

Can Neutrophil-to-lymphocyte Ratio and Platelet-to-lymphocyte Ratio be Used as Inflammatory Markers to Predict Length of Hospital Stay After Total Laparoscopic Hysterectomy for Benign Indications?

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ABSTRACT

Objective: To investigate the possible effects of inflammatory parameters obtained from complete blood count in the postoperative first day of total laparoscopic hysterectomy on the length of hospital stay in patients without any complications.

Methods: Linear regression analysis was performed to find associations between hospital stay and the associated variables. Receiver operating characteristic (ROC) curve analysis was performed to determine the cut-off values of postoperative neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and C-reactive protein (CRP) for long hospital stay (>3 days).

Results: Postoperative values of NLR ($r=0.332$, $p<0.001$), PLR ($r=0.325$, $p<0.001$), and CRP ($r=0.404$, $p<0.001$) were moderately associated with the duration of hospital stay. In ROC analysis, the post-op cut-off value of 25 mg/L for CRP predicted long hospital stay with a sensitivity of 65% and specificity of 63% [area under the curve (AUC): 0.657, $p=0.002$, confidence interval (CI) 0.563-0.752], the post-op cut-off value of 159 for PLR with a sensitivity of 60% and specificity of 58% (AUC: 0.688, $p<0.001$, CI 0.600-0.776) and the post-op cut-off value of 4.96 for NLR with a sensitivity of 60% and specificity of 58% (AUC: 0.618 $p=0.017$, CI 0.520-0.717).

Conclusion: We observed a direct correlation between postoperative first-day values of NLR, PLR, and CRP with the length of hospital stay. NLR, PLR, and CRP values may be helpful to predict the length of hospital stay and can be used instead of each other.

Keywords: Benign gynecologic surgery, hospital stay, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, total laparoscopic hysterectomy

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INTRODUCTION

Inflammatory response after surgery is an ordinary outcome which ends up with tissue repair. The increase in neutrophil levels accompanied with a decrease in lymphocyte levels are characteristics for the inflammatory response. Therefore, neutrophil-to-lymphocyte ratio (NLR) comes out as a simple index of inflammation (1). In the literature, NLR was shown to be associated with surgical complications and the length of hospital stay in certain surgeries (2,3). Another inflammatory marker calculated from hemogram is the platelet-to-lymphocyte ratio (PLR). As a result of endothelial tissue damage, platelets (PLTs) are gathered in the affected area. Therefore, an increase in the number of PLTs is inevitable for inflammation. Hence, PLR appears to be another simple inflammation index due to increase in PLT count and decrease in lymphocyte count (Lym#) (4,5). PLR has also been shown to be associated with the length of hospital stay in various surgeries (6). NLR and PLR are both newly recommended inflammatory markers to estimate the prognosis of surgical treatment in clinics. Investigations regarding NLR and PLR concerning prognosis of patients after surgeries including gynecological cancer, cardiac surgeries, and emergency surgeries are available in prior literature (7). Women need surgical intervention due to benign uterine lesions, which is mainly a hysterectomy. Hysterectomy is the second leading cause of total surgeries after cesarean section (8). With medical advancements and available laparoscopic equipment, open surgery is becoming less preferred where minimally invasive techniques have been replaced with classical methods. Due to short hospital stay, rapid return to work, less pain and good cosmetic results, laparoscopic hysterectomy (LH) has substantially increased the era of hysterectomy procedures especially for the last two decades (9). The main reason for this is probably that LH leads to fewer inflammatory responses when compared to open abdominal hysterectomy (10). Although the inflammatory response is supposed to be lower with total laparoscopic hysterectomy (TLH), unpredictable inflammatory response as a result of the operation has been still unenlightened and it can be associated with hospital stay. On the other hand, there is no data to date on the relationship between the length of hospital stay and hemogram inflammatory parameters in patients who have undergone TLH for benign indications. The purpose of this study is to investigate the possible effect of inflammatory parameters that can be easily obtained from complete blood count on the postoperative first day of TLH on the length of hospital stay in patients without any complications for the first time.

METHODS

Patients who underwent TLH without any postoperative complications and biochemical abnormality between January 2014 and November 2018 in a training and research hospital were enrolled in this retrospective cohort study. Informed consent was obtained from each patient before surgery to allow the use of medical data related to their operation for research at our

clinic. Ethical approval was obtained from the University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital Clinical Research Ethics Committee and the study was planned in accordance with the declaration of Helsinki (decision no: 90, date: 28.05.2020). The patients with endometriosis, endometrial cancer, cervical cancer, a new diagnosis of chronic lymphocytic leukemia, Behçet's disease, biochemical abnormality, the patients who used anti-inflammatory medications, and the patients who had severe intraabdominal adhesions were excluded. In addition, the patients with ureter injury, bladder injury, bowel injury, superficial inferior mesenteric artery injury, vaginal cuff hematoma and vaginal cuff dehiscence were also excluded from the study. Patients who underwent TLH without any postoperative surgical complications such as severe hemorrhage, high fever, ureteral, colon or vascular injuries were enrolled in the study. Patients with a uterus greater than 16 weeks of gestation and patients with gynecologic cancer were excluded from the study due to possible long operation time triggering more inflammation (Figure 1). Indications for the operations were as follows: myoma uteri, endometrial hyperplasia, abnormal uterine bleeding, adenomyosis, ovarian cysts, cervical dysplasia, and endometrial polyps. All patients were examined with ultrasound at least two times, in which the first examination was performed in outpatient clinic and the second one was performed one day before the operation by a gynecologist. Endometrial sampling was performed in patients with abnormal uterine bleeding prior to surgery. Final pathology of benign uterine disorders was confirmed from the paraffin blocks of hysterectomy material of all patients. The physical condition classification of the American Society of Anesthesiologists (ASA) was similar (ASA1-ASA2) in both groups. Standard antibiotic prophylaxis with cefazolin 2 g was applied just before the operation. All the operations were performed under general anesthesia with endotracheal tube intubation. TLH was performed conventionally with all intraabdominal steps with four ports, including the vaginal closure, and the specimen was taken out through the vaginal way. Oophorectomy was optional, although salpingectomy was performed in all patients. Hemostasis in the operations was performed with the use of bipolar dissection. Medical data such as age, body mass index (BMI), parity, operation time, intraoperative bleeding, duration of hospital stay, history of cesarean section, and smoking were obtained from the medical records. BMI was calculated by dividing weight (kg) by square of height (meters). Operation time was determined as the duration from starting the skin incision to merging incision sides. The amount of bleeding during the operation was calculated by subtracting the irrigation fluid from the total amount of suction fluid. Only suction material was considered in patients in whom no irrigation was used. Duration of hospital stay was determined as the time from the first day of operation until discharge of the patient. Patients were discharged from the hospital when their vital signs became normal, bowel activity returned, and ambulation of the patient was achieved with no further need for analgesics. A complete blood count was recorded on the last

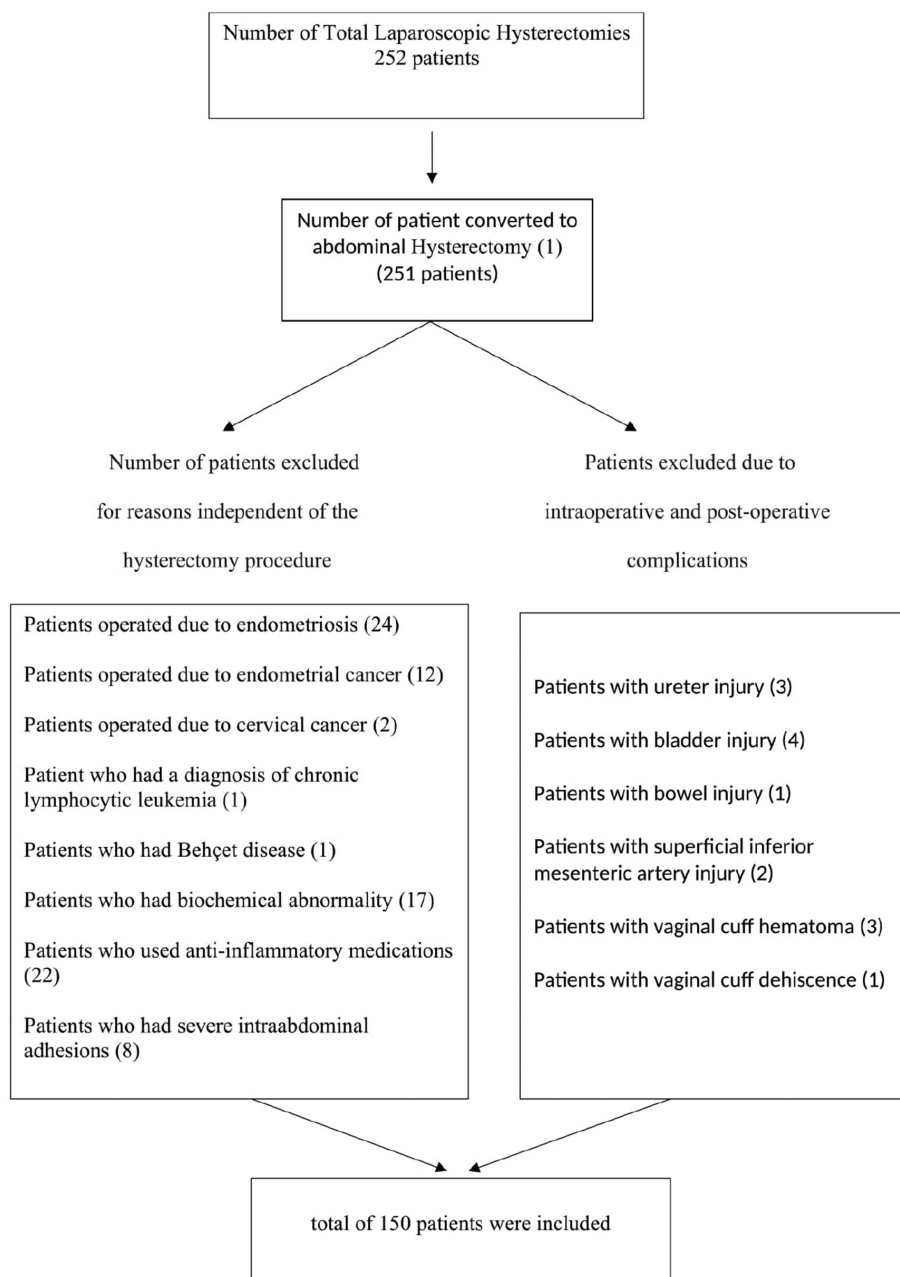


Figure 1. Flow chart of the patient selection

preoperative day and the first day after the operation. Levels of C-reactive protein (CRP) are routinely seen on the first day of operation in our clinic. Intramuscular dexamethasone is applied twice and low molecular weight heparin is used in all patients postoperatively. Any of the patients received perioperative or postoperative blood transfusion. Analysis of the hemogram was performed using Variant II Hemoglobin Testing System (Dubai Biotechnology and Research Park, Dubai, United Arab Emirates). Analysis of CRP levels were performed by using Uni Cell DxI 800 chemistry system (Beckman Coulter, Fullerton, Calif., USA). Inflammatory indicators in hemogram that we recorded were: neutrophil count (Neu#) of 2 to 8 $10^3/\mu\text{L}$; Lym# of 1 to 5 $10^3/\mu\text{L}$ and PLT count of 150 to 400 $10^3/\mu\text{L}$. NLR and PLR

were calculated by dividing the absolute number of neutrophil and absolute number of PLTs to the absolute number of lymphocytes, respectively. These two indices of inflammation were compared between patients who were hospitalized for more than 3 days and equal to or less than 3 days. Choosing day 3 as a threshold was because the mean length of hospital stay after LH was shown as up to a maximum of 3 days in literature (11).

Statistical Analysis

The SPSS version 22 (IBM Corp., Armonk, N.Y., USA) was used for statistical analysis. The variables were expressed as mean \pm standard deviation or median (minimum-maximum) or number (%). The normality distribution of variables was evaluated using

Kolmogorov-Smirnov test. Comparisons of continuous variables between two groups were performed with Student's t-test or Mann-Whitney U test. Chi-squared test was used to compare nominal variables. Linear regression analysis was performed to find possible associations between hospital stay and the associated variables. Correlation analysis of hospital stay with variables was performed with Pearson correlation test. Receiver operating characteristic (ROC) curve analysis was performed to determine the cut off values of NLR, PLR, and CRP for long hospital stay (>3 days). $P < 0.05$ was considered to be statistically significant and all p-values were two-sided.

RESULTS

A total of 150 patients with sufficient medical data were involved in this retrospective cross-sectional study. Demographic and clinical properties are included in Table 1. The mean age of this population was 48.7 ± 7.26 (30-76) with mean BMI of 30.43 ± 4.62 (18.1-45). One third percent of the patients were smokers. The mean value of preoperative hemoglobin was 11.9 ± 1.61 g/dL. An intraoperative bleeding volume of 421 ± 226 cc was observed in operations lasting within a mean value of 110.8 ± 36 minutes. The mean hospital stay was 3.23 ± 1.41 days. The mean preoperative NLR and PLR values were 2.29 ± 0.91 and 146.2 ± 49.5 , respectively. When looking through the postoperative values for the same ratios, the mean value for NLR was 6.18 ± 4.5 and the mean value of PLR was 172.2 ± 77.8 . Pre- and postoperative

values of mean PLT volume were found as 9.1 ± 1.0 and 9.0 ± 1.3 , respectively. Postoperative mean value of CRP was 29.6 ± 21.8 mg/L. The most common indication for TLH was myoma uteri followed by abnormal uterine bleeding (Figure 2). Endometrial hyperplasia was the third most common indication of operation. The patients were further divided into two groups to evaluate the duration of hospital stay and its related factors. The two groups were identified by 52 patients who were hospitalized for three days or less and 98 patients hospitalized for more than three days. There was no statistical difference (Table 2) regarding age, BMI, parity status, history of cesarean section, smoking, operation time, intraoperative bleeding volume, preoperative NLR, and preoperative PLR. On the other hand, there were statistically significant differences between the groups in terms of postoperative NLR, PLR, and CRP values with p-values of 0.009, <0.001, and 0.002, respectively.

The correlation between the duration of hospital stay with age, BMI, operation time, intraoperative bleeding, preoperative NLR, postoperative NLR, preoperative PLR, postoperative PLR, and postoperative CRP were demonstrated in Table 3. Correlation of duration of hospital stay was found with postoperative NLR ($p < 0.001$), postoperative PLR ($p < 0.001$), and postoperative CRP ($p < 0.001$) values. There was no correlation between age, BMI, operation time, intraoperative bleeding, preoperative NLR, preoperative PLR, and hospital stay.

Regression analysis was performed to find the possible variables associated with the length of hospital stay. Postoperative CRP, NLR, and PLR values were found to be associated with long hospital stay ($p < 0.001$). ROC analysis showed postoperative CRP, NLR, and PLR values to be significant predictors of long hospital stay. A postoperative CRP value of 25 was found to be able to estimate a long hospital stay with a sensitivity of 65% and specificity of 63% [area under the curve (AUC): 0.657, $p = 0.002$, confidence interval (CI) (0.563-0.752)]. Similarly, a postoperative PLR value of 159 was

Table 1. Demographic and clinical properties of the patients

Patients (n=150)	
	n (%)
Multiparity	137 (91.3)
Cesarean section history	35 (33.3)
Smokers	50 (33.3)
	Mean \pm SD (range) min-max
Age (years)	48.7 ± 7.26 (30-76)
BMI (kg/m ²)	30.43 ± 4.62 (18.1-45)
Preoperative hemoglobin (g/dL)	11.9 ± 1.61 (6.4-15.1)
Intraoperative bleeding (cc)	421 ± 226 (50-1100)
Operation time (minute)	110.8 ± 36 (45-200)
Hospital stay (days)	3.23 ± 1.41 (1-8)
Preoperative NLR	2.29 ± 0.91 (0.71-8.25)
Preoperative PLR	146.2 ± 49.5 (19.5-354)
Postoperative NLR	6.18 ± 4.5 (0.51-28.8)
Postoperative PLR	172.2 ± 77.8 (46-428)
Preoperative MPV	9.1 ± 1.0 (7.1-13.5)
Postoperative MPV	9.0 ± 1.3 (0.3-11.6)
Postoperative CRP (mg/L)	29.6 ± 21.8 (3-120)

Data are given as mean \pm standard deviation (minimum-maximum) or number, percent.

BMI: body mass index, NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, MPV: mean platelet volume, SD: standard deviation, CRP: C-reactive protein, min: minimum, max: maximum

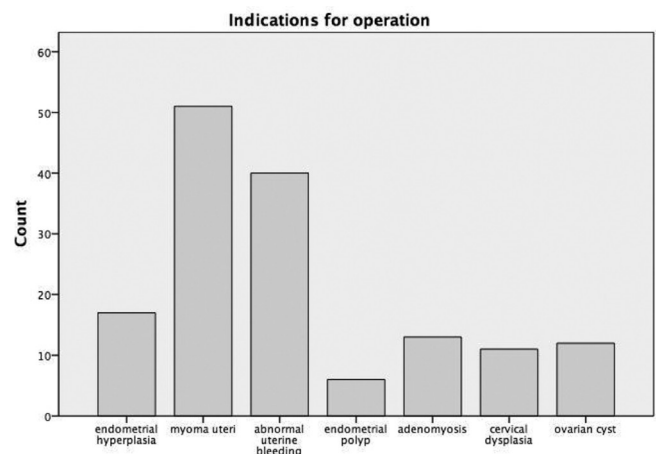


Figure 2. Distribution of indications for total laparoscopic hysterectomy

Table 2. Comparison of the patients with hospital stay ≤ 3 days and >3 days

Hospital stay, n	≤ 3 days (98 patients)	>3 days (52 patients)	p-value
Age (y)	49.0 \pm 6.8	48.2 \pm 8.0	0.533**
BMI (kg/m ²)	30.6 \pm 4.5	30.0 \pm 4.9	0.515**
CS history n (%)	26 (28)	9 (18)	0.168
Preoperative hb	12.0 \pm 1.7	11.7 \pm 1.5	0.217**
Smoker, n (%)	30 (31)	20 (39)	0.332
Operation time (days)	107 \pm 35.3	118 \pm 36.6	0.104*
Intraoperative bleeding (cc)	405 \pm 210.4	451 \pm 253	0.351*
Preoperative NLR	2.3 \pm 0.8	2.3 \pm 0.9	0.648*
Preoperative PLR	144.6 \pm 49.9	149.2 \pm 49.3	0.707*
Postoperative NLR	5.2 \pm 3.4	7.8 \pm 5.7	0.009*
Postoperative PLR	153.5 \pm 66.3	207.7 \pm 86.0	<0.001*
Preoperative MPV (fL)	9.2 \pm 0.9	9.1 \pm 1.0	0.676**
Postoperative MPV (fL)	9.2 \pm 0.9	8.8 \pm 1.9	0.230**
Postoperative CRP (mg/L)	25.0 \pm 17.0	38.3 \pm 27.0	0.002*

The results are given as mean \pm standard deviation or number, percent (%). BMI: body mass index, CS history: cesarean history, hb: hemoglobin, NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, MPV: mean platelet volume, CRP: C-reactive protein

*Mann-Whitney U test was used for statistical analysis

**Independent t-test was used

Table 3. Correlation of the length of hospital stay with associated variables

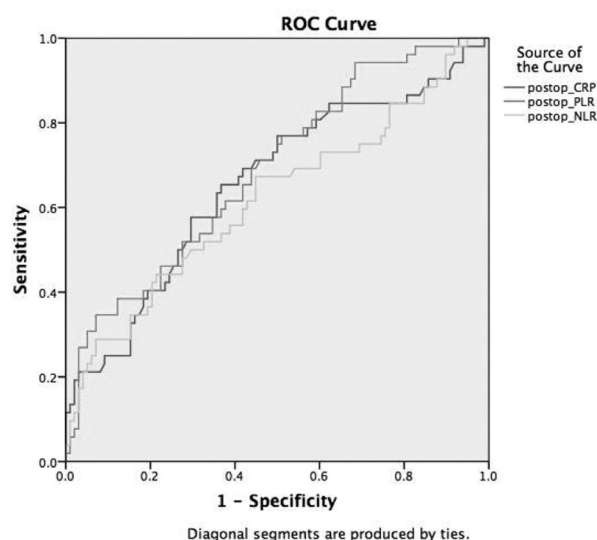
	r	p-value
Age	0.033	0.686
BMI	0.072	0.381
Operation time	0.080	0.331
Intraoperative bleeding	0.056	0.493
Preoperative NLR	0.056	0.497
Preoperative PLR	0.055	0.501
Postoperative NLR [‡]	0.332	<0.001
Postoperative PLR [‡]	0.325	<0.001
Postoperative CRP (mg/L)	0.404	<0.001

BMI: body mass index, NLR: neutrophil-to-leucocyte ratio, PLR: platelet-to-lymphocyte ratio, CRP: C-reactive protein

found to have a sensitivity of 60% and specificity of 58% (AUC: 0.688, $p < 0.001$, CI 0.600-0.776) and postoperative NLR value of 4.9% was found to have a sensitivity of 60% and specificity of 58% (AUC: 0.618, $p = 0.017$, CI 0.520-0.717) (Figure 3).

DISCUSSION

The associations of NLR, PLR, and CRP values with length of hospital stay in patients who underwent TLH without any postoperative complication was investigated in this study. Postoperative values of NLR, PLR, and CRP were found to be associated with the length of hospital stay. A 4.9% cut-off value of postoperative NLR and 159 cut-off value of postoperative PLR were found to have sensitivity of 60%, specificity of 58% and sensitivity of 60%, specificity of 58%, respectively, to predict the

**Figure 3.** Receiver operating characteristic curves for neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and C-reactive protein for the prediction of long hospital stay

CRP: C-reactive protein, NLR: neutrophil-to-leucocyte ratio, PLR: platelet-to-lymphocyte ratio, ROC: receiver operating characteristic

duration of hospital stay more than 3 days. These findings were similar to the sensitivity and specificity of CRP to predict a long hospital stay. Since 1989, annually performed laparoscopic hysterectomies have gradually increased in clinical practice. The main reasons for the preference of the laparoscopic approach are shorter hospital stay, faster return to normal life, and not being appropriate for vaginal hysterectomy (12). The length of hospitalization, even after an optimum laparoscopic surgery, can

still result in differences among the patients, lasting up to 8 days (13). Inflammatory response or autoimmune characteristics of the patients can differ due to different phenotypes with a complex mechanism that is not fully elicited yet (14). Although laparoscopic surgeries lead to fewer inflammatory responses compared to open surgeries, the difference between patients may be due to the underestimated individual inflammatory response determined by multiple underlying factors. There are few studies investigating the association between the length of hospital stay and NLR for benign surgical interventions. Sengul et al. (15) demonstrated that preoperative NLR could add approximately one more day to the length of hospital stay in patients with complicated and uncomplicated appendicitis. Erdolu et al. (16) evaluated preoperative NLR in patients who underwent coronary artery by-pass surgery and showed that high NLR indicated not only a long hospital stay but also a long stay in the intensive care unit. A retrospective study conducted by Asada et al. (17) revealed that prolonged hospitalization was associated with high preoperative NLR. Paliogiannis et al. (18) investigated the indicators determining the hospital stay in open elective thoracic surgery and demonstrated weak correlation between preoperative NLR and hospital stay. In our study, the preoperative value of NLR was not found to be associated with long hospital stay because there was no ongoing preoperative inflammatory process and all of them were elective surgeries. Hence, the mean value of preoperative NLR did not differ between the groups. Postoperative NLR is also discussed in some studies of benign indications for predicting hospital stay. Zheng et al. (19) showed that postoperative NLR was lower in patients who underwent minimally invasive distal pancreatectomy when compared to patients who underwent open access and that the patients who underwent open access stayed in hospital more than 4 to 5 days. Da Silva et al. (2) studied the utility of NLR for predicting outcomes of bariatric surgery and showed that a NLR value of greater than 10 at the postoperative first day of surgery was associated with a prolonged hospital stay, corresponding to 3.7 times more than the patients having NLR less than 10. Bath et al. (20) discovered that not only the preoperative NLR but also the postoperative NLR were associated with long hospital stay stressing that especially postoperative NLR values tended to be higher in patients who underwent open surgery. In our study postoperative NLR was correlated with long hospital stay (>3 days) ($p<0.001$). Furthermore, in regression analysis, NLR was found to be a variable that was associated with long hospital stay. In ROC analysis, a cut off value of 4.96 for postoperative NLR with a sensitivity of 60% and specificity of 58% (AUC: 0.618, $p=0.017$, CI 0.520-0.717) predicted long hospital stay, which was similar to CRP [cut off the value of postoperative CRP was 25 with a sensitivity of 65% and specificity of 63% AUC: 0.657, $p=0.002$, CI (0.563-0.752)]. We assumed that the difference in the postoperative NLR values in such a standardized group was associated with the individual inflammatory response characteristics of each patient. As per the range of pre-op hemoglobin levels, some patients had anemia of varying

severity. That is in itself a cause of increased infection rate. But still, our results are significant in predicting who will be infected more, even if they are anemic. Furthermore, NLR is a ratio and should not be affected from global decrease of complete blood count parameters. The structure of neutrophils and lymphocytes don't include iron therefore the amount of these again shouldn't be affected from anemia as they are inflammatory markers. Our findings were compatible with the literature in terms of predicting long hospital stay by using postoperative NLR values.

The PLR is another simple index that can be easily obtained from a complete blood count. This ratio is associated with surgical outcomes in the literature, one of which is the length of hospital stay but in a limited number. A retrospective study conducted by Xu et al. (21) found that the preoperative NLR and PLR with cut-off values of 2.9 and 129.5, respectively in ROC analysis were significantly higher in patients who underwent percutaneous nephrolithotomy. Therefore, the length of hospital stay was longer in that group (21). Another study, conducted by Pehlivanlı and Aydin (22), demonstrated that preoperative PLR together with NLR were increased in patients with perforated appendicitis compared to acute appendicitis or normal appendix. Consequently, prolonged hospitalization was an inevitable result for patients with perforated appendicitis (22). In our study, preoperative PLR was not associated with long hospital stay. We believe that non-inflammatory, elective gynecological indications cannot trigger the inflammatory process formerly; therefore, the preoperative ratios will be in normal range. To date, postoperative PLR has not been found to be associated with the length of hospital stay for any kind of benign surgical intervention in any known literature. In our study, elevated postoperative PLR was correlated with a long hospital stay. In addition, it was found to be associated with long hospital stay in regression analysis. In ROC analysis, a cut-off value of 159 for postoperative PLR with a sensitivity of 60% and specificity of 58% (AUC: 0.688, $p<0.001$, CI 0.600-0.776) predicted long hospital stay. This was similar to both CRP and NLR [cut off value of postoperative CRP was 25 with a sensitivity of 65% and specificity of 63% (AUC: 0.657, $p=0.002$, CI 0.563-0.752), cut-off value of postoperative NLR was 4.96 with a sensitivity of 60% and specificity of 58% (AUC: 0.618, $p=0.017$, CI 0.520-0.717)].

Study Limitations

In this study, we have some limitations. Although all biochemical indicators of the patients, both pre- and post-operatively were normal, tests were not performed for diabetes mellitus or insulin resistance. Diabetes mellitus, which is an important metabolic disease affecting wound healing, can be an indicator associated with inflammatory response. Secondly, ovarian status in surgery can be another variable. We did not mention whether an oophorectomy was performed or not under the assumption that hormonal status would not be affected within one month postoperatively. However, this could be an indicator interfering with the inflammatory response due to extra vessel sealing. Furthermore, we did not discuss the peritoneal drainage, and this

could also affect serum biomarkers.

CONCLUSION

Postoperative NLR, PLR, and CRP were found to be associated with length of hospital stay in our population with benign gynecologic indications in whom the surgical intervention type was TLH without any surgical complication. The NLR value together with CRP and PLR, at the postoperative first day of TLH could be suggestive for predicting the length of hospital stay and could be used instead of each other independently because all predictive values of these 3 indexes in ROC curve were similar. Moreover, CRP is not a routine test used in daily practice after non-complicated benign gynecological surgeries. So, calculating NLR and PLR from complete blood count is cheap and easy for clinicians to assess the individual and unpredictable inflammatory response. In patients exceeding the described cut-off values, new anti-inflammatory treatments targeting the various steps of inflammation may be tried to shorten the length of hospital stay or antibiotics can be used in these patients to slow down the inflammatory response. It may be that preventing the aggregation of PLTs with medications may also contribute positively to slow down the inflammation. In future studies, NLR and PLR can be studied for detection of urinary, bowel or vessel injury. Randomized controlled trials with enlarged sample size are needed to enhance strategies in achieving shorter length of hospital stay and predicting possible complications after TLH or any other surgical interventions.

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Informed Consent: Informed consent was obtained from each patient before surgery to allow the use of medical data related to their operation for research at our clinic.

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