The Delta Neutrophil Index is an Early Predictive Marker of Acute Pyelonephritis in Patients with Ureteral Stone

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ABSTRACT

Objective: To determine the predictive value of the delta neutrophil index (DNI) for acute pyelonephritis (APN), which increases in conditions of infection and inflammation.

Study Design: Observational, comparative cross-sectional study.

Place and Duration of Study: Department of Urology, Kahramanmaraş Sütçü İmam University, Turkey, from December 2014 to November 2019.

Methodology: The data of 205 patients, diagnosed with ureteral stone and urinary tract infection (UTI), were evaluated. For comparison, patients were categorised into two groups: those with lower UTI (LUTI) and those with APN. Together with demographic data of patients and ureteral stone, DNI, C-reactive protein (CRP), white blood cell (WBC) and other biochemical parameters were analysed.

Results: There were 165 patients (80.5%) in the LUTI group and 40 patients (19.5%) in the APN group. In univariate analysis, age (p=0.023), creatinine (p=0.001), PT/INR (p=0.007), WBC (p <0.001), CRP (p=0.002) and DNI (p <0.001) were identified as predictors of APN. In multivariate analysis, CRP (p=0.019) and DNI (p=0.009) were significantly associated with the predictors of APN. Cut-off values were 11.75 mm^3 for WBC, 22.2 mg/dL for CRP, and 1.3% for DNI. DNI value was positively correlated with WBC and CRP (r=0.369 *vs.* 0.740 and p <0.001, each).

Conclusion: As an infection marker that can be monitored with a complete blood count and does not require additional costs, DNI can be used as an early predictor of APN. Patients with a DNI value of >1.3% should be considered for early intervention.

Key Words: *Ureteral stone, Acute pyelonephritis, Delta neutrophil index, C-reactive protein, White blood cell.*

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INTRODUCTION

Ureteral stone is one of the most common urological emergencies. As of 2017, the prevalence of urolithiasis has doubled from 5.2% in 1994.[1] Urinary tract infection (UTI) is very common in patients with urolithiasis. Obstruction of urinary flow overextends the urinary tract, disrupting the mechanisms of local mucosal resistance, increasing the amount of residual urine and creating a continuous environment for bacterial reproduction, thereby leading to complicated urinary system infection.[2] Acute pyelonephritis (APN), which develops as a result of obstructive uropathy, can progress to urosepsis and cause serious problems such as septic shock and disseminated intravascular coagulation (DIC).[3] Therefore, it is important to distinguish between APN and lower UTI (LUTI) quickly and correctly and start treatment immediately.

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To make a differential diagnosis, clinical findings, biochemical parameters such as white blood cell (WBC) count and C-reactive protein (CRP) level and radiological imaging are the most commonly used procedures.[4] However, it is not always easy to make this distinction.

Immature granulocyte (IG) is an indicator of increased myeloid cell production and its level increases in conditions such as inflammation and infection.[5] Recent studies have identified the delta neutrophil index (DNI) as an indicator of IG in peripheral blood. DNI can be measured by new generation complete blood count instruments by detecting neutrophil differentiation and nuclear lobularity changes.[6] Therefore, DNI can be used as an effective marker for detecting inflammation and infection in patients in an outpatient clinic or emergency room, because it can be included in routine complete blood counts.

In literature review, no studies were found on the clinical utility of DNI to ensure early detection of APN that may develop owing to urolithiasis. It was, therefore, hypothesised that DNI predicts complicated UTI at an early stage.

The aim of this study was to determine the diagnostic value of DNI level in patients with APN owing to obstructive ureteral

stone and to compare the DNI level with other routine markers of infection such as WBC count and CRP level.

METHODOLOGY

This observational study was carried out using the information system of the Sütçü İmam University Hospital. A total of 205 patients, who were directly admitted to this clinic or consulted at the emergency room between December 2014 and November 2019 and diagnosed to have UTI with ureteral stones, were evaluated.

All patients with UTI and ureteral stone, detected by non-contrast computed tomography (NCCT), were included in this study. Pregnant patients, those with haematological abnormalities, those receiving granulocyte colony-stimulating factors, glucocorticoids or other immunosuppressant agents before the study, and those with malignancies were excluded from the study as these factors could alter DNI levels. In addition, patients with renal stones together with ureteral stones, those with infection in any other organ, and those with solitary kidney were excluded from the study.

Demographic data, including age, gender, additional diseases such as diabetes mellitus (DM) and hypertension (HT), size, location and laterality of stone, degree of hydronephrosis, and symptoms on admission were recorded.

Stone size was determined by measuring the largest dimension of the stone on NCCT. Obstructive stone was defined as stone causing UTI, acute renal failure (estimated glomerular filtration rate [eGFR] ≤ 60 ml/min), permanent obstruction or pain despite adequate analgesia.[7] The degree of hydronephrosis was classified according to ultrasound (USG) or NCCT findings as follows: (a) absence of calyx and renal pelvis dilatation as no hydronephrosis; (b) only pelvic dilation as mild hydronephrosis; (c) pelvic dilation accompanied by mild calyx dilation as moderate hydronephrosis; and (d) advanced calyx dilation accompanied by renal parenchymal atrophy as severe hydronephrosis.

For comparison, patients with ureteral stones were categorised into two groups: those with LUTI and those with APN. APN was defined as >5 white blood cells (WBC)/high power field (hpf) in a centrifuged urine sample, ≥104 colony-forming units (CFU)/mL, >38°C fever, flank pain or costovertebral angle tenderness.4 Patients not meeting the above criteria were included in the LUTI group.

Percutaneous nephrostomy (8.5-french) was placed in the angiographic suite under routine local anaesthesia (1% Lidocaine, 5–10 cc) by certified interventional radiologists. Urethral double-J stent (JJ stent, 5-french) was placed in the operating room by urologists under general or spinal anaesthesia.

Specific automatic cell analyser (XN 3000; Sysmex Corp., Kobe, Japan) was used to determine the DNI level. This device automatically measures DNI using two independent leukocyte counting methods: myeloperoxidase (MPO) and lobularite/nuclear density-channel.8 Complete blood cell counts were measured using an automated haematological analyser (XN 3000; Sysmex Corp., Kobe, Japan). CRP levels were measured using an automated biochemical analyser (Cobas C-702 module, Roche Diagnostics, Basel, Sweden).

Statistical Package for the Social Sciences version 22.0 (SPSS Inc, Chicago, IL, USA) and MedCalc Statistical Software version 17.5.3 (Ostend, Belgium) was used for statistical analysis. Continuous variables were presented as mean and standard deviation or median and interquartile ranges (IQR). Categorical variables were presented as frequencies and percentages. The independent t-test or Mann–Whitney U-test was used for assessing continuous variables. The Chi-square test or Fisher's exact test was used for categorical variables. The suitability of the data for normal distribution was investigated using the Shapiro–Wilk test. Pearson correlation analysis was performed to evaluate correlations between DNI and other inflammatory parameters. The independent factors associated with APN were evaluated using univariate and multivariate logistic regression analysis. The optimal cut-off points, sensitivity and specifity of the inflammatory factors were evaluated using receiver operating characteristic (ROC) curves and maximum Youden index; p <0.05 was considered statistically significant in all analyses.

RESULTS

Patients with ureteral stones were categorised into two groups: LUTI (165 patients, 80.5%) and APN (40 patients, 19.5%). The mean age of the LUTI group was 42.4 ± 17.92 years, and the APN group was 49.6 ± 16.07 years (p = 0.021). Male: female ratio was 1.9:1 in the LUTI group; whereas, it was 0.3:1 in the APN group (p < 0.001). There was no significant difference between groups in terms of median stone size (p = 0.676), stone location (p = 0.546), and the degree of hydronephrosis (p = 0.102). Serum creatinine and PT-INR were significantly higher in the APN group (p <0.001, each). Of the patients with bacterial reproduction in urine culture, 16 (9.7%) were in the LUTI group and 38 (95%) were in the APN group, and the difference was statistically significant (p <0.001). For emergency decompression of the collecting duct system, one patient was treated with percutaneous nephrostomy in the LUTI group; whereas, nine patients received nephrostomy in the APN group (p < 0.001). Median length of hospital stay was 20.0 (18.0-40.0) hours and 290.0 (240.0-320.0) hours in the LUTI and APN groups, respectively (p <0.001).

Median WBC counts, CRP levels and DNI values were all significantly different between the LUTI and APN groups (7.87 mm^3 vs. 14.01 mm^3; 3.44 mg/dL *vs*. 105.50 mg/dL; 0.30 *vs.* 2.60 and p <0.001, each). Comparison of parameters between groups are presented in Table I.

In univariate logistic regression analysis, age (p = 0.023), creatinine (p = 0.001), PT-INR (p = 0.007), WBC count (p 0.001), CRP level (p = 0.002) and DNI value (p <0.001) were identified as predictors for APN.

Table I: Baseline and clinical characteristics of patients with urolithiasis.

Variables	LUTI (n=165, 80.5%)	APN (n=40, 19.5%)	p-value
Mean age, years (SD)	42.4 (17.92)	49.6 (16.07)	0.021
Gender, n (%)			<0.001
Male	108 (65.5)	10 (25)	
Female	57 (34.5)	30 (75)	
Median stone size in mm (range)	10.0 (7.0-15.0)	10.0 (7.0-14.0)	0.676
Laterality, n (%)			0.715
Right	69 (41.8)	18 (45)	
Left	96 (58.2)	22 (55)	
Stone location, n (%)			0.546
Upper	125 (75.8)	28 (70)	
Mid	12 (7.3)	5 (12.5)	
Lower	28 (16.9)	7 (17.5)	
Hydronephrosis, n (%)			0.102
None	40 (24.2)	3 (7.5)	
Mild	71 (43.0)	19 (47.5)	
Moderate	45 (27.3)	16 (40.0)	
Severe	9 (5.5)	2 (5)	
Median symptoms duration, days (range)	2.0 (1.0-4.0)	3.0 (1.0-4.0)	0.024
Diabetes, n (%)			<0.001
Negative	159 (96.4)	31 (77.5)	
Positive	6 (3.6)	9 (22.5)	
Hypertension, n (%)			0.257
Negative	150 (90.9)	34 (85.0)	
Positive	15 (9.1)	6 (15.0)	
Median laboratory tests (range)			
WBC (mm^3)	7.87 (6.71-9.71)	14.01 (10.84-18.58)	<0.001
CRP (mg/dL)	3.44 (3.02-4.12)	105.50 (88.62-138.25)	<0.001
DNI (%)	0.30 (0.20-0.40)	2.60 (2.32-2.80)	<0.001
Creatinine (mg/dL)	0.88 (0.70-1.10)	1.10 (0.80-2.0)	<0.001
PT-INR	0.96 (0.91-1.00)	1.01 (0.98-1.14)	<0.001
Platelets ($10^3/\mu L$)	274.0 (240.0-318.50)	239.50 (200.50-312.25)	0.099
Urine culture, n (%)			<0.001
Negative	149 (90.3)	2 (5)	
Positive	16 (9.7)	38 (95)	
Double-J insertion, n (%)			0.583
Negative	27 (16.4)	8 (20.0)	
Positive	138 (83.6)	32 (80.0)	
Nephrostomy, n (%)			<0.001
Negative	164 (99.4)	31 (77.5)	
Positive	1 (0.6)	9 (22.5)	
Median hospital stay, hours (range)	20.0 (18.0-40.0)	290.0 (240.0-320.0)	<0.001

SD = Standard deviation, WBC = White blood cells, CRP = C-reactive protein, DNI = Delta neutrophil index, PT-INR = Prothrombin time-international normalised ratio.

In multivariate logistic regression analysis CRP level (OR = 1.13, 95% CI = 1.02–1.25, P = 0.019) and DNI value (OR = 15.09, 95% CI = 1.96–116.21, P = 0.009) were significantly associated with the predictors of APN. WBC count (odds ratio (OR) = 1.11, 95% confidence interval (CI) = 0.95–1.31, p = 0.195) was not significant predictor of APN (Table II).

The cut-off value for WBC was 11.75 mm^3 with 72.5% sensitivity and 93.3% specificity (AUC = 0.852 95% CI = 0.796–0.898, p <0.001), cut-off value for CRP was 22.2 mg/dL with 97.5% sensitivity and 99.4% specificity (AUC = 0.997, 95% CI = 0.977–1.000, p <0.001) and cut-off value for DNI was 1.3% with 100% sensitivity and 97.6% specificity (AUC = 0.993 95% CI = 0.969–1.000, p <0.001).

Correlation analysis showed that the DNI value was positively correlated with WBC count and CRP level in the APN group (r = 0.369 vs. 0.740, respectively and p <0.001, each).

Table II: Univariate and multivariate analyses for the prediction of acute pyelonephritis.

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	1.02 (1.00-1.05)	0.023	0.91 (0.81-1.03)	0.135
Hydronephrosis	3.57 (0.99-12.80)	0.138		
Stone size	1.00 (0.95-1.05)	0.913		
Creatinine	1.88 (1.28-2.76)	0.001	1.81 (0.93-3.50)	0.079
PT-INR	71.62 (3.25-1579.72)	0.007	46.28 (0.81-2639.94)	0.063
Platelets	1.00 (0.99-1.00)	0.870		

WBC	1.30 (1.17-1.44)	<0.001	1.11 (0.95-1.31)	0.195
CRP	1.14 (1.05-1.23)	0.002	1.13 (1.02-1.25)	0.019
DNI	26.59 (10.07-70.21)	<0.001	15.09 (1.96-116.21)	0.009

OR = Odds ratio, CI = Confidence interval, PT-INR = Prothrombin time-international normalised ratio, WBC = White blood cells, CRP = C-reactive protein, DNI = Delta neutrophil index.

DISCUSSION

Urolithiasis and UTI are two interrelated pathological conditions. UTI creates a basis for the formation of urolithiasis and is one of the most common complications in patients with urolithiasis.[2] Approximately 10% of UTI cases concomitant with urinary tract obstruction can develop urosepsis, Moreover, septic shock is very likely to occur in APN associated with urinary tract obstruction.[9] Lack of emergency drainage of the renal collecting system in ureteral stone obstruction and resulting APN leads to increased mortality risk.[10] Yoshimura *et al*. concluded that the risk factors for emergency drainage in patients with stones in the urinary system were age, gender, and performance status.[11] In another study, it was reported that the most useful parameters for determining emergency drainage in patients with renal colic, owing to upper urinary tract stones, were age and high CRP levels.[12]

If there are symptoms of severe urosepsis or septic shock in complicated APN cases with urinary tract obstruction owing to urolithiasis, effective intravenous antibiotic administration within one hour and emergency decompression of the collecting system together with ureteral stenting or nephrostomy is highly important.[13] Mokhmalgia *et al.* concluded that percutaneous nephrostomy may be superior to ureteral stents.[14] Ramsay *et al.* reviewed two randomised trials comparing ureteral stenting and percutaneous nephrostomy and concluded that neither method was superior for renal collecting system decompression.[15] In addition, there is no consensus regarding the time between emergency drainage and elective URS. Commonly accepted opinion is that elective URS should be performed when clinical improvement is observed in the patient.[16] Percutaneous nephrostomy is usually preferred for patients with severe hydronephrosis and suboptimal renal performance conditions; ureteral stenting is done for patients with mild hydronephrosis and relatively good clinical performance. Consequently, in this study, all patients in the APN group were drained urgently with a ureteral stent or nephrostomy.

Univariate analysis showed that age, creatine levels, prolonged PT-INR, WBC, CRP and DNI were risk factors; but only CRP and DNI remained as significant factors in the multivariate analysis. CRP is an acute-phase reactant synthesised in the liver, which increases under conditions of inflammation owing to infection or tissue damage, and it has a half-life of 4–6 hours.[17] As a result of inflammatory changes occurring in the ureter owing to stone, serum CRP level increases. This is associated with increased intensity of inflammation owing to the degree of obstruction. Particularly, in cases where the severity of inflammation increases, such as pyelonephritis, serum CRP level may increase 20 times compared with its normal value, and patients with such a condition require early intervention.[18] Yamamichi *et al.* concluded that CRP level of ≥10 was a risk factor for the development of septic shock in ureteral stone-related obstructive APN.[13] In this study, we calculated a cut-off value of 22.2 mg/dL for CRP at sensitivity and specificity of 97.5% and 99.4%, respectively, using the ROC curve.

IGs are indicative of increased myeloid cell production. They are increased under conditions of inflammation and infection. DNI is a novel inflammatory marker that shows circulating immature granulocyte fractions. With DNI measurement now made using automated devices, it can be quickly and simultaneously studied with a complete blood count.[19] Data shows that DNI is useful in the differentiation of bacterial and viral meningitis, in the separation of renal rejections and pyelonephritis and in the differentiation of community-acquired pneumonia and upper respiratory tract infection.[20] Furthermore, DNI values assessed in emergency services have been found to be useful for gastrointestinal emergencies such as acute cholecystitis and acute appendicitis.[21,22]

It has also been shown that DNI provides information about early diagnosis in sepsis, indicating the severity of the disease and prognosis. Seok *et al.* found DNI values of 0.8%, 3.4%, and 18.6% in systemic inflammatory response syndrome, sepsis and severe sepsis groups, respectively,[23] and they reported that the differences among the groups were significant. Another study reported that high DNI levels could help identify patients at risk of developing severe sepsis or septic shock. They evaluated the diagnostic accuracy of DNI in infected patients as a predictive and prognostic factor.[24] Park *et al.* reported that DNI was a useful parameter in the diagnosis of infected patients and prediction of mortality, and it should be used more widely in clinical practice.[25] In this study, DNI significantly increased in APN due to obstructive ureteral stones. In addition, DNI at 1.3% cut-off with 100% sensitivity and 97.6% specificity is a better predictive factor than WBC, and a similar predictive factor to CRP. This may be owing to limitations in the interpretation of the WBC count because as the infection progresses, the transition from leukocytosis to leukopenia may occur.[17] The present retrospective clinical study has several limitations. One of these limitations was the non-homogeneity in these cases in the duration from the onset of APN until hospitalisation. Another limitation was the relatively small sample size; and the study data were based on a single tertiary referral centre. The effectiveness of the present research, which is a preliminary study, can be increased by further prospective, multi-centric series

conducted with more patients. The most important strength of the present study is that it demonstrates the utility of DNI test, which is an easy-to-access and inexpensive examination, in predicting APN in patients visiting the outpatient clinic or emergency room owing to ureteral stone.

CONCLUSION

DNI value is an indicator of infection and can be useful in the prediction of APN during follow-up in patients with UTI associated with ureteral stone. DNI can be examined with a complete blood count, can be obtained quickly and does not incur additional costs. Careful management should be considered if the DNI value is > 1.3% in patients who are admitted to the Emergency Department or urology outpatient clinic owing to ureteral stones and suspected to have APN.

ETHICAL APPROVAL:
All procedures performed in this study involving human participants were in accordance with the ethical standards of the İnstitutional Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by Kahramanmaraş Sütçü İmam University Medical Ethics Committee, (Ref No. 2019/21/07 Date: 13.11.2019) Turkey.

PATIENTS' CONSENT:
Informed consents were obtained from all participants included in the study. Additional informed consents were obtained from all participants for whom identifying information is included in this article.

CONFLICT OF INTEREST:
All authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
OB: Conception of the work, analysis or interpretation of data for the work, discussion and literature review.
MKD: Data analysis, results, and discussion.
EBB: Literature search, analysis and interpretation of data.
TS: Conception and design, acquisition of data.
SR: Critical revision of the manuscript.

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