal washing. Regarding minor post-operative complications, the following occurred: 1 abdominal hematoma; 1 post-operative ileus that required nasogastric tube insertion and parenteral nutrition in a patient with ovarian cancer; 2 nerve injuries with neuropathic pain and paresthesia in patients with advanced cancer (1 ovarian and 1 cervical cancer); 1 cardiological complication in an obese patient with endometrial cancer; 1 respiratory complication in a patient with endometrial cancer. The overall post-operative complication rate in surgeries for malignant disease was 4.5% (29/651): the rate of postoperative major complications was 3.2%.

The median operation time and estimated blood loss were 150 ± 40 min (range 30–600) and 150 (range 0–600) mL, respectively. The median duration of hospitalization was 3 (range 1–5) days.

Association between levels of fibrinogen, WBC count, and other inflammatory parameters and the postoperative complications

The mean fibrinogen levels determined on appearance of symptoms indicative of an irregular post-operative course increased significantly in patients who developed major surgical complications (mean increase + 211.25 ± 90 mg/dL; $p = 0.005$); the postoperative fibrinogen change (calculated from the first postoperative day) was significantly different in comparison to patients without major complications ($p < 0.001$) (Table 3). The value of fibrinogen change assessed at the appearance of symptoms indicative of an irregular post-operative course or at the time of re-hospitalization for persistent symptoms correlated with the diagnosis of a major postoperative complication (correlation index 0.875, $p < 0.001$). Moreover, postoperative changes in fibrinogen concentrations were directly associated with an increase in the Clavien-Dindo grade ($p < 0.001$).

A significant postoperative (calculated from the first postoperative day) increase in WBC count levels was also observed in patients who developed major postoperative complications (mean increase + 3501 ± 1100 cells/μl; $p = 0.028$) in comparison to patients who developed no major complications ($p = 0.048$) (Table 3). The WBC count increase assessed in presence of symptoms indicative of an irregular postoperative course or at the time of re-hospitalization for persistent symptoms correlated significantly with the diagnosis of a major postoperative complication (correlation index 0.543, $p = 0.024$).

The diagnostic accuracy of fibrinogen and WBC change (%) for predicting major complications was evaluated using the AUC (Table 4). ROC analysis was used to find the best cut-off value for all parameters as predictors of post-operative complications. As shown in Fig. 1, the ROC curve of fibrinogen concentration assessed in the presence of symptoms indicative of an irregular postoperative course or at the readmission for persistent symptoms yielded a superior diagnostic accuracy with an AUC of 0.931 (95% confidence interval [CI], 0.773–1.019, $p < 0.0001$). The Youden index identified an optimal cutoff for increase > 20% with a sensitivity of 89% and a specificity of 99%. Regarding the predictive potential of WBC count, the ROC curve only yielded an AUC of 0.663 (95%CI, 0.406–0.864, $p = 0.120$): The Youden index identified an optimal cut-off for increase > 40% with a sensitivity of 70% and a specificity of 75% (Fig. 1).

In univariate regression analysis, both Fbg % and WBC % increases were significantly associated with postoperative complications (Fbg: R^2 coefficient 0.4566, 95% CI 5.7477–21.5023, $p = 0.0012$; WBC: R^2 coefficient 0.3025, 95%CI 0.1074–0.9926, $p = 0.0180$). On multivariate logistic regression, only fibrinogen increase was seen to be an independent factor predictive of the onset of post-operative complications. The results of multivariate logistic regression analysis are summarized in Table 5.

The values of the additional markers CRP and IL-6, which were assessed if complications were suspected based on the fibrinogen level increase, were seen to be significantly positively correlated with changes in the fibrinogen level (data not shown).

It should be specified that in patients with advanced-stage malignancies, although the fibrinogen level is typically increased as a consequence of the inflammatory status associated with cancer (as widely demonstrated in several papers by our group), a fibrinogen change > 20%

Table 3 Mean values of fibrinogen and WBC count preoperatively, at first postoperative day and on the appearance of symptoms indicative of an irregular post-operative course

Parameters	Patients who developed major complications			Patients without major complications			
	Preoperative	First POD	Re-evaluation	Preoperative	First POD	Re-evaluation	*p* value**
Fibrinogen (mean ± SD)	339 ± 98	423 ± 90	615 ± 95*	352 ± 102	430 ± 86	480 ± 104*	< 0.001
WBC (mean ± SD)	4542 ± 1104	6779 ± 1770	11,367 ± 1700*	4021 ± 2350	6100 ± 1900	8144 ± 1540*	0.048

Abbreviations: *POD* postoperative day, *SD* standard deviation, *WBC* white blood cell count

*p value < 0.05 in comparison to first postoperative day value as calculated by Student's t test for paired data

**p value calculated by Student's t test for mean change difference between groups

Table 4 ROC curve analysis to detect sensitivity and specificity of %change of fibrinogen and WBC for identifying major postoperative complications after laparoscopic gynecological surgery

Parameter	Cut-off value	Sensitivity (%)	Specificity (%)	Younden index	AUC	*p* value
Fibrinogen	> 20%	89	99	0.900	0.931	< 0.0001
WBC	> 40%	70	75	0.450	0.663	0.120

Abbreviations: *WBC* whole blood count, *AUC* area under the curve

was found to be associated with the development of a postoperative major complication.

Discussion

Although minimally invasive surgery in gynecology with laparoscopic procedures is now a very common and well-established practice, the incidence of complications is variable and often unpredictable. In the present study, we observed that the rate of major complications after gynecological laparoscopic surgery in the total population was 2.85%, with a rate of 3.2% seen after surgery for malignant diseases. This is within the range reported in previously published studies [7, 20, 21]. The early identification of patients with complications would be undoubtedly of great clinical value because it would facilitate optimal timing of therapeutic interventions to minimize the sequelae of such complications, particularly major ones that require surgical intervention for correction with a significant threat to short- and long-term outcomes [22]. In the present study, we investigated the ability of fibrinogen concentration to enable clinicians to rapidly identify postoperative complications following gynecological laparoscopic procedures. We found that the increase in fibrinogen concentration on postoperative days had a high diagnostic accuracy to identify postoperative complications early, with an AUC of 0.90 ($p = 0.012$), sensitivity of 0.89, and specificity of 0.84. Moreover, we identified that a postoperative change in the fibrinogen concentration $\geq$ 20% was useful for predicting postoperative major complications following gynecologic laparoscopic surgeries.

The role of acute-phase proteins in predicting the development of postoperative complications have been already investigated, but, to date, the majority of studies have focused on CRP [23–32].

Moreover, although the data in different surgery settings for both malignant and benign pathology are numerous, to date, the data in the setting of laparoscopic gynecologic surgery are very scarce and of low quality [33, 34]. One prospective study carried out in patients who underwent laparoscopic bowel resection for deep infiltrating endometriosis showed that postoperative CRP values were significantly higher in those patients who developed postoperative anastomotic leakage or ureteral injury, while on the contrary, the decrease in CRP levels was associated with an uncomplicated postoperative course [35].

Another laboratory parameter, historically used as a marker of complications, is the WBC count. In our study population, the changes in postoperative WBC counts showed a low predictive ability of postoperative

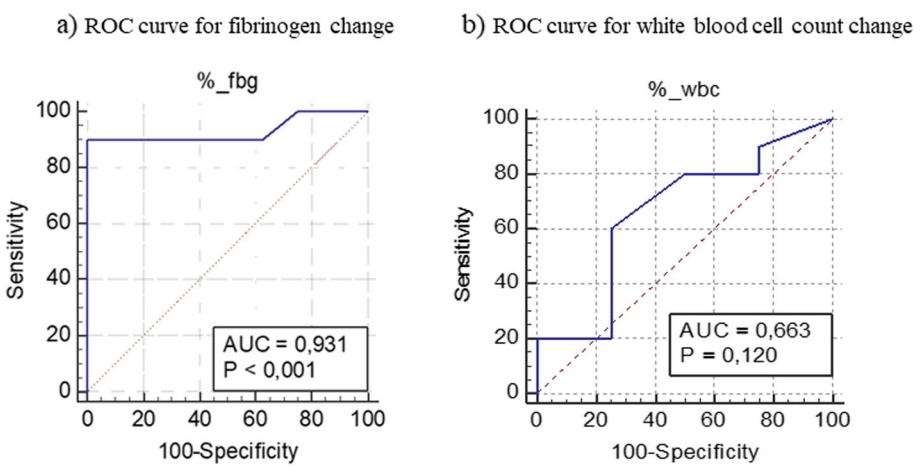

Fig. 1 ROC curve for postoperative fibrinogen and WBC level changes. **a** Plot of the receiver operating characteristic curve of the fibrinogen change levels assessed at the appearance of symptoms indicative of an irregular post-operative course for the diagnosis of postoperative complication after laparoscopic gynecologic surgery. **b** Plot of the receiver operating characteristic curve of the whole blood count (WBC) change levels assessed at the appearance of symptoms indicative of an irregular post-operative course for the diagnosis of postoperative complication after laparoscopic gynecologic surgery

Table 5 Univariate and logistic multivariate regression analysis between laboratory parameters and the onset of major postoperative complications

Multivariate logistic regression analysis			
Laboratory parameters	Odds ratio	95% confidence interval	*p* value
Fibrinogen increase (< 20% versus ≥ 20%)	9.82	2.92–33.06	< 0.001
WBC increase (< 40% versus ≥ 40%)	4.48	1.68–11.97	0.053

Abbreviations: *WBC* white blood cell count

complications. This result is in accordance with those of other studies [16, 32, 36]. In particular, Swets et al. [36] found that significant changes in the WBC count occurred 7 days after surgery when most postoperative complications have already had a negative clinical evolution. In the present study, we also measured IL-6 levels. This has recently been reported as a predictor, in particular, of postoperative infectious complications after major abdominal surgery [37]. In the present work, IL-6 was considered as an additional parameter. In fact, several of our previous studies have demonstrated that the increase in IL-6 levels correlates perfectly with the increase in fibrinogen levels [38, 39]. However, the use of IL-6 as routine marker is more expensive (less cost-effective) than fibrinogen.

The results of the present study also report a significant association between the magnitude of the postoperative changes in the fibrinogen levels and complication severity, using the Clavien-Dindo grade, following laparoscopic surgery for gynecological diseases. These findings are consistent with those of some previous studies that have shown a significant association between the magnitude of the postoperative systemic inflammatory response, measured by CRP levels, and the severity of complications following surgery for colorectal, gastric, and esophageal cancers [30, 40, 41].

Notably, our study revealed that in patients with early complications the high fibrinogen level may lead to prompt identification of the complication; however, in those with late complications, this increase is always associated with the core symptoms of the complication that results in readmission of the patient. Therefore, during hospitalization, when the patient's clinical condition does not progressively improve as expected, the assessment of fibrinogen levels could help determine whether the patient has a previously unnoticed or misdiagnosed complication during surgery. This evidence would allow the diagnosis of the complication very early and to allow us to adopt any measure to promptly resolve the complication in the shortest possible time before it compromises the clinical picture and increases morbidity and hospitalization costs. Thus, the early diagnosis of complications, particularly after laparoscopic gynecological surgery, is essential for better outcome of the patient. It is especially very important when the patient is planned to undergo an early discharge, as in minimally invasive laparoscopic surgery.

Conclusions

The findings of the present study suggest that an increase in the fibrinogen levels can enable early detection of postoperative complications after laparoscopic gynecological surgery. This evidence is novel, because at present, data regarding the use of such acute-phase reactants as early markers of complications after gynecological minimally invasive surgery are very limited. However, the present study has some limitations. Mainly, we used the same population in which we derived the optimal cutoffs of laboratory variables to determine sensitivity and specificity. Ideally, the predictive value of these thresholds should be confirmed in a second independent patient sample to obtain definitive conclusions. Further prospective multi-center studies in selected populations should be conducted to confirm our results.

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Authors' contributions

AM designed the study, enrolled patients, performed surgery, collected, analyzed, and interpreted the data, and was a major contributor in writing the manuscript. GC, PK, FL, RN, and PO enrolled the patients, performed the surgery, and collected and analyzed the data. ES enrolled the patients, collected, analyzed, and interpreted data, and contributed to writing the manuscript. VM analyzed and interpreted data, and contributed to writing the manuscript. CM enrolled the patients, performed the surgery, collected, analyzed, and interpreted the data, and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

Data were collected from medical charts and are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Following the institutional rules, the study was notified to the Local Institutional Ethics Committee. All enrolled patients gave written informed consent for the surgical procedures and data collection.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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