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Can Neutrophil Count, Lymhocyte Count and Neutrophil-to-lymphocyte Ratio Predict Fever Following Percutaneous Nephrolithotomy in Patients Without Risk Factors?

Risk Faktörü Olmayan Hastalarda, Perkütan Nefrolitotomi Sonrası Ateşi Öngermede, Nötrofil, Lenfosit Sayısı ve Nötrofil-lenfosit Oranı Etkin Midir?

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What's known on the subject? and What does the study add?

Preoperative blood parameters could be good indicator to define patients without risk factors for post-percutaneous nephrolithotomy fever.

Abstract

Objective: To examine the relationship of neutrophil counts, lymphocyte count and neutrophil-to-lymphocyte ratio (NLR) with postoperative fever in patients undergoing percutaneous nephrolithotomy (PCNL).

Materials and Methods: A total of 519 patients aged over 18 years, who underwent PCNL between January 2005 and January 2013 and had a preoperative white blood cell count between 4000-12,000/µL, were included in this study. Conditions that could lead to postoperative fever or impact blood parameters constituted the exclusion criteria. At the postoperative period, the patients were divided into two groups based on the presence of fever. Age, gender, Body Mass index, stone size, number of percutaneous access, duration of operation, preoperative white blood cell count, neutrophils, lymphocytes, and NLR were compared. The relationship of these parameters with fever was evaluated with univariate and multivariate analyses.

Results: The group with fever included 50 patients and the group without fever, 469 patients. The difference between the two groups was statistically significant in terms of neutrophil and lymphocyte counts, and NLR. Univariate analysis revealed that preoperative thrombocyte count, lymphocyte count, neutrophil count, and NLR were the parameterss significantly related with fever, yet, in multivariate analysis, the only statistically significant parameters related with post-PCNL fever were age, thrombocyte count, and white blood cell count.

Conclusion: When risk factors for fever are excluded, lymphocyte count and NLR appear to be easy-to-use and affordable diagnostic markers to predict postoperative fever in patients undergoing PCNL.

Keywords: Bacteremia, Fever, PCNL, Neutrophil-lymphocyte ratio

Öz

Amaç: Perkütan nefrolitotomi (PNL) yapılan hastalarda lenfosit sayısı ve nötrofil lenfosit oranı (NLO) ile post operatif ateş arasındaki ilişkiyi değerlendirmek.

Gereç ve Yöntem: Ocak 2005 - Ocak 2013 tarihleri arasında PNL yapılan 519 hasta çalışmaya alındı. Çalışmaya; 18 yaş ve üzeri, preoperatiferatif beyaz küre sayısı 4000-12,000 10^3/µL arasında olan hastalar alındı. Postoperatif dönemde ateş yapabilecek ya da kan parametrelerini etkileyecek durumlar çalışma dışı bırakıldı. Postoperatif dönemde hastalar ateşi 38,5 °C üzeri olan ve ateşi olmayan olarak iki gruba ayrıldı.

Bulgular: Ateş olan grupta 50 hasta, ateş olmayan grupta 469 hasta vardı. Gruplar arasında yaş, cinsiyet, Beden Kitle indeksi, giriş sayısı, taş boyutu, beyaz küre ve trombosit sayısı bakımından istatistiksel olarak anlamlı farklılık yoktu. Ancak nötrofil sayısı, lenfosit sayısı ve NLO değerleri arasında

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her iki grup arasındaki fark istatistiksel olarak anlamlı bulundu. Univaryant analizde preopeatif trombosit, lenfosit, nötrofil sayısı ve NLO anlamlıyken multivaryant analizde yaş, trombosit ve beyaz küre sayısı anlamlı çıkmıştır.
Sonuç: PNL yapılan hastalarda ateş oluşturabilecek risk faktörleri dışladığında lenfosit sayısı ve NLO postoperatif ateşi öngörmede kullanılabilecek kolay ve ucuz bir tanı aracı olarak gözükmektedir.
Anahtar Kelimeler: Bakteriyemi, Ateş, PNL, Nötrofil-lenfosit oranı

Introduction

Percutaneous nephrolithotomy (PCNL) is a minimally-invasive method commonly used to remove kidney stones. The frequency of postoperative fever has been reported at a rate of 16.7% to 35% even in patients undergoing appropriate prophylactic antibiotic therapy and having a sterile urine culture (1,2,3). Urinary extravasation and bacteremia are the most likely causes of fever after PCNL (1). Although it is very important to isolate the causative microorganism for the diagnosis of bacterial infection in the postoperative period, it is not always possible and urinary and blood cultures may return negative. On the other hand, the techniques performed to elucidate the etiology of fever are time-consuming and may also generate pseudo-negative results due to many factors, antibiotics used for prophylactic purposes being in the first place (4,5). This leads to a prolonged hospital stay and an increased cost of patient care. Despite their limited use in early diagnosis of bacterial infections, C-reactive protein, white blood cell count and neutrophil count are the most commonly used parameters (6,7,8). More superior parameters include procalcitonin, pro-adrenomedullin, IL-6, and IL-8 (9). However, the fact that they are not available in all centers and impose higher costs limits their use. Recently, neutrophil-to-lymphocyte ratio (NLR) seems to be an effective biomarker as a simple and useful parameter for early diagnosis of bacterial infections (10,11). These tests, however, are used for early diagnosis of bacterial infection after emergence of fever. No single parameter has been proposed yet to predict postoperative fever even after the exclusion of preoperative factors that may cause fever.

In the present study, we aimed to investigate whether neutrophil count, lymphocyte count, and NLR obtained from routine preoperative blood tests can be used in predicting fever following PCNL in patients with no risk factors for infection.

Materials and Methods

The local ethical committee approved the study. Written and verbal consent was obtained from all patients before the operation. Data of 1.039 patients, who underwent PCNL between January 2005 and January 2013 and had complete patient records, were retrospectively evaluated. The study included patients of both genders aged over 18 with a preoperative white blood cell count between 4000 and 12,000/µL. The exclusion criteria included preoperative urinary system obstruction, proliferation in preoperative and/or postoperative urine culture, preoperative and/or postoperative blood transfusions, preoperative urinary diversion and/or intervention, presence of postoperative residual stone, presence of malignancy, and presence of hematologic diseases. Patients who had postoperative complication Clavien grade II and above were excluded from the study. The cohort was composed of patients who had only Clavien grade I complication. A total of 519 patients were included.

Ceftriaxone and ciprofloxacin were used for prophylaxis in the preoperative period while the patients were on the operating table. Conventional PCNL technique was employed. In the lithotomy position, a 6 Fr ureteral catheter was placed first, and then prone position was given. Under X-ray fluoroscopy percutaneous access was made with an 18 G needle after retrograde pyelography via ureteral catheter. Once the guide wire was sent to the pelvicalyceal system, the tract was dilated up to 30 Fr and an access sheath was placed. The stone was visualized with a 26 Fr nephroscope, broken into pieces by pneumatic and ultrasonic lithotripters, and collected with forceps. At the end of operation, a 20 Fr nephrostomy tube was placed in all cases. The postoperative nephrostomy tube was removed in 2-4 days after hematuria resolved. All operations were performed by three experienced surgeons who had completed their individual learning curve. Routine analgesic regimen-deksketoprofen trometamol IV/p.o.- twice a day was ordered for all patients until the nephrostomy tube was removed. Postoperative observation of a body temperature of 38.5 °C in three consecutive measurements in the ear at hourly intervals was accepted as fever. Body temperature measurement was used because it was the only available method during the study period. The patients were divided into two groups as those with and without fever. Age, gender, body mass index, stone size, number of percutaneous access, duration of operation, postoperative counts of white blood cells, neutrophils, lymphocytes, and thrombocytes were all recorded and NLR was calculated.

Statistical Analysis

The Kolmogorov-Smirnov test was used to test the normality of the study data. Categorical variables in both groups were compared using the chi-square test. The Mann-Whitney U test

was used to compare non-parametric variables. A p value of less than 0.05 was considered statistically significant. To predict postoperative fever, a receiver operating characteristic (ROC) analysis was performed for the variables that were significantly different between the two groups. Sensitivity, specificity, area under curve, confidence interval, positive predictive value (PPV) and negative predictive value (NPV), as well as Youden index (J index) values were calculated. To define potential preoperative factors associated with post-PCNL fever, univariate and multivariate analyses with logistic regression were performed.

Results

The group with fever included 50 patients (33 males and 17 females), while the one without fever included 469 patients (296 males and 173 females). The median age in the group with fever was 44 years (24-80), while it was 46 (18-83) years in the group without fever. The age, gender, Body Mass index, number of percutaneous access, stone size, duration of operation, preoperative counts of white blood cells, neutrophils, lymphocytes, and thrombocytes, and NLR values are summarized in Table 1.

Table 1. Baseline characteristics of the patients with fever and without fever

	Fever (+) n=50	**Fever (-) n=469**	**p**
Age (years)	44 (24-80)	46 (18-83)	**0.994**$^{\infty}$
Sex (n)	-	-	-
Male/female	33/17	296/173	0.679*
Body Mass index (kg/m^2)	24.7	27.5	**0.134**$^{\infty}$
(min-max)	(21-37)	(17.4-49.6)	-
#of Access (n)	1	1	**0.866***
(min-max)	(1-3)	(1-6)	-
Stone size (mm^2)	220	250	**0.376**$^{\infty}$
(min-max)	(100-1600)	(100-1200)	-
Operative time (min)	70	90	**0.387**$^{\infty}$
(min-max)	(15-220)	(10-572)	-
White blood cell count	7720	6810	**0.062**$^{\infty}$
(min-max)	(1770-11980)	(4200-11710)	-
Neutrophil count	5280	3930	**<0.001**$^{\infty}$
(min-max)	(1610-9110)	(1100-10100)	-
Lymphocyte count	1657	2500	**<0.001**$^{\infty}$
(min-max)	(520-2450)	(100-6820)	-
Thrombocyte count	252	262	**0.074**$^{\infty}$
(10^3/µL) (min-max)	(53-416)	(111-522)	-
NLR	3.295	2.050	**<0.001**$^{\infty}$
(min-max)	(1.46-12.85)	(0.35-32.4)	-

*: Pearson's chi-squared test, $^{\infty}$: Mann-Whitney U test, p<0.05, min: Minimum, max: Maximum, NLR: Neutrophil-to-lymphocyte ratio

There was no significant difference between the two groups in terms of age, gender, Body Mass index, number of percutaneous access, stone size, and preoperative white blood cell and thrombocyte counts. However, the difference between the two groups was significant in terms of neutrophil count, lymphocyte count, and NLR values. Sensitivity, specificity, area under curve, cut-off value, 95% confidence interval, PPV, NPV, and J index value were calculated for neutrophil count, lymphocyte count, and NLR values with the help of ROC analysis. NLR had a sensitivity of 86%, specificity of 55.2%, area under curve of 0.733, PPV of 16%, NPV of 97%, J index of 0.4122; neutrophil count had a sensitivity of 60%, specificity of 71%, area under curve of 0.670, PPV of 18%, NPV of 94%, and J index of 0.3186; and lymphocyte count had a sensitivity of 88%, specificity of 58%, area under curve of 0.725, PPV of 18%, NPV of 97%, and J index of 0.4621 (Table 2, Table 3). ROC curves calculated for neutrophil count, lymphocyte count, and NLR values are provided in Figure 1. Univariate analysis revealed that age (p=0.006), preoperative neutrophil count (p<0.001), lymphocyte count (p<0.001), NLR (p=0.038) and thrombocyte count (p=0.05) were significant factors affecting post-PCNL fever. The significant parameters in multivariate analysis, on the other hand, were age (p=0.025), thrombocyte count (p=0.011) and white blood cell count (p=0.045), which were not significant in univariate analysis (Table 4).

Ceftriaxone was used in 498 patients and ciprofloxacin was used in 21 patients. Fever was observed in 48 (9.6%) patients given ceftriaxone for prophylaxis and 2 (9.5%) (patients given ciprofloxacin. There was no difference between fever rates of two types of prophylactic antibiotics (p=0.671).

Discussion

Various regimens of antibiotic prophylaxis are implemented to prevent upper urinary system infections and urosepsis (12,13,14). There is a general tendency to apply a short-term antibiotic course, which typically lasts 48 hours after PCNL (15). However, as we showed in our previous study, application of a single-dose preoperative antibiotic is sufficient in patients with a clean preoperative urine culture and no risk factor for upper urinary system infection (16).

Today, there is no diagnostic test to predict post-PCNL fever preoperatively. Different prophylactic and therapeutic protocols may be employed if this possibly-bacteriologic complication is foreseeable, thus the cost of unnecessary antibiotics and overtreatment of patients can be prevented. Previous studies have shown that inflammatory processes increase neutrophil count and reduce lymphocyte count, while NLR is a simple and useful parameter to detect systemic inflammation (17). Goodman et al. (18) demonstrated NLR, rather than lymphocyte

Table 2. Sensitivity, specificity, area under curve, 95% confidence interval, positive and negative predictive values, and Youden index of receiver operating characteristic analysis

	Cut-off value	Sensitivity (%)	Specificity (%)	Area under curve (%95 CI)	± SE	PPV (%)	NPV (%)	J index
NLR	>2.21	86	55.2	0.733 (0.693 -0.770)	0.0290	16	97	0.4122
Neutrophil (10^3/µL)	>5	60	71.8	0.670 (0.628-0.710)	0.0421	18	94	0.3186
Lymphocyte (10^3/µL)	≤2.17	88	58.2	0.725 (0.685-0.763)	0.0262	18	97	0.4621

SE: Standard error, CI: Confidence interval, PPV: Positive predictive value, NPV: Negative predictive value, NLR: Neutrophil-to-lymphocyte ratio, J Index: Youden index

Table 3. Cross table of neutrophil counts, lymphocyte counts, and neutrophil-lymphocyte ratio

		Fever (+) n (%)	Fever (-) n (%)	Total n
Neutrophil count (103/µL)	>5	30 (60%)	133 (28%)	163
	<5	20 (40%)	336 (72%)	356
Lymphocyte count (10^3/µL)	<2.17	44 (88%)	196 (41%)	240
	>2.17	6 (12%)	273 (59%)	279
Neutrophile-lymphocyte ratio	>2.21	43 (86%)	210 (44%)	253
	<2.21	7 (14%)	259 (56%)	266
Total (n)	-	50	469	-

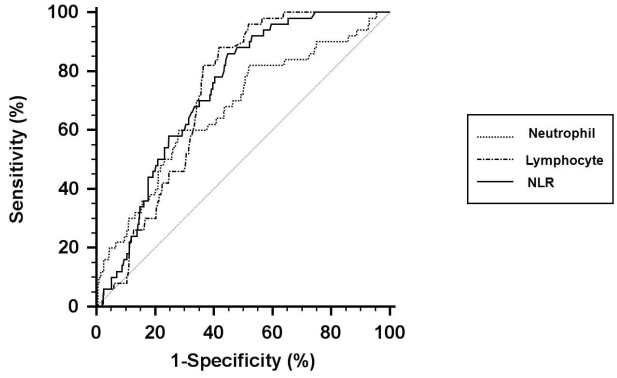

Figure 1. Receiver operating characteristic curves of neutrophil, lymphocyte, neutrophil-to-lymphocyte ratio

NLR: Neutrophil-to-lymphocyte ratio

count, to be a more specific parameter for appendicitis. It has also been shown that lymphocytopenia and NLR predict bacteremia to a better extent than common infectious disease parameters in emergency care units (10). Another study found eosinophil count and NLR to be prognostic factors in bacteremia (11). NLR has been found to predict community-acquired pneumonia-associated mortality better than neutrophil, white blood cell, and lymphocyte count as well as CRP (19). De Jager et al. (10) reported a sensitivity, specificity, PPV, and NPV of 72%, 63%, 67.6%, and 73.4%, respectively, for NLR. They found an area under curve of 0.73 for lymphocyte and NLR.

According to our results, we detected that lymphocyte count and NLR were more sensitive in predicting post-PCNL fever for patients without fever. In addition, we found that lymphocyte count was the most sensitive parameter with respect to J index. We found cut-off levels of ≤2170/µL and >2.21 for lymphocyte count and NLR, respectively. These cut-off levels may show variability depending on the patient population, and type and severity of inflammation. The reason for lower PPV in this study may be the high number of patients who were included in the fever (-) group. Presence of more patients in the fever (-) group makes NPV more important. According to the results of our study, 97% of patients without postoperative fever can be estimated by considering NLR and lymphocyte count. We think that postoperative fever and bacteremia can be prevented by various antibiotic prophylaxis strategies and therapeutic

Table 4. Univariate and multivariate analysis for potential factors associated with fever after percutaneous nephrolithotomy

			Post-PCNL Fever			
		Univariate			Multivariate	
	Odds ratio	95% CI*	p	Odds ratio	95% CI	p
Sex	0.881	0.477-1.629	0.687	-	-	-
Neutrophil count	1.432	1.207-1.699	<0.001	-	-	-
Lypmhocyte count	0.408	0.201-0.608	<0001	-	-	-
NLR	1.061	0.996-1.131	0.038	-	-	-
Stone size	1	0.998-1.001	0.749	-	-	-
BMI	0.948	0.868-1.036	0.239		-	-
Thrombocyte count	0.996	0.992-1.000	0.050	0.992	0.987-0.998	0.011
White blood cell count	1.142	0.963-1.355	0.126	1.262	1.005-1.584	0.045
Age in years	1.031	1.009-1.054	0.006	1.035	1.004-1.067	0.025

*CI: Confidence interval, NLR: Neutrophil-to-lymphocyte ratio, PCNL: Percutaneous nephrolithotomy, BMI: Body Mass index

regimens in patient groups considered at risk (NLR ≥2.21, lymphocyte count ≤2170) based on NLR and lymphocyte count.

Lymphocyte count, neutrophil count, NLR and platelet count are statistically significant preoperative factors affecting post PNCL fever in univariate analysis. In multivariate analysis, this is only valid for age, platelet count and white blood cell count. Upon a look into the literature, Tang et al. (20) emphasized that NLR ratio was an independent factor in predicting post-PCNL Systemic Inflammatory Response syndrome. Similar to our study, Cetinkaya et al. (21) indicated that NLR was important in predicting post-PCNL fever in univariate analysis, but not in multivariate analysis. Sen et al. (22) demonstrated that the NLR after post-PCNL septicemia was an independent factor in multivariate analysis with a threshold value which is close to the one in our study (>2.5). We think that the reason as to why the NLR value in our study was not significant in the multivariate analysis was the varying number of patients in the two groups (469 vs 50).

In addition to its retrospective nature, other weaknesses of this study may be listed as follows: having a small number of patients with fever, absence of stone analysis and culture data, lack of risk analysis for patients' comorbidities, and the fact that NLR was a significant factor in univariate analysis but not in multivariate analysis. Also, the fact that two different antibiotics were used for prophylaxis is another limiting factor in this study. Many studies showed that sepsis rates are not different for ceftriaxone and ciprofloxacin (16). Moreover, fluoroquinolones are not recommended anymore due to potential side effects in the current Urological Infection Guideline by the European Urology Association (23). In this study, ceftriaxone was used for prophylaxis mostly. Ciprofloxacin was used in a small group of patients and fever rates were not different between two antibiotics. Due to the retrospective nature of this study patients given ciprofloxacin as prophylaxis were included in this study. We have not used fluoroquinolones for prophylaxis before PCNL since 2012.

Conclusion

Post-PCNL fever is encountered at a considerable rate despite all prophylactic measures. A simple and affordable diagnostic modality to predict it would prevent unnecessary antibiotic use and decrease treatment costs. In addition, appropriate prophylaxis would prevent postoperative fever. Hence, we think that preoperative neutrophil and lymphocyte counts, as well as NLR are diagnostic tools to predict postoperative fever when risk factors for fever are excluded. Further prospective, randomized studies are needed on this subject.

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Ethics

Ethics Committee Approval: The local ethical committee approved the study. Abdullah Demirtaş, Numan Baydilli (protocol no.: 2013/198).

Informed Consent: Written and verbal consent was obtained from all patients before the operation.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.D., Design: A.D., Data Collection or Processing: N.B., G.S., Ş.T.T., T.D., Analysis or Interpretation: A.D., N.B., T.D., Literature Search: A.D., N.,B., Ş.T.T., Writing: A.D., N.B., Ş.T.T.

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