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Predictive Ability of the Combination of White Blood Cell and C Reactive Protein Levels for Infections Following Laparoscopic Hysterectomy

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Objective: In the present retrospective study, we evaluated potentially predictive factors and determined receiver operating characteristic (ROC) curve cut-off values for effective detection of patients at higher risk of re-hospitalization due to postoperative infection after total laparoscopic hysterectomy.
Materials and Methods: We included 168 patients who had undergone laparoscopic hysterectomy. Data were collected from medical records. Patients were classified into non-infection (n = 161) and infection (n = 7) groups based on whether they developed fever after hospital discharge. We evaluated factors conventionally known to affect postoperative infection in general, and values of white blood cell (WBC) and C-reactive protein (CRP) determined on postoperative days 1 and 3–5.
Results: There were significant differences in WBC 3–5 days postoperatively (WBC POD3–5) (p = 0.049), CRP 3–5 days postoperatively (CRP POD3–5) (p = 0.018) and CRP POD3–5 × WBC 1 day postoperatively (WBC POD1) (p = 0.002). Area under the ROC curves for CRP POD3–5 and CRP POD3–5 × WBC POD1 were 0.81 and 0.84, and cutoffs were 4.46 mg/dL and 46885.5, respectively.
Conclusion: If CRP POD3–5 or CRP POD3–5 × WBC POD1 is high, the physician should be alert to postoperative infection, and the patient should be under careful management and supervision.

Key words: laparoscopy, surgical site infection

INTRODUCTION

The incidence of postoperative infections in laparoscopic hysterectomy is lower than that in abdominal hysterectomy [1]. The merits of laparoscopic surgery include minimal invasiveness and lower postoperative infection; therefore, postoperative infections should be avoided as much as possible. In obstetrics and gynecology, there are several indications for laparoscopic surgery, including hysterectomy. There is a risk of developing postoperative infections, such as vaginal stump infections, following laparoscopic hysterectomy because it involves transvaginal removal of the uterus. Postoperative vaginal stump infections occur in 0–8.3% of patients [2]. Risk factors associated with the development of infections following total hysterectomy include lack of prophylactic antibiotic therapy, heavy intraoperative blood loss, anemia, use of intermittent indwelling catheters, and postoperative laxative and cholinergic drug use [3].

Postoperative infections can be serious complications of hysterectomy, sometimes requiring invasive interventions such as drainage and re-hospitalization. Therefore, it is important to understand the predictive factors of postoperative infections to ensure adequate postoperative management.

The CRP levels on day 3 after colon cancer surgery are reportedly higher in patients who develop postoperative infections than in those who do not [4].

Specific figures in blood sampling after total laparoscopic vaginal hysterectomy are rarely given.

We aimed to determine the predictive factors the usefulness of WBC and CRP of postoperative infections following total laparoscopic hysterectomy (TLH) or laparoscopic-assisted vaginal hysterectomy (LAVH) to help prevent postoperative infections in clinical practice.

MATERIALS AND METHODS

This study was approved by our institution's Ethics Committee for Clinical Research (No: 2021–10). Informed consent was not obtained as this is a retrospective study. In addition, the hospital's ethics approval and de-identified data were used. We recruited 168 patients who had undergone TLH or LAVH between July 2015 and March 2021 at our institute and collected clinical data from their medical records. We retrospectively analyzed cases of laparoscopic hysterectomy performed at a single institution. Postoperative infection was defined as patients requiring re-hospitalization. We evaluated the following factors: age, body mass index (BMI), method of hysterectomy (TLH or LAVH), operative time (minutes), intraoperative blood loss (ml), preoperative hemoglobin (Hb) level (g/dL),

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Table 1 Patients classified into two groups: postoperative non-infection (n = 161) and infection group (n = 7)

	Initial model		
	postoperative non-infection group	postoperative infected group	P value
Number (cases)	161	7	
Age (years)	51.3 ± 10.3	46 ± 7.7	0.18
BMI	24.2 ± 4.0	25.0 ± 4.0	0.61
Procedure of hysterectomy			
TLH	141	7	
LAVH	20	0	
Operation time (minutes)	186.3 ± 57.7	195.7 ± 41.8	0.67
Intraoperative blood loss (ml)	124.0 ± 206.2	77.1 ± 62.9	0.55
Preoperative Hb (g/dL)	12.8 ± 1.5	12.7 ± 1.4	0.92
Presence of certificated doctor (cases)	85	5	0.45
anti-adhesion agent (cases)			
Interseed®	77	4	
Seprafilm®	54	2	
Adspray®	13	0	

BMI: Body Mass Index, TLH: Total Laparoscopic Hysterectomy, LAVH: Laparoscopically-Assisted Vaginal Hysterectomy

Table 2 Compared the two groups on multiple variables

	Initial model		
	postoperative non-infection group	postoperative infected group	P value
preoperative WBC (μL)	5908.1 ± 1786.8	6642.9 ± 2826.0	0.30
WBC (POD1) (μL)	8987.0 ± 2794.0	11042.9 ± 2961.3	0.059
WBC (POD3-5) (μL)	5960.4 ± 2316.5	7771.4 ± 3420.4	0.049
CRP (POD3-5) (mg/dL)	4.85 ± 3.41	8.59 ± 3.12	0.018
WBC (POD1) × CRP (POD3-5)	44317.5 ± 39526.6	102783.8 ± 64666.6	0.002
WBC (POD3-5) × CRP (POD3-5)	33022.5 ± 36428.1	54089.2 ± 35216.2	0.21
WBC (POD1)/WBC (POD3-5)	1.65 ± 0.90	1.68 ± 0.88	0.92
WBC (POD3-5)/WBC (POD1)	0.70 ± 0.48	0.72 ± 0.31	0.92
CRP (POD3-5)/WBC (POD3-5)/WBC (POD1)	7.12 ± 5.44	18.12 ± 11.0	0.09
CRP (POD3-5)/WBC (POD1)/WBC (POD3-5)	4.00 ± 5.48	4.53 ± 1.61	0.82
CRP (POD3-5) × WBC (POD1)/WBC (POD3-5)	3.96 ± 5.47	4.53 ± 1.61	0.82

WBC: White Blood Cell, POD1: from the 1st postoperative day, POD3-5: from the 3rd to the 5th postoperative day, CRP: C Reactive Protein

presence or absence of a doctor certified in gynecological laparoscopic surgery, type of anti-adhesion agent used, white blood cell (WBC) counts (/μL) (before surgery, on postoperative day 1 [WBC POD1], and postoperative days 3-5 [WBC POD3-5]), and blood C-reactive protein (CRP) level (mg/dL) at 3-5 days post-surgery (CRP POD3-5).

ROC curves were generated and evaluated for the WBC POD3-5, CRP POD3-5, and CRP POD3-5 × WBC POD1 values.

Patients were classified into infection and non-infection groups. The data were analyzed using Student's t-test and Mann-Whitney U test for continuous variables and the chi-squared test and Spearman's correlation coefficient for categorical variables. A two-sided test was performed, and p-values < 0.05 were considered statistically significant. This study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

RESULTS

We recruited 168 patients (148 cases of TLH and 20 of LAVH). Seven (4.2%) patients developed postoperative infections. The remaining 161 patients were classified into the "non-infection" group. There were no statistically significant differences between the infection and non-infection groups in the following factors: age (46.0 vs. 51.3 years, respectively, p = 0.18), BMI (25.0 vs. 24.2 kg/m^2, p = 0.61), operation time (195.7 vs. 186.3 minutes, p = 0.67), intraoperative blood loss (77.1 vs. 124 ml, p = 0.55), preoperative Hb level (12.7 vs. 12.8 g/dL, p = 0.92), presence of certificated doctor (85 vs. 5 cases, p = 0.45). Intraoperatively, Interseed®(Johnson&Johnson, Tokyo, Japan), Seprafilm®(KAKEN PHARMACEUTICAL CO.,LTD., Tokyo, Japan) and Adspray® (TERUMO CORPORATION, Tokyo, Japan), were used as anti-adhesion agents in 81, 56, and 13 patients, respectively. Among these, postoperative infections developed in four, two, and zero cases, respectively; however, these differences were not statistically significant (Table 1). Preoperative WBC count (6643 vs. 5908 /μL, p = 0.30), WBC POD1 (11043 vs. 8987 /μL, p = 0.059), WBC POD3-5 × CRP POD3-5 (54089 ± 35216 vs. 33023 ± 36428; p = 0.21), rate of change from WBC POD3-5 to WBC POD1 (WBC POD1/WBC POD3-5) (1.68 ± 0.88 vs. 1.65 ± 0.90; p = 0.92), rate of change from WBC POD1 to WBC POD3-5

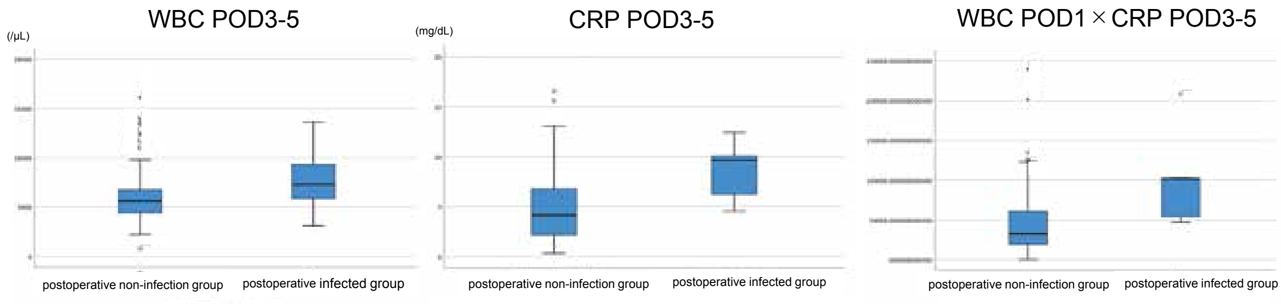

Fig. 1 Box plots were used to evaluate the three items for which significant differences were found.

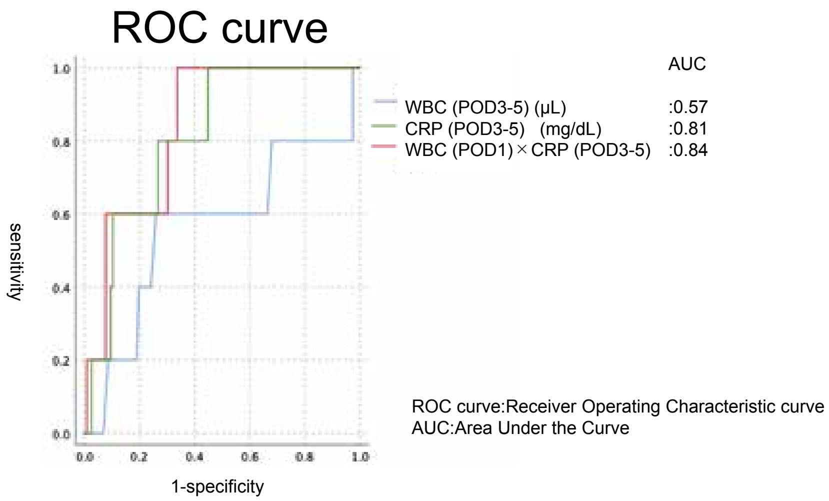

Fig. 2 ROC curves were used for the three items for which significant differences were observed; AUC are also provided.

(WBC POD3-5/WBC POD1) (0.72 ± 0.31 vs. 0.70 ± 0.48; p = 0.92), CRP POD3-5 divided by WBC POD3-5/WBC POD1 (18.12 ± 11.0 vs. 7.12 ± 5.44; p = 0.09) and by WBC POD1/WBC POD3-5 (4.53 ± 1.61 vs. 4.00 ± 5.48; p = 0.82), and CRP POD3 WBC POD1/WBC POD3-5 (4.54 ± 1.6 vs. 3.96 ± 5.47; p = 0.82).

The infection group had a significantly higher mean WBC POD3-5 (7771 vs. 5960 /μL; p = 0.049), CRP POD3-5 (8.59 ± 3.16 vs. 4.85 ± 3.41 mg/dL; p = 0.018), and CRP POD3-5 × WBC POD1 (1022784 ± 64667 vs. 44317 ± 39526; p = 0.002) than the non-infection group did (Table 2, Fig. 1). The WBC POD3-5 area under the ROC curve (AUC) was 0.57 (95% CI: 0.27-0.87), and the cutoff value was 2850 /μL (sensitivity: 100%, specificity: 2.5%). The CRP POD3-5 AUC was 0.81 (95% CI: 0.67-0.96), and the cutoff value was 4.46 mg/dL (sensitivity: 100%, specificity: 55.2%). The CRP POD3-5 × WBC POD1 AUC was 0.84 (95% CI: 0.72-0.97) and the cutoff was 46885.5 (sensitivity: 100%, specificity: 56.7%)(Fig. 2). The patients in the infection group were readmitted to the hospital 5-16 days (median, 11 days) after the surgery. The bacteria isolated from the vaginal cultures of patients who developed postoperative infections were *Enterobacter spp.*, *Klebsiella pneumoniae*, Group B Streptococcus (GBS), *Bacteroides fragilis*, *E. coli*, *Enterococcus faecalis*, and *Citrobacter freundii*.

DISCUSSION

High postoperative blood CRP levels are associated with increased risks of postoperative infection and are a consequence of prolonged inflammation. The practice of laparoscopic hysterectomy has increased significantly worldwide since 1989 [5]. In 2010, > 400,000 patients underwent laparoscopic hysterectomy in the United States because of its advantages over abdominal hysterectomy which include: faster return to daily life, lower incidence of postoperative fever, shorter hospital stay, lower intraoperative blood loss, fewer wound complications, less postoperative pain, and lower mortality [6]. For these reasons, postoperative infections are less frequent in laparoscopic hysterectomies than in open abdominal hysterectomies [1]. However, there is a non-negligible risk of developing postoperative infections following laparoscopic hysterectomy (e.g., vaginal stump infections could occur because of the transvaginal removal of organs, such as the uterus).

This study determined that patients with high blood CRP levels on postoperative days 3-5 were at a higher risk of developing postoperative infections. A high CRP level indicates prolonged postoperative inflammation even in the absence of fever. CRP is an acute-phase reactant (appearing during the inflammatory response) whose blood levels indicate the presence of inflammatory cytokines such as interleukin-6. Highly invasive surgery can trigger the production of inflammatory cytokines and increase the CRP levels [7]. Blood CRP levels are also elevated in bacterial infections and do not vary with sex, age, or blood Hb levels. When an inflammatory reaction occurs in the body, plasma CRP levels increase within 24–72 h, with a half-life of approximately 19 h. CRP is believed to be highly diagnostic of infection-related diseases [8] and is widely used as a marker of acute infection. Several studies have shown that high blood CRP levels are associated with postoperative wound infections, anastomotic insufficiency, and poor prognosis. In a retrospective study evaluating postoperative infections in 192 patients who underwent spinal surgery, patients who developed surgical site infection on postoperative days 7–8 had significantly higher CRP levels (sensitivity: 92.9%; specificity: 78.2%) than non-infection patients [9]. Furthermore, the CRP levels on day 3 after colon cancer surgery are reportedly higher in patients who develop postoperative infections than in those who do not [4]. Postoperative blood CRP levels are also clinically useful in predicting surgical site infection-related complications such as anastomotic suture failure [10]. Platt *et al.* showed that the CRP levels on postoperative day 3 was an independent prognostic factor in the multivariate analysis. The high CRP levels suggested a poor postoperative prognosis after radical resection for colorectal cancer. Although reports have shown that CRP levels can predict the onset of postoperative infections, they may also indicate other conditions, such as trauma, burns, autoimmune diseases, ischemic diseases (such as myocardial infarction), and tumors. Blood CRP levels may also increase following the production of inflammatory cytokines after surgery, especially when surgical invasion is significant, even in the absence of infection [11]. Blood CRP levels may also increase as the severity of surgical trauma, volume of blood loss, or operative time increases [12]. Blood CRP level is a useful negative predictor of the onset of colon anastomotic leak 3–5 days after surgery [12]. Other indicators of postoperative infection, such as WBC count, neutrophil count, procalcitonin (PCT) level, and fibrinogen level, should also be considered. CRP, WBC counts, and neutrophil counts are useful markers for detecting intra-abdominal leakage or abscess formation following laparoscopic sleeve gastrectomy (LSG) [13]. In a study involving 208 patients who underwent LSG, eight (3.8%) developed intra-abdominal leakage. Furthermore, blood samples collected 24 hours post-surgery revealed a CRP level ≥ 9 mg/dL, PCT level ≥ 0.85 ng/ml, and fibrinogen level ≥ 600 mg/dL, which were suggestive of intra-abdominal leakage [14].

A well-known marker associated with infection is WBC count. The WBC count increases with inflammatory responses, including in bacterial infections. In one study, WBC count was not identified as a marker of postoperative complications after hypospadias surgery [8]. In orthopedics, CRP is considered a better postoperative inflammatory marker than WBC count [15]. The levels of PCT, a precursor of calcitonin, increases with bacterial infection and is an excellent diagnostic indicator of sepsis. PCT is also an excellent early predictor of major anastomotic leaks 3–5 days after surgery [16]. Routine measurements of CRP and PCT showing normal range values on postoperative day 3 often indicate that patients are less likely to develop postoperative anastomotic leakage. Fibrinogen levels are also elevated in patients with postoperative anastomotic leakage, along with CRP and PCT levels [14, 17]. In our study, 12 patients in the non-infection group had blood CRP levels > 10 mg/dL on postoperative days 3–5; however, none developed postoperative infections. This shows that a high blood CRP level on postoperative days 3–5 does not always predict the onset of postoperative infection. In such cases, evaluation of the WBC count, neutrophil count, PCT level, and fibrinogen level may help ascertain the diagnosis of postoperative infection. One risk factor of postoperative infection that does not involve blood analysis is the presence of a vaginal stump hematoma after total hysterectomy. This hematoma can easily be infected by ascending vaginal bacteria. CT-guided drainage of postoperative pelvic abscesses is effective, with a success rate of 81% [18]. Transvaginal drainage is an effective treatment for vaginal stump abscess. In the infection group in our study, transvaginal drainage was performed in two patients, and an improvement was observed with antibacterial treatment. It is necessary to examine the vaginal stump postoperatively; if there are signs of infection, therapeutic interventions such as drainage should be considered.

Several bacterial species were isolated from the vaginal cultures of patients with postoperative infections in our study. Therefore, it may be appropriate to administer antibiotics with good bacterial coverage at the onset of postoperative infections.

This study was limited because it was a single-center retrospective study with several biases. Furthermore, the incidence of postoperative infection was low (4.2%, 7/168), resulting it a small sample size. Therefore, future studies with larger sample sizes are needed to appropriately determine the predictive factors of postoperative infections and evaluate the efficacy of intraoperative antibiotics.

In conclusion, patients with high postoperative CRP levels are at higher risk of developing postoperative infections because of prolonged postoperative inflammation. Furthermore, patients with high blood CRP levels are at a higher risk of developing infections.

Based on the ROC curve, the CRP level on postoperative days 3–5 (4.46 mg/dL) and CRP POD3–5 × WBC POD1 value (46885.5) are useful predictive factors in postoperative management. In such cases, it is advisable to ask the patient to visit the outpatient clinic before the expected day of readmission (postoperative days 5–16), keeping postoperative infections in mind.

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CONFLICTS OF INTEREST

None

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