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Effect of platelet large cell ratio (PLCR) and immature granulocyte (%IG) values on prognosis in surgical site infections

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Ethics Committee Approval
The study protocol was approved by the Ethics Committee of Istanbul Education and Research Hospital (date: 07/02/2020, issue number: 2176) All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Surgical site infections (SSI) are serious operative complications that occur in approximately 2% of surgical procedures, although rates vary widely according to the type of procedure. Measurement of immature granulocyte percentage (%IG) and Platelet Larger Cell Ratio (PLCR) may be used as a marker of serious bacterial infections. The study aims to evaluate whether the %IG and PLCR are useful additional predictive markers of surgical site infections.

Methods: This retrospective cohort study included 50 patients with surgical site infections and 50 control individuals. Patients who were hospitalized in the Istanbul Education and Research Hospital Gynecology and Obstetrics Department between October 2017 and January 2019 were scanned. The Mann-Whitney U test was used to compare continuous variables, and the chi-square test was utilized to compare categorical data.

Results: A cut-off of 30.1 for PLRC and 0.35 for %IG had 72% sensitivity and 45% specificity, and 97% sensitivity and 78% specificity (AUC: 0.95), respectively, for the diagnosis of wound site infections. The PLRC and %IG values of the patients with and without wound site infections significantly differed (P=0.052, and P<0.05, respectively). PLRC value slightly negatively correlated with hospitalization duration (r = -0.102), and strongly negative correlated with antibiotic use (r = -0.01).

Conclusion: PLCR and %IG can be used as easy, reliable, cost-effective, and fast biomarkers for the detection and evaluation of severity in wound infection.

Keywords: Surgical site infections, Platelet large cell ratio (PLCR), Immature granulocytes (IG)

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Introduction

Among hospitalized patients, surgical site infection (SSI) makes up 14-16% of all nosocomial infections and is the third most frequent nosocomial infection. SSI can be classified into three categories according to the depth of the wound and the severity of the infection from superficial incisional to organ/space involvement, based on the Center for Disease Control and Prevention (CDC) reports [1].

Proper diagnosis of SSI is vital since its progression may lead to significant morbidity, and socio-economic problems if overlooked [2]. After obstetric and gynecologic procedures, SSIs are frequently encountered as a postoperative complication.

SSI is the most common reason for prolonged hospital stay and readmission. By checking the patient's routine laboratory analysis, initially white blood cell (WBC) count and C-reactive protein (CRP) levels, infections, and related complications were evaluated by physicians. In the past decade, other markers have been used to detect infections.

Platelets, 3-5μm in diameter and 4.5-11fL in volume, are cytoplasmatic fragments of megakaryocytes that are present in the bone marrow [3]. In addition to their critical role in thrombosis and hemostasis, evidence by many reports suggests that platelets contribute to the microbial host defense, inflammatory process, angiogenesis, wound healing, and remodeling [4].

Platelets act as first responders during the injury process and hemostasis. To aid tissue regeneration and wound sterilization, following surgical incision, platelets actively migrate from the inflamed or leaky vessel wall [5]. Platelet activity has been monitored by PLCR, which is defined as the percentage of circulating larger platelets (>12 fL).

PLCR and immature granulocytes are automatically measured while obtaining a complete blood count. The normal range is between 15-35% [6].

Recently, the role and several functions of platelets in the inflammation process were defined. A significant number of studies have shown that platelets play an essential role in the pathogenesis of various inflammation-related clinical circumstances.

The role of platelets from severe infection to systemic inflammatory reaction syndrome (SIRS), trauma, and thrombotic events have been researched by numerous groups who defined the activation of the coagulation system and changes in platelet volume, size, and different indices [7].

Currently, modern automated hematology analyzers are available. They measure other usable infection markers, such as PLCR and immature granulocyte percentage (%IG), to be used as parameters of severe bacterial infections [8, 9]. As a potential marker, some recent studies have searched the function of %IG to estimate the severity of infection [10, 11]. These studies were predominantly based on adult patients with a critical illness hospitalized in the intensive care units.

Our study aimed to compare the PLCR and %IG values in patients with and without SSI in the Obstetrics and Gynecology clinic and their significance in diagnosis, along with their relationship with disease severity by assessing the correlation of PLCR and %IG values with parametric values such as duration of hospitalization and antibiotic treatment.

Materials and methods

Our study was performed retrospectively in the Gynecology and Obstetrics department of a tertiary level education and research hospital. From October 2017 to January 2019, all patients diagnosed with surgical complications were evaluated for inclusion in the study. The inclusion criteria were being between 18–40 years of age, and developing incisional SSI after the gynecologic, gynecologic oncologic, or cesarean operations. Control patients were selected randomly between 18–40-year-old patients who were referred to our Gynecology and Obstetrics outpatient clinic for a routine follow-up examination without any signs of urinary tract infection or pelvic inflammatory disease. Patients with serious trauma, an infection occurring immediately after surgery, cardiac shock, those receiving immunotherapy, those with autoimmune diseases, paraneoplastic syndrome, acute versus host disease, and deep infections with organ and/or space involvement were excluded from the study. Infections which affect the skin or subcutaneous tissue within 30 days of the procedure are defined as incisional SSIs. At least one of the following signs must be documented to diagnose a patient with incisional SSI: Purulent drainage from the wound, redness and/or swelling of the incision, and wound separation.

Patients who developed SSI according to the CDC criteria were treated either in inpatient or outpatient settings. Blood samples were obtained from patients for complete blood count (CBC), CRP, and sedimentation analysis. Leukocyte count, PLCR, and% IG were measured using an automated hematological analyzer (XN-1000; SysmexCorp.), from blood samples obtained at the first admission to the outpatient clinic or the emergency room. PLCR and% IG values were calculated by semiconductor flow cytometry using the data obtained from CBC analysis. Intravenous antibiotic therapy was started with metronidazole and a second-generation cephalosporin.

Statistical analysis

Data were presented as median (interquartile) and continuous, non-normally distributed data were analyzed with the Mann–Whitney U-test. The qualitative data were analyzed by either Fisher's test or chi-square test. Correlation analysis between PLCR and %IG value and parametric variables was conducted with either Pearson's for interval scale or Spearman's for ordinal scales analysis.

The study protocol was approved by the Ethics Committee of Istanbul Education and Research Hospital (date: 07/02/2020, issue number: 2176) and conducted in accordance with the Declaration of Helsinki.

Results

Fifty females who developed SSI after surgery and 50 control individuals were enrolled in our study. Among 50 SSI patients, 9 patients had undergone a cesarean section, 14 patients, a gynecologic-oncologic operation (endometrium, ovarian and cervical cancer) and 27 patients had undergone gynecologic operations (salpingectomy, myomectomy, hysterectomy, sacrocolpopexy). All patients had superficial wound infections.

As shown in Table 1, the mean ages of the SSI and control patients were 44.1 years and 36.3 years, respectively. The median PLRC values of the SSI and control patients were 25.1 and 28.2 respectively, and the median %IG values of the SSI and control patients were 1.62 and 0.27 respectively. Significant differences were found between the PLRC and %IG values of patients with and without wound infections (P=0.052, and P<0.05, respectively). The mean BMI, CRP and WBC values of SSI patients were 32 kg/m^2, 103.9 mg/L, and 11.7x10^9/L, respectively, while those of the control patients were 29.2 kg/m^2, 6.1 mg/L and 7x10^9/L, respectively. Thirty-four out of 50 SSI patients (68%) had normal WBC count at admission to the hospital. The mean hospitalization duration was 18.2 days among SSI patients.

Table 1: Demographic data of the study population

	SSI(n=50)	Control(n=50)	*P*-value
Age (years)	44.1	36.3	<0.05
PLRC	25.1	28.2	<0.05
%IG	1.62	0.27	<0.05
BMI (kg/m^2)	32	29.2	>0.05
CRP (mean)	103.9	6.1	<0.05
ESR mean)	79.6		
WBC (x 10^9/L)	11.7	7.00	<0.05

PLRC: platelet large cell ratio, %IG: immature granulocyte percentage, BMI: body mass index, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, WBC: white blood cell

The mean %IG value of culture-negative and culture-positive SSI patients were 2.61, and 0.97, respectively (P=0.002).

A cut-off of 30.1 for PLRC and 0.35 for %IG had 72% sensitivity and 45% specificity, and 97% sensitivity and 78% specificity (AUC: 0.95), respectively, for the diagnosis of wound site infections (Figures 1 and 2).

Figure 1: ROC curve analysis of PLRC value in wound infection patients

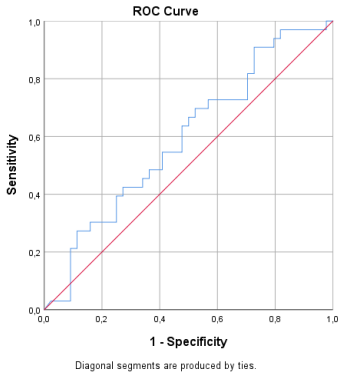
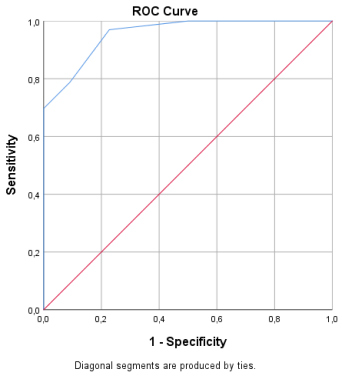


Figure 2: ROC curve analysis of %IG value in wound infection patients



PLRC value slightly negatively correlated with hospitalization duration (r = -0.102), and strongly negatively correlated with duration of antibiotic use (r = -0.01) (Figures 3 and 4), while %IG value slightly negatively correlated with hospitalization duration (r = -0.110), and slightly negatively correlated with duration of antibiotic use (r = -0.023) (Figures 5 and 6).

Among the SSI infection group, there were 30 culture-negative and 20 culture-positive patients. Among culture-positive patients, 2 had methicillin-resistant Staphylococcus aureus (MRSA), 1 had Candida spp., 3 had Escherichia coli (E.coli), 3 had Pseudomonas spp., 1 had Enterococcus spp., 1 had Klebsiella spp., 1 had S.capitis, 2 had S.epidermidis, 1 had Morganella morganii, 2 had Enterobacteria sp., 1 had S.haemolyticus, 1 had P. mirabilis, 1 had Acinetobacter infection.

Figure 3: Correlation analysis of hospitalization time with PLRC value

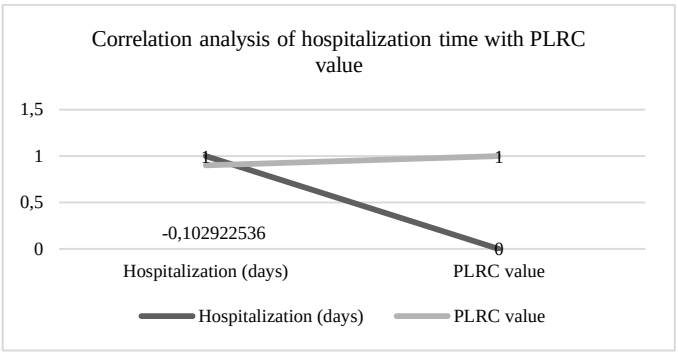


Figure 4: Correlation analysis of duration of antibiotic use with PLRC values of patients

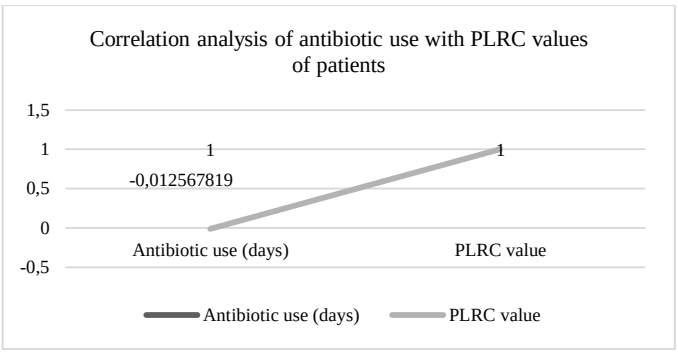


Figure 5: Correlation analysis of hospitalization time with %IG

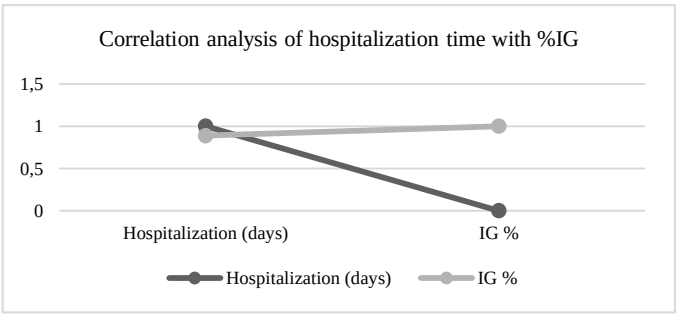
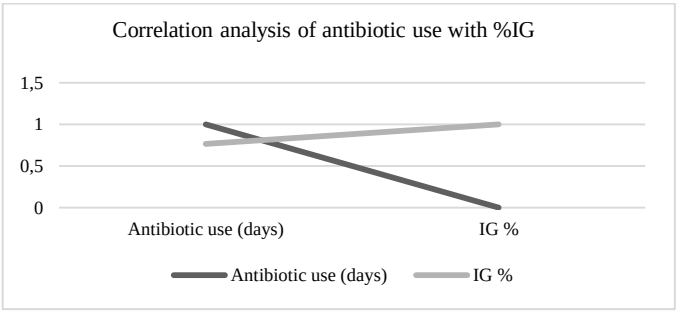


Figure 6: Correlation analysis of antibiotic use with %IG (There was a slight negative correlation between antibiotic use and %IG (correlation coefficient = -0.023).



Discussion

PLCR is another substitute marker that defines the largest size fraction of platelets for platelet volume, and an increase usually indicates the production of new platelets. Only a few reports studied PLCR value in sepsis and/or infection patients. Our study is one of the first studies to provide a PLCR cut-off value among gynecology patients. Gao et al. [12] analyzed 124 patients with septic shock retrospectively, and several important results were reported. In the non-surviving group (n=88), platelet and procalcitonin decreased while mean platelet volume (MPV), PLCR, and platelet distribution width (PDW) increased with time. PLCR was more sensitive to platelet size changes but was mostly correlated with MPV. Contrary to our results, their PLCR values were higher in their non-survivor group of patients, but their study population was critically ill. We

also found a negative correlation between PLCR and SSI severity, and we conclude that PLCR first decreases in number at the beginning of the inflammatory cascade, then starts to increase as the disease progresses to septic shock. Our findings are in concordance with the results of Zhan et al. [13] who found that PLCR value was significantly lower in patients with active periodontitis compared to the healthy control group.

Babu et al. [14] showed that the PLCR levels were parallel to MPV and PDW values and are inversely related with platelet count, which may help form a link between these two parameters. Comparative studies are needed on which one is superior and/or of equal value in estimation of progression and severity.

Some studies suggest that the %IG is a useful and an easily obtainable adjuvant marker to predict the severity and invasiveness of microbial infection in critically ill patients [15].

In earlier studies, contrary to our results, %IG was elevated in non-critically ill adults and neonates with infection [16,17,18,19,20]. Since our patients had a relatively mild infection at the beginning, as disease progresses, %IG values start to decrease, which is valuable for determining disease progression, since we found a negative correlation of %IG value with a duration of antibiotic use. More than half of our patients had normal WBC count during admission. One study showed that %IG predicts infection better than total WBC count [18]. Some studies conclude that %IG values better reflect the severity of sepsis than CRP, WBC, and procalcitonin, and attribute equivalent discrimination power to lactate [21]. We also found a negative correlation between %IG values, and disease progression and severity.

Another challenge in diagnosing sepsis is that infection is not always confirmed even if treatment is started and only in 30–40% of cases, a positive culture sepsis is present [22].

Early diagnosis and no delay in the treatment of sepsis with antibiotics can be lifesaving since sepsis is the most common cause of mortality in intensive care units [23].

However, obtaining culture results normally takes 24-48 hours, which generates a delay in treatment and diagnosis. In some clinics, broad-spectrum antibiotic therapy is initiated while waiting for culture results. However, this option is expensive and may pose a risk as unnecessary and prophylactic antibiotics may induce the development of highly resistant microorganisms [23]. More than half of our patients had negative culture results but delaying treatment while waiting for the culture results or because of non-confirmed microorganisms may put the patient's life at risk. Accordingly, examinations that allow faster diagnosis with higher specificity are required.

Nierhaus et al. [24] reported that in SIRS patients, especially within the first 48 hours, the %IG value significantly differentiates infected patients from uninfected ones ($P < 0.0001$), with a sensitivity of 89.2% and a specificity of 76.4%. They found that IG value had higher diagnostic value than other laboratory parameters such as CRP, interleukin-6 (IL-6), and lipopolysaccharide-binding protein (LBP), which had less than 68% sensitivity. The ROC curve analysis showed a higher positive predictive value for % IG compared to other parameters in the first 5 days of meeting the SIRS criteria.

Lee et al. [25] showed that blood cultures are positive only in one-third of patients who show clinical features of sepsis. Contamination of blood cultures is another aspect of difficulty in the diagnosis of sepsis which may lead to misuse of antibiotics. Even though contaminated blood cultures were excluded from their study, IG% <2.0% helped rule out sepsis even before blood culture results. Future comparative studies with contaminated culture results may help validate the discriminative power of % IG. Ansari-Lari et al. [26] also found that the %IG value was better correlated with positive blood culture results and infection than WBC count.

Contrary to our results, as we found higher %IG values in culture-negative patients, Pavare et al. [27] found that %IG added valuable information regarding the performance of children with different infection degrees in all age groups. Their results were parallel with the previous studies and suggest an association between positive blood bacterial culture and higher IG%. Furthermore, higher levels of %IG are seen in culture-positive patients and suspected septicemia [15,24].

The wound infection patients in our study group were not critically ill, and our group of patients were younger, which led to less secondary morbidities associated with changes in hematological parameters. It is safe to assume that our values give more insight into infection pathogenesis in the early phase of the inflammatory cascade.

Ours is one of the first studies investigating PLCR and %IG values in SSI after gynecological operations.

Limitations

Since PLCR and %IG were recently incorporated into total blood count analyses, comparative studies are lacking in the Gynecology and Obstetrics Department. Even though postpartum cesarean patients were small in sample size, we included both postpartum cesarean and gynecology patients in our study. Therefore, there is a need for studies that analyze these two patient groups independently, although, when plasma volume begins to increase, hematocrit values return to normal within 3-5 days after birth. However, studies evaluating the values of hemoglobin longitudinally in the postpartum period show that it takes at least 4-6 months to transform the pregnancy-associated changes to non-pregnant psychology. Since studies comparing PLRC and %IG values in postpartum cesarean and control patients are lacking, normal reference values in the postpartum population needs to be determined by further studies. Our control group was randomly selected from patients without genitourinary infection, but patients with respiratory or other site infections could not be excluded from the study.

This study could provide a basis for future large-scale studies, by making it possible to validate our results. Including PLCR, and %IG in the SSI treatment protocol, and initiating treatment earlier when needed leads to greater recovery possibilities for post-operative gynecology patients.

Conclusions

We investigated the clinical significance of the PLCR and %IG count as new markers of acute inflammation. PLCR and %IG count showed infection even without leukocytosis and in case of negative culture results. We found that low PLCR and high % IG count can be used in early diagnosis and most importantly, the tendency of PLCR value to increase from

baseline indicates that the infection is getting more complicated, and vice versa applies for %IG value. Compared with other available inflammation markers, PLRC and IG count are rapidly generated with routine CBC analysis with no delay in sample analysis and without any extra cost.

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