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The role of neutrophil to lymphocyte ratio and procalcitonin in prediction of systemic inflammatory response syndrome and sepsis after percutaneous nephrolithotomy

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Abstract
Background: percutaneous nephrolithotomy (PCNL) is an effective and minimally invasive technique used in the treatment of kidney stones, but it carries the risk of intraoperative and postoperative complications such as bleeding, extravasation, systemic inflammatory response syndrome (SIRS) and sepsis.
The current study was designed to assess the role of preoperative neutrophil lymphocyte ratio and procalcitonin in prediction of postoperative SIRS, sepsis and septic shock after PCNL for urolithiasis.
Patients and Methods: This prospective observational study included 70 aged ≥ 18 years old who underwent percutaneous nephrolithotomy (PCNL) for renal stones. NLR and procalcitonin was recorded peroperative, at day 1 (day of surgery) and 2nd day.
Patients were followed up after PCNL and were classified into non-SIRS/Sepsis group and SIRS/Sepsis group. Receiver operating characteristic (ROC) curve was analyzed to assess the ability of NLR and procalcitonin to predict SIRS and sepsis.
Results: Both groups showed comparable results in the majority of preoperative and intraoperative data; however, the NLR and procalcitonin were significantly increased in SIRS/Sepsis group in comparison with non-SIRS/Sepsis group.
Conclusion: Preoperative neutrophil lymphocyte ratio with cut off value > 2.5 and preoperative procalcitonin with cut off value > 0.25 (ng/ml) can predict SIRS and sepsis following PCNL surgery with sensitivity of 80% and 85% and specificity of 82.5% and 87.5% respectively.

Keywords: Neutrophil lymphocyte ratio, Procalcitonin, Sepsis, percutaneous nephrolithotomy

Introduction
Common urologic diseases like urolithiasis can be treated with open surgery or endoscopic procedures like ureteroscopy and percutaneous nephrolithotomy (PCNL) [1]. One of the recognized treatment of choice for renal and upper ureteric calculi greater than 2 cm is percutaneous nephrolithotomy (PCNL) [2]. Despite being a minimally invasive procedure, PCNL still involves some degree of invasiveness and bears a risk of both intraoperative and postoperative complications, including bleeding, extravasation, SIRS, and even sepsis [3, 4]. For a variety of reasons, PCNL is considered to be associated with a higher risk of infection and sepsis than other endourological treatments. First off, bacterial colonization of large renal stones may prevent urine from being sterilized prior to PCNL even with antibiotic treatment [5]. Second, preoperative stone burden blockage of some or all of the urinary system may hinder the drainage of infected material, resulting in the formation of a prolonged bacterial niche resembling an abscess [5]. Finally, while PCNL is minimally invasive, there is a chance that it will raise intrarenal pressure, which could lead to the introduction of bacteria into the systemic circulation [5, 6]. Preoperative neutrophil-to-lymphocyte ratio (NLR) may be a promising marker for prediction of infection and sepsis in surgical patients who undergo PCNL for urolithiasis. This marker is inexpensive, easy to measure, and convenient to use in everyday practice [7, 8]. The total number of neutrophils and lymphocytes as well as their relative numbers in complete blood count can be used to

calculate NLR. The significance derives from the fact that immune cells become less and neutrophils become more numerous during physiological stress. Sepsis induces lymphocyte apoptosis and septic shock results in a sharp drop in lymphocyte numbers, which eventually causes the NLR ratio to rise sharply [9].

Procalcitonin is a peptide precursor involved in calcium homeostasis and consists of 116-amino acid [10]. Procalcitonin can be used as a biomarker for early and accurate prediction of sepsis as it is produced in response to bacterial endotoxin or inflammatory mediators [i.e IL-6 and tumor necrosis factor (TNF)-α]. There is a substantial correlation between the severity and extent of bacterial infections and procalcitonin [10]. In healthy individuals, the plasma level of procalcitonin is often less than 0.1 ng/ml. It has been demonstrated that procalcitonin levels increase with sepsis severity. When stimulated, procalcitonin grows quickly within 6–12 hours, and when the infection is controlled due to antibiotic medication or the host immune system, the levels of PCT in circulation drop [11].

Patients and Methods

This prospective observational study was carried out in the anesthesia and surgical ICU department after we obtained approval from institutional ethical committee (Registry number 35373/3/22, approved on March, 2022). The informed consent from patients included in our study was obtained.

70 patients, aged ≥ 18 years old who underwent PCNL for renal stones were enrolled in our study. Exclusion criteria included patient refusal, pregnancy, uncorrected coagulopathy, major comorbidities as heart or renal failure, malignancy, patients who received immunosuppressant and active urinary tract infection. Patients with congenital malformations such as polycystic kidney and horseshoe kidney as well.

General anesthesia was established by fentanyl (1-2 mcg/kg), propofol (1.5-2.5 mg/kg) and atracurium (0.5 mg/kg). Prophylactic antibiotic (3rd generation cephalosporins) was administered for all patients. Maintenance of anesthesia was accomplished with isoflurane and fentanyl as required and atracurium (0.1 mg/kg).cystoscopy was performed while patients were in lithotomy position and a ureteric catheter (6F) with a guide wire was advanced into the kidney, then a Foley's urethral catheter was fixed with the ureteric catheter. Patients were turned into prone position and percutaneous access was established by retrograde instillation of contrast for opacification of collecting system, then under fluoroscopic guidance in vertical position of C-arm, 18 gauge Chiba needle was advanced through skin to be directed to the neck of the desired calyx. Following successful access, a super-stiff guide wire was inserted into the collecting system and dilatation of the tract was performed with Teflon dilators from 8 to 12. The Stone fragments were extracted using forceps or a dormia basket after the stones were broken up using laser, ultrasonic, and/or pneumatic lithotripsy.

Demographic data (Age, sex and BMI) and preoperative data that included procalcitonin level, neutrophils lymphocyte ratio (NLR), peripheral blood white blood cells, urine analysis (Pus cells) and basic laboratory data were obtained for all cases. The intraoperative data that included duration of surgery, number of access and characteristics of renal stones (Size, number and location) were recorded. Postoperative data that included procalcitonin level, neutrophils lymphocyte ratio (NLR) and peripheral blood white blood cells were recorded at day 1 (Day of surgery) and 2nd day.

The aim of this study was to evaluate the role of preoperative neutrophil lymphocyte ratio and procalcitonin in prediction of postoperative systemic inflammatory response syndrome (SIRS) and sepsis after percutaneous nephrolithotomy (PCNL) for renal stones.

Systemic inflammatory response syndrome (SIRS) is defined as the occurrence of any 2 or more of the following criteria: temperature >38 or < 36, white blood cell count >12000/ mm^3 or <4000/ mm^3, heart rate > 90/ min and respiratory rate >20/min [12].

Patients with suspected infection can be promptly identified at the bedside with quick sepsis-related organ failure assessment (qSOFA) which includes alteration in mental status, systolic blood pressure < 100 mmHg and respiratory rate > 22 [12].

The means (SD) and frequency (%) of the data were displayed. Unpaired Student's t test and Mann Whitney U test were employed to analyze continuous variables, while chi-squared test and Fisher's exact test were used to analyze categorical variables. The level of significance was set at $p \leq .05$.

Results

There were 70 patients enrolled in this study, 4 patients refused to participate in the study and 6 patients did not meet the inclusion criteria. According to clinical and laboratory data, the 60 patients were categorized into two groups; group I (non-SIRS/Sepsis) (n=40) and group II (SIRS/Sepsis) (n=20) [Figure 1]. There was non-significant difference between the groups regarding demographic data [Table 1]. Number and location of stones were insignificantly different between both groups, while size of stones was significantly larger in group II (SIRS/Sepsis) compared to group I (non-SIRS/Sepsis) (32.28±2.65 mm vs 28.47±3.18 mm $p< 0.001$). Moreover, duration of surgery was significantly increased in group II (SIRS/Sepsis group) compared to group I (non-SIRS/Sepsis group) (122.0±14.27 min vs 99.18±6.05 min $p< 0.001$) and the number of access was increased in group II compared to group I ($P = 0.006$), Whereas, Preoperative pyuria and Preoperative white blood cells count were insignificantly different between both groups [Table 1].

The mean (± SD) of NLR measurements was significantly increased in group II (SIRS/Sepsis) compared to group I (non-SIRS/Sepsis) preoperatively (2.72±0.593 vs 1.878±0.457 $p< 0.001$) and at the day of surgery (4.795 ± 1.248 vs 3.09±0.77 $p< 0.001$) and at the 2nd day of surgery (4.99 ±1.019 vs 3.105±1.050 $p< 0.001$), as seen in [Figure 2]. Meanwhile, The mean (±SD) of procalcitonin measurements was significantly increased in group II (SIRS/Sepsis) compared to group I (non-SIRS/Sepsis) preoperatively (0.272±0.079 vs 0.087±0.085 $p< 0.001$) and at the day of surgery (2.085±0.656 vs 0.470±0.180 $p< 0.001$) and at the 2nd day of surgery (3.635±1.372 vs 0.392±0.198 $p< 0.001$). [Figure 3]

Preoperative NLR can significantly predict SIRS and sepsis at cut-off value > 2.5 with 80% sensitivity, 82.5% specificity, 69.6% PPV, 89.2% NPV and AUC of 0.858 with P value <0.001. NLR at the day of surgery can significantly predict SIRS and sepsis at cut-off value > 3.5

with 85% sensitivity, 82.5% specificity, 70.8% PPV, 91.7% NPV and AUC of 0.878 with P value <0.001. NLR at the 2nd day of surgery can significantly predict SIRS and sepsis at cut-off value > 3.5 with sensitivity 90%, specificity 85%, PPV 75% and NPV 94.4 and AUC of 0.890. [Figure 4]
Preoperative procalcitonin can significantly predict SIRS and sepsis at cut-off value > 0.25 with 85% sensitivity, 87.5% specificity, 77.3% PPV, 92.1% NPV and AUC of 0.901 with P value <0.001. Procalcitonin at the day of surgery can significantly predict SIRS and sepsis at cut-off value > 0.7 with 95% sensitivity, 90% specificity, 82.61% PPV, 97.3% NPV and AUC of 0.986 with P value <0.001. Procalcitonin at the 2nd day of surgery can significantly predict SIRS and sepsis at cut-off value >0.7 with 95% sensitivity, 92.5% specificity, 86.4% PPV, 97.4% NPV and AUC of 0.996 with P value <0.001. [Figure 5].

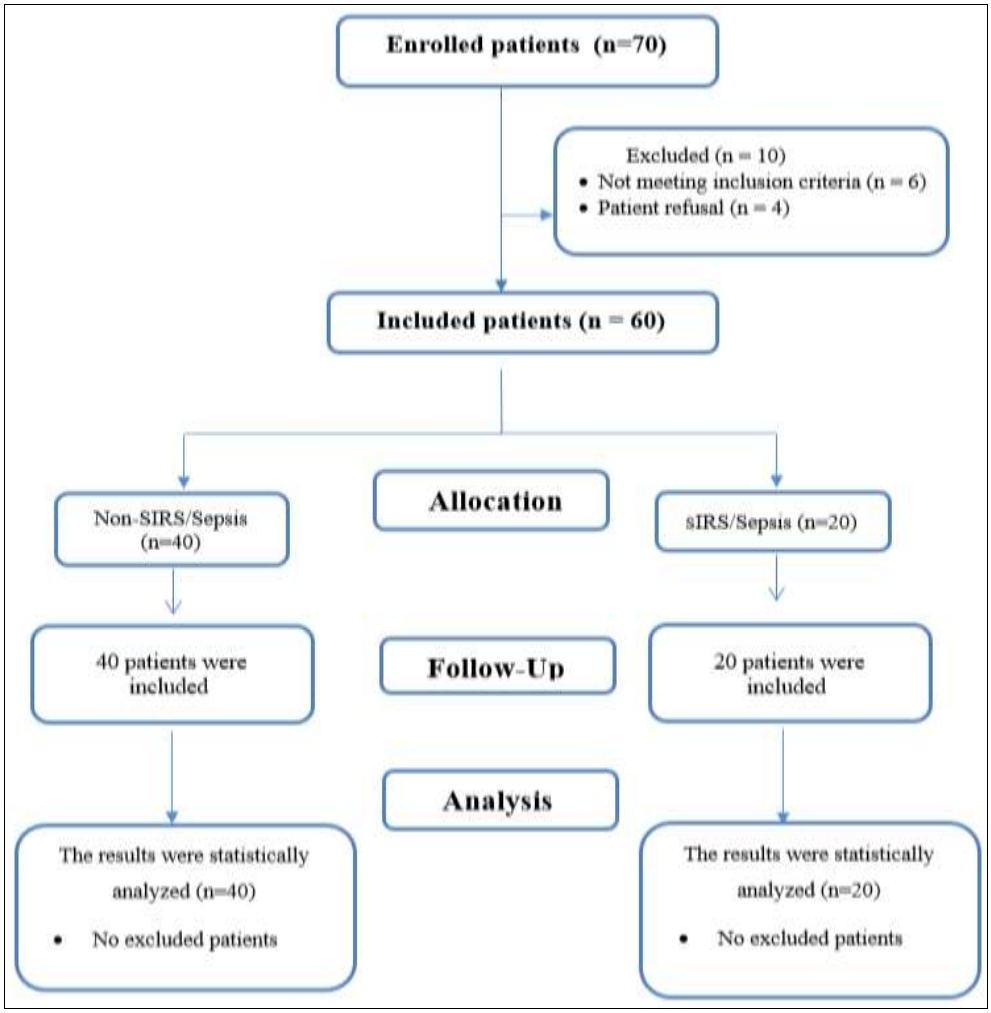

Fig 1: Patients flow diagram

Table 1: Patient characteristics in both group.

		Group I (n=40)	Group II (n=20)	P
Age (years)		43.15 ± 6.18	44.90 ± 4.79	0.272
Sex	Male	20 (50%)	11 (55%)	0.715
	Female	20 (50%)	9 (45%)	
BMI (kg/m2)		25.56 ± 3.20	26.72 ± 3.48	0.202
Duration of surgery		99.18 ± 6.05	122.0 ± 14.27	<0.001*
Size of renal stone		28.47 ± 3.18	32.28 ± 2.65	<0.001*
Number of renal stone	Single	20 (50%)	14 (70%)	0.141
	Multiple	20 (50%)	6 (30%)	
Loc Location of renal stone	Calyceal	20 (50%)	11 (55%)	0.755
	Renal pelvis	20 (50%)	9 (45%)	
Number of access	Single	36 (90%)	11 (55%)	0.006*
	Multiple	4 (10%)	9 (45%)	
Preoperative pyuria	0 – 5	16 (40%)	6 (30%)	0.532
	5 – 10	8 (20%)	6 (10%)	
	10 – 15	8 (20%)	6 (10%)	
	15 – 20	8 (20%)	2 (10%)	
Preoperative WBCs		7.85± 1.18	8.27± 1.33	0.113

Data are presented by Mean ± SD or as number and percent ratio of patients. Group I: Non-SIRS/Sepsis, Group II: SIRS/Sepsis, BMI: Body mass index, WBCs: white blood cells *: Significant statistical difference in group I in comparison with group II as $p \leq 0.05$.

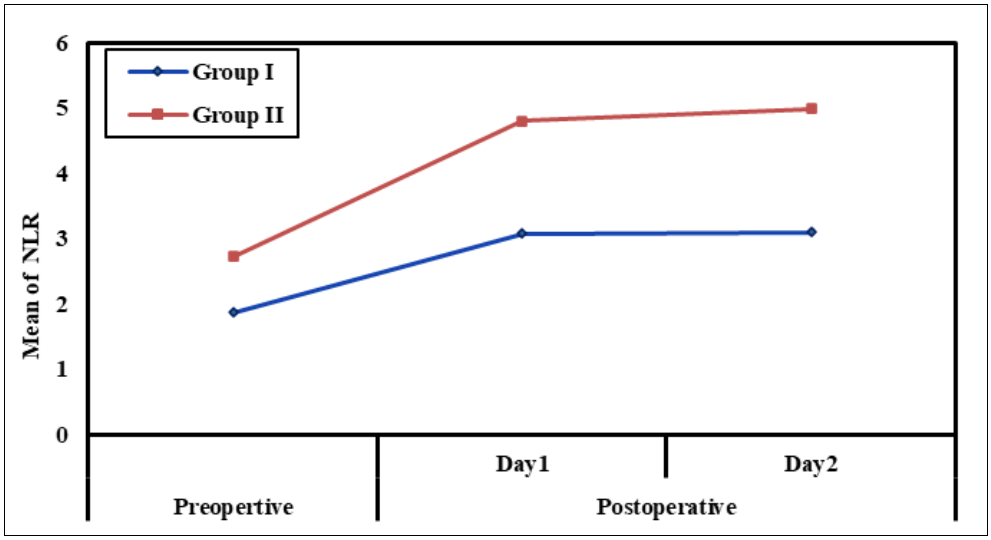

Fig 2: NLR measurements in the two studied groups.

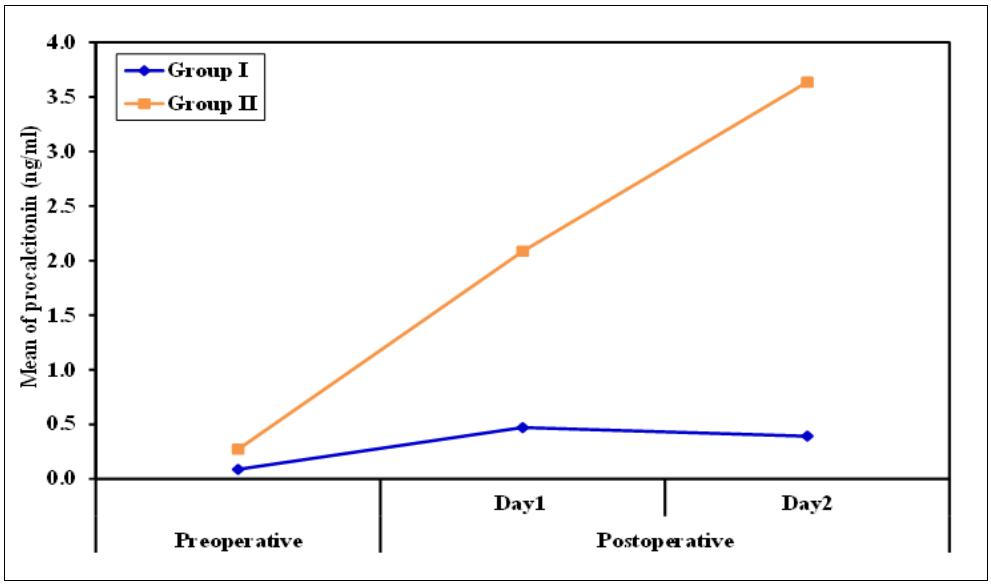

Fig 3: Procalcitonin measurements in the two studied groups.

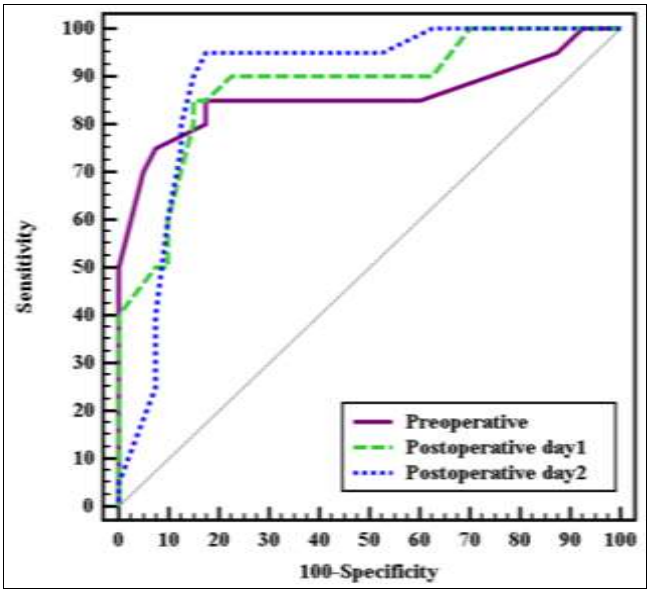

Fig 4: ROC curve for NLR (preoperative, postoperative day1 and day2) to discriminate SIRS/Sepsis (n = 20) from Non-SIRS/Sepsis (n = 40)

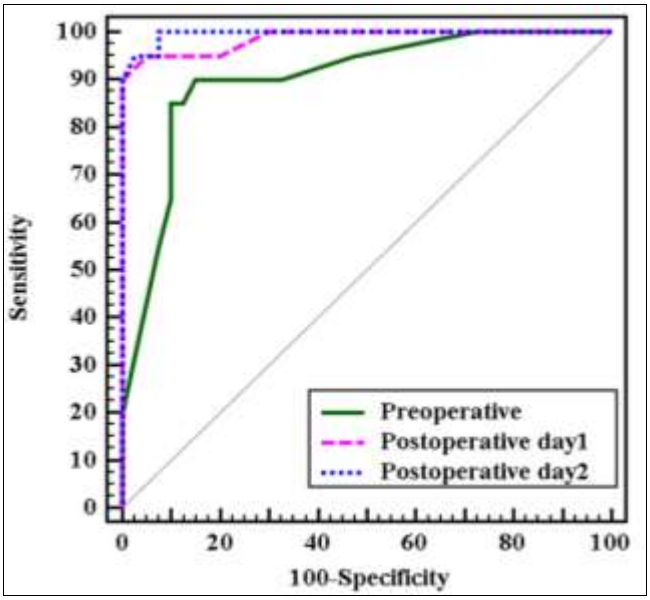

Fig 5: ROC curve for Procalcitonin (ng/ml) (preoperative, postoperative day1 and day2) to discriminate SIRS/Sepsis (n = 20) from Non- SIRS/Sepsis (n = 40).

Discussion

Postoperative infection is more common following PCNL surgery. SIRS and possibly urosepsis are quite likely to develop after PCNL [13]. Most calculi have a high concentration of endotoxins and colonized bacteria [14]. Before the procedure, the stones may cause a partial or complete blockage of the urinary tract, which allows bacteria to develop easily [15]. Additionally, to maintain a clear visual field during the procedure, a significant volume of normal saline is required for high-pressure perfusion. Bacteria and endotoxins can enter the bloodstream through a variety of renal pelvic veins, renal pelvic tubules, and other channels when the pressure increases [5].

The current study revealed that there was no significant difference between the groups as regard patient's characteristics including age, gender, BMI. Moreover, there was no significant difference between both groups as regard number and location of stones, while size of the stones was significantly larger in group II compared to group I In concordance with our study Wang *et al*., [16] who enrolled in their study 246 patients found that there was no statistically significant difference between two groups regarding the number and location of the stones, while the size of the stones was statistically significant between two groups. Also Deng *et al*. [17] found that the size of the stones was statistically significant and independent risk factors for postoperative fever following PCNL.

In the current study, duration of surgery and number of tracts were significantly increased in group II (SIRS/Sepsis group) compared to group I (non-SIRS/Sepsis group). Haifeng *et al*, [18] and Siming *et al*., [19] found that duration of surgery was significantly increased in SIRS group than non-SIRS group Moreover, Liang *et al*., [20] conducted study on 209 patients who underwent PCNL and found that number of tracts was statistically significant between SIRS and non-SIRS group.

In the present study, NLR measurements were significantly increased in group II (SIRS/Sepsis group) compared to group I (Non-SIRS/Sepsis group) preoperatively, at the day of surgery and at the 2nd day of surgery. Akshay *et al*., [21] included in their study 517 patients who underwent PCNL. They concluded that, preoperative NLR can predict postoperative SIRS with cut-off value 2.03 with 82% sensitivity. Also, Yousef *et al*., [22] concluded that preoperative NLR > 2.5 was accompanied by sepsis after PCNL surgery with specificity 98.0% and the area under the curve (AUC) was 0.824. Moreover, Tang *et al*, [23] found that NLR were significantly higher in nephrolithiasis patients than control group with area under the curve (AUC) 0.831.

In contrast to our results, Palomero *et al*, [24] found that NLR value is not useful for diagnosis postoperative septic complications after pediatric major surgery. This may be due to the differences in the inflammatory response in children in comparison with adults.

In the present study, procalcitonin measurements were significantly increased in group II (SIRS/Sepsis group) compared to group I (non-SIRS/Sepsis group) preoperatively, at the day of surgery and at the 2nd day of surgery.

The role of procalcitonin after PCNL was confirmed by Zheng *et al*., [25] who conducted retrospective study on 267 patients undergoing PCNL for renal stones. They concluded that PCT > 0.3 ng/ml had a better predictive accuracy for urosepsis after PCNL and its sensitivity 90.3% and specificity 94.3% with the area under the ROC curve 0.960. Also, Canat *et al*., [26] found that serum procalcitonin (PCT) can be used in the early diagnosis of urosepsis with sensitivity of 100% and specificity of 93.8% and area under the ROC curve was 0.976.

In addition, Amanai *et al*., [27] conducted study on 114 surgical patients and found that there were significant differences in PCT levels between infected and non-infected patients as levels of procalcitonin increased in the pstoperative period between the first to the third postoperative day. Moreover, Wang *et al*., [28] and Haifeng *et al*., [29] concluded that procalcitonin was independent risk factors for development of SIRS and sepsis after PCNL in their multivariate logistic regression analysis.

In contrast to our results, Parli *et al*., [30] found that CRP is better than procalcitonin in prediction of bacterial infection and sepsis in postoperative patients. This may be due to Procalcitonin levels can rise as a result of trauma or surgery, even in the absence of an infection as there is an early rise in PCT within 24 hours of surgery, followed by a rapid decrease.

In the current study, Preoperative pyuria and preoperative white blood cells count were insignificantly different between both groups, Similarly, Tang *et al*. [10] found that preoperative pyuria and white blood cells count were insignificantly different between both groups.

From the results of our study, it is recommended that preoperative neutrophil lymphocyte ratio and procalcitonin could be used as a predictor of SIRS and sepsis following PCNL surgery for renal stones.

Conclusion

Size of stones, number of tracts and duration of surgery are risk factors for SIRS and sepsis following PCNL surgery. While, preoperative pyuria and white blood cells count have no role in the prediction of SIRS and sepsis following PCNL surgery for renal stones. Preoperative neutrophil lymphocyte ratio with cut off value > 2.5 and preoperative procalcitonin with cut off value > 0.25 (ng/ml) can predict SIRS and sepsis following PCNL surgery with sensitivity 80.0% and 85.0% and specificity 82.50% and 87.50% respectively.

Conflict of Interest: Not available

Financial Support: Not available

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