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Original article

Monitoring of Hypertension, Pyuria and Neutrophil-to-Lymphocyte Ratio in DKA Patients

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Abstract

Background: Diabetic ketoacidosis (DKA) is characterized by uncontrolled hyperglycemia, metabolic acidosis, and increased body ketone concentration. It is a life-threatening complication of diabetes, usually seen in patients with type-1 diabetes mellitus. **This study aimed to** assess hypertension, pyuria and neutrophil to lymphocyte ratio (NLR) in DKA patients and their relation to severity, complications and mortality. **Methods**: This cross sectional study included 100 children with DKA. All the participants were subjected to full history taking, clinical examination and laboratory investigations. **Results**: Most cases had severe DKA (41%), 32% had moderate DKA and 27% had mild DKA. Heart rate, respiratory rate, systolic and diastolic blood pressure were significantly higher in severe DKA group compared to mild and moderate groups. Patients with severe DKA had statistically higher HbA1c, WBCs, neutrophils and NLR, and statistically lower lymphocytes compared to mild and moderate groups. Children with severe DKA group had statistically significant higher frequency of pyuria, complication, and longer duration of hospital stay compared to mild and moderate groups. ROC analysis was done to assess the performance of NLR to detect severe DKA; at a cutoff point $\geq$ 5.5, the sensitivity was 68.5% and specificity was 94.9%, $p<0.001$. **Conclusion:** Hypertension and pyuria were frequent in children with DKA and were associated with severe DKA. NLR was statistically higher in severe DKA. NLR is an easy, cheap and quick test which showed a good predictive poor of cases with severe DKA.

Keywords: Hypertension; pyuria; neutrophil-to-lymphocyte ratio; DKA

Introduction

Diabetic ketoacidosis (DKA) represents the most common acute hyperglycaemic emergency in children and adolescents with diabetes mellitus (1). Based on the *International Society for Pediatric and Adolescent Diabetes* (ISPAD) guidelines, it is characterized by the biochemical triad of hyperglycaemia (serum glucose > 11 mmol/L or >200 mg/dL), ketonemia (β-hydroxybutyrate concentrations > 3.0 mmol/L) and/or moderate or large ketonuria, and a high anion-gap metabolic acidaemia (venous pH < 7.3 and/or bicarbonate < 18 mmol/L) (2)**.**

In children and adolescents, DKA commonly occurs at the initial diagnosis of T1DM, with the incidence varying from 13% to 80% in different populations (1).

The mortality rate of DKA in children is reported as <1% in developed countries, caused primarily by cerebral injuries and cerebral oedema. Nonetheless, among children with T1DM, DKA is the leading cause of mortality accounting for >50% of all deaths (3)**.**

The expected hemodynamic response to hypovolemia is tachycardia and hypotension. However, children with severe DKA have been reported to have hypertension. The pathophysiology of this paradoxical hypertension is not understood. Both subtle and more severe cerebral injuries can occur in children with DKA and several studies document abnormalities in cerebral blood flow during DKA. It is possible that hypertension in children with DKA might reflect neurophysiological changes resulting from altered brainstem perfusion (4)**.**

Acute kidney injury (AKI) occurs frequently in children with diabetic ketoacidosis (DKA) and episodes of AKI during pediatric DKA have been linked to increased risk of diabetic kidney disease. The mechanisms responsible for AKI during DKA, as well as the mechanisms linking AKI to future kidney dysfunction, are unclear. Inflammation may be an important factor in the pathogenesis of organ injuries in children with DKA (5)**.**

The role of inflammation in DKA-related renal injury is unclear, however, the presence of pyuria in the absence of infection would suggest involvement of the cellular immune system in causing or contributing to renal inflammation (6)**.**

Although complete blood counts (CBCs) are a part of the routine evaluation in diabetic patients, white blood cell (WBC) fractions did not receive significant attention from diabetes specialists in the past. In recent years, there has been growing interest regarding the neutrophil-to-lymphocyte ratio (NLR) as a marker of systemic inflammation in cardiac diseases, neoplasms, and obesity, as well as in diabetes-related complications such as diabetic foot ulcers and retinopathy (7)**.**

This study aimed to assess hypertension, pyuria and neutrophil-to-lymphocyte ratio (NLR) in DKA patients and their relation to severity, complications and mortality.

Patients and methods

This cross sectional study included 100 children with DKA and admitted to Banha University Hospital Matria Teaching Hospital and The National Institute of Diabetes, during the period from October 2023 to July 2024. Patients were divided in to three groups according to disease severity, the American Diabetes Association criteria (8) for DKA severity was used:

- Group 1 (**mild DKA);** included 27 children with $7.20 \leq pH < 7.30$
- Group 2 (**moderate DKA):** included 32 children with $7.10 \leq pH < 7.20$;
- Group 3 (**severe DKA)**: included 41 children with $pH < 7.10$

Inclusion criteria:

- Both sexes included.
- Age 1 to 18 years old
- Children with a diagnosis of diabetic ketoacidosis (defined as a plasma glucose level > 11 mmol/L, a urine ketone level defined as moderate to high (+ to +++), and an arterial pH value < 7.30 at the time of admission

Exclusion criteria:

- Underlying disorders that could affect mental status testing or neurocognitive evaluation; concurrent alcohol or narcotics use, head trauma.
- Infectious states,
- Any other medical conditions that could alter hematological parameters.

Ethical consideration:

The whole study design was approved by the local ethics committee, Faculty of Medicine, Benha University (**Approval code; MS 3-11-2023).** Confidentiality and personal privacy were respected in all the levels of the study. Guardians were free to withdraw from the study at any time without any consequences. Collected data were not and will not be used for any other purpose.

All the participants were subjected to full history taking, complete clinical examination and laboratory investigations as random blood sugar, glycated Hb (HbA1c), complete blood count (CBC) with differential, C-reactive protein (CRP), Alanine aminotransferase (ALT) and aspartate aminotransferase (AST), serum urea and creatinine, arterial blood gases (ABG), serum electrolytes (Na, K, Ca) and urine analysis and urine culture

Pyuria is classified as; **None** (dipstick leukocyte esterase [LE] negative, or microscopy with <5 white blood cells [WBCs]/ high-power field [hpf]). **Mild** (dipstick LE small, or 5-9 WBCs/hpf). **Moderate** (dipstick LE moderate or

large, or 10-24 WBCs/hpf). **Severe** (≥25 WBCs/hpf) (6). The outcome included follow up until discharge or death, length of stay (LOS) and complications.

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 24.0**. (**Armonk, NY: IBM Corp**)**. Qualitative data were described using number and percent. **The Kolmogorov-Smirnov test** was used to verify the normality of distribution. Quantitative data were described using range (minimum and maximum), mean, standard deviation, median. Significance of the obtained results was judged at the 5% level. **The used tests were Chi-square test;** For categorical variables, to compare between different groups. **Student t-test;** For normally distributed quantitative variables, to compare between two studied groups. **One way ANOVA;** For normally distributed quantitative variables, to compare between more than two studied groups. **Spearman coefficient:** To correlate between two distributed abnormally quantitative variables. **Receiver operating characteristic curve (ROC):** It is generated by plotting sensitivity (TP) on Y axis versus 1-specificity (FP) on X axis at different cut off values. The area under the ROC curve denotes the diagnostic performance of the test. Area more than 50% gives acceptable performance and area about 100% is the best performance for the test. The ROC curve allows also a comparison of performance between two tests.

Results

This study included 100 children with DKA, most cases had severe DKA (41%), 32% had moderate DKA and 27% had mild DKA. Positive family history was significantly higher in mild disease (81.5%) compared to moderate and severe disease (71.8% and 73.2%, respectively. There was significant difference between groups as regarding to presenting symptoms as most of mild cases (88.9%) presented with polyuria and polydipsia, while in the severe group the most common presentation was DCL (73.2%). However, there was no significant difference between mild, moderate and severe groups as regards to sex, age, history of DM or duration of symptoms, table 1.

Heart rate, respiratory rate, systolic and diastolic blood pressure were significantly higher in severe DKA group compared to mild and moderate groups. Moreover, severe group had significantly higher frequency of hypertension, table 2.

Patients with severe DKA had statistically higher HbA1c, WBCs, neutrophils, NLR, urea and creatinine and statistically lower lymphocytes, PH and HCO3 compared to mild and moderate groups. While there was no significant difference between groups as regarding to RBS, hemoglobin, platelets, CO2, ALT, AST, sodium, potassium, calcium or C reactive protein, table 3.

Children with severe DKA group had statistically significant higher

frequency of pyuria, complication, mortality and longer duration of hospital stay compared to mild and moderate groups, table 4.

There was a significant positive correlation between NLR and (heart rate, systolic and diastolic blood pressure, HbA1c, urea, creatinine, length of hospital stay) and there was a significant negative correlation between NLR and (PH and HCO3), table 5.

ROC analysis was done to assess the performance of NLR to detect severe cases of DKA; AUC was 0.843 (95% confidence interval: 0.767-0.920), p<0.001. At a cutoff point ≥ 5.5, the sensitivity was 68.5% and specificity was 94.9%, figure 1.

Table 1: Sociodemographic and presenting history as regards to DKA severity

		Severity						Test	P value
		Mild		Moderate		Severe			
		N=27	%	N=32	%	N=41	%		
Sex	**Male**	14	51.9%	15	46.9%	26	63.4%	X^2=2.1	0.34
	Female	13	48.1%	17	53.1%	15	36.6%		
Age (years)	**Mean ±SD**	8.07±2.99		8.69±2.96		9.83±3.83		F=2.6	0.09
History of DM	**1st presentation**	22	81.5%	23	71.9%	31	75.6%	X^2=0.75	0.68
	known Type I DM	5	18.5%	9	28.1%	10	24.4%		
Family history	**No**	5	18.5%	9	29.2%	11	26.8%	X^2=6.5	0.039*
	Yes	22	81.5%	23	71.8%	30	73.2%		
Presenting symptoms	**Polyuria & polydepsia**	24	88.9%	19	59.4%	25	61.0%	X^2=7.4	0.024*
	Abdominal pain	17	63.0%	19	59.4%	21	48.8%	X^2=1.1	0.59
	Vomiting	15	55.6%	19	59.4%	23	43.9%	X^2=0.11	0.94
	Weight loss	14	51.9%	13	40.6%	18	43.9%	X^2=0.78	0.67
	DCL	0	0.0%	3	9.7%	30	73.2%	X^2=59.0	<0.001*
Duration of symptoms/ days	**Mean ±SD**	9.3±5.4		9.7±5.3		8.4±3.3		F=0.71	0.49

X^2: Chi-square test, F: F value of one way ANOVA, *: significant

Table 2: Vital signs as regards to DKA severity

		Severity Mild Mean ±SD		Moderate Mean ±SD		Severe Mean ±SD		Test	P value
Respiratory rate/min.		26.3±2.3		26.4±3.2		29.4±4.3		F=2.8	0.047*
Heart rate/min.		95.6±7.05		102.6±12.1		109.7±11.69		F=4.1	0.019*
Systolic blood pressure (mmHg)		100.8±5.9		100.9±8.6		112.3±24.3		F=5.7	0.004*
Diastolic blood pressure (mmHg)		65.9±3.9		66.3±7.8		73.3±14.3		F=5.8	0.004*
Blood pressure	**Normal**	27	100.0%	29	90.6%	27	65.9%	X^2=15.3	0.010*
	Hypertension	0	0.0%	3	9.4%	14	34.1%		
	Hypotension	0	0.0%	0	0.0%	0	0.0%		

X^2: Chi-square test, F: F value of one way ANOVA, *: significant

Table 3: Laboratory investigations of the studied patients as regards to DKA severity

	Severity Mild Mean ±SD	Moderate Mean ±SD	Severe Mean ±SD	Test	P value
RBS (mg/dl)	482.5±77.4	478.5±71.9	496.4±58.1	F=3.1	0.067
HbA1c	10.4±0.53	11.1±0.82	11.8±0.66	F=30.6	<0.001*
Hemoglobin (mg/dl)	10.7±0.7	10.8±0.8	11.1±0.9	F=2.1	0.19
WBCs (x10^3 /L)	8.4±2.8	11.5±3.6	13.5±3.0	F=22.9	<0.001*
Neutrophils (%)	58.8±10.5	66.1±12.8	76.3±7.04	F=25.5	<0.001*
Lymphocytes (%)	32.8±9.12	19.5±5.02	15.7±4.8	F=31.9	<0.001*
NLR	2.1±1.1	3.9±1.5	5.9±2.1	F=39.4	<0.001*
Platelets (x10^3/L)	285±51	269±69	284±61	F=2.7	0.11
PH	7.23±0.03	7.15±0.03	7.07±0.02	F=85.8	<0.001*
CO2	22.2±3.5	23.1±2.9	22.6±2.4	F=0.63	0.53
HCO3	8.7±1.5	7.8±1.9	6.7±1.5	F=12.2	<0.001*
ALT (U/L)	29.8±5.3	29.6±4.8	28.3±3.9	F=0.81	0.44
AST (U/L)	29.2±5.9	29.1±6.6	28±5.06	F=0.49	0.61
Urea (mg/dl)	36.1±13.3	44.9±11.2	44.5±18.1	F=3.3	0.041*
Creatinine (mg/dl)	0.67±0.16	0.60±0.26	0.74±0.06	F=5.7	0.004*
Sodium (mmol/L)	135.3±5.6	137.4±3.7	134.8±3.7	F=1.2	0.33
Potassium (mmol/L)	3.9±0.9	3.85±0.92	3.99±0.53	F=0.33	0.71
Total calcium (mg/dl)	9.8±0.89	9.65±0.88	9.46±0.9	F=1.5	0.22
C-reactive protein (mg/dl)	6.2±2.9	5.8±2.8	6.3±3	F=0.33	0.71

F: F value of one way ANOVA, *: significant

Table 4: Complications and outcome as regards to DKA severity

		Severity						Test	P value
		Mild		Moderate		Severe			
		N=27	%	N=32	%	N=41	%		
Pyuria	**None**	22	81.5%	26	81.3%	22	53.7%	X^2=16.9	0.010*
	Mild	5	18.5%	3	9.4%	7	17.1%		
	Moderate	0	0.0%	3	9.4%	5	12.2%		
	Severe	0	0.0%	0	0.0%	7	17.1%		
Compli	**None**	27	100.0%	32	93.8%	24	58.5%	X^2=14.2	0.007*
cations	**Hypokalemia**	0	0.0%	2	6.2%	5	12.2%		
	Hyperkalemia	0	0.0%	0	0.0%	3	7.3%		
	Hyponatremia	0	0.0%	0	0.0%	3	7.3%		
	Cerebral edema	0	0.0%	0	0.0%	4	9.8%		
	AKI	0	0.0%	0	0.0%	2	4.9%		
Outcome	**survived**	27	100.0%	32	100.0%	39	97.5%	X^2=2.9	0.23
	not survived	0	0.0%	0	0.0%	1	2.5%		
Length of hospital stay/days (Mean ±SD)		3.74±0.94		5.97±1		6.98±2.21		F=33.5	<0.001*

X^2: Chi-square test, F: F value of one way ANOVA, *: significant

Table 5: Correlation between neutrophils to lymphocytes ratio (NLR) and disease parameters

	NLR	
	r	P value
Duration of symptoms/ days	-0.058	0.566
Respiratory rate/min.	0.139	0.213
Heart rate/min.	0.449	<0.001*
Systolic blood pressure (mmHg)	0.586	<0.001*
Diastolic blood pressure (mmHg)	0.601	<0.001*
RBS (mg/dl)	0.240	0.066
HbA1c	0.465	<0.001*
PH	-0.741	<0.001*
CO2	0.272	0.051
HCO3	-0.337	0.002*
ALT (U/L)	-0.201	0.073
AST (U/L)	0.127	0.209
Urea (mg/dl)	0.511	<0.001*
Creatinine (mg/dl)	0.303	0.016*
Length of hospital stay /days	0.724	<0.001*

r: Correlation coefficient, *: significant

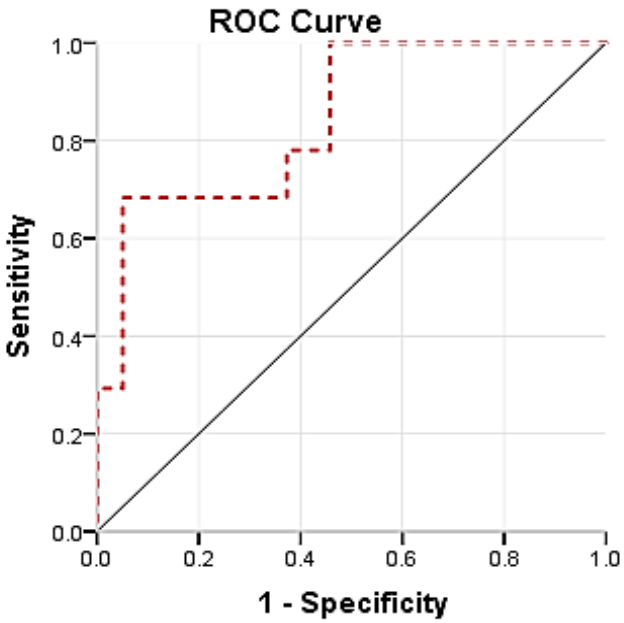

Figure 1: ROC curve of performance of NLR to detect severe cases of DKA

Discussion

Diabetic ketoacidosis (DKA) is characterized by uncontrolled hyperglycemia, metabolic acidosis, and increased body ketone concentration. It is a life-threatening complication of diabetes and is usually seen in patients with type-1 diabetes mellitus (9).

In the current study, the mean respiratory rate was 26.4±3.5/min, the mean heart rate was 99.3±11.1/min, the mean systolic blood pressure was 105.6±17.5 mmHg, the mean diastolic blood pressure was 69.1±10.9 mmHg. Most cases (83%) had normal blood pressure, 17% had hypertension, while none had hypotension.

In a previous study (4), the researchers studied hypertension during diabetic ketoacidosis in children, Among 1258 DKA episodes, hypertension was documented at presentation in 154 (12.2%) and hypotension was noted in 2 patients (0.2%) at presentation.

Oother reseachers (10)**,** studied hypertension despite dehydration during severe pediatric diabetic ketoacidosis, All 33 patients had both admission (pre-treatment) systolic and diastolic blood pressures recorded, either at the referring facility or at our institution. Nineteen (58%) patients had admission systolic hypertension (SBP ≥ 95th %) and fourteen of those also had diastolic hypertension (DBP ≥ 95th %). Diastolic hypertension occurred only in the presence of systolic hypertension. Sixteen (85%) of 19 patients with systolic hypertension had severe hypertension with SBP ≥ 99th % for age/height/gender. None of the 33 patients had hypotension on admission.

Hypertension despite dehydration in diabetic patients likely reflects

systemic pathophysiological processes that may be unique to DKA. Various theories have been put forth to explain paradoxical hypertension in individuals with DKA. These include overactivity of the renin–angiotensin– aldosterone system (RAAS), sympathetic nervous system and vasopressin system (11)**.**

Low plasma levels of atrial natriuretic peptide (ANP) are seen in patients with severe DKA due to hypovolaemia. ANP inhibits the vasoconstrictor action of norepinephrine and decreases the secretion of vasopressin, renin and aldosterone. Thus, low levels of ANP can result in an unopposed action of these hormones, leading to hypertension (12)**.**

Antidiuretic hormone (ADH) release due to hyperosmolality and volume depletion may also increase the BP via V2 receptors and increase the peripheral vascular resistance (4)**.**

Hypovolemia is responsible for the initial activation of the RAAS, ANP and ADH. In addition, the associated severe acidosis stimulates stress reactions, thereby activating the compensatory mechanisms. This increases the production of counter-regulatory hormones (e.g. glucagon, cortisol and growth hormone) and proinflammatory cytokines in patients with DKA, which can lead to hypertension. Restoring the fluid status and correcting acidosis will ameliorate some of these mechanisms and help in reducing the BP (11)**.**

In the present study, Patients with severe DKA had statistically higher HbA1c, WBCs, neutrophils and NLR, and statistically lower lymphocytes compared to mild and moderate groups. While there was no significant difference between groups as regarding to RBS, hemoglobin, or platelets.

Our results were in the same line with other researchers (7)**,** who observed that there was a significant difference in the total and differential WBC counts regarding the four groups, especially regarding total WBCs, neutrophils, and NLR which increased with DKA severity ($p <$ 0.0005). Lymphocytes were statistically lower in severe DKA patients compared to those with mild and moderate DKA. However, HbA1c levels were approximately equal in the four groups (mean = 11.40 ± 2.01).

In the present study, patients with severe DKA had statistically higher urea and creatinine, and statistically lower PH and HCO3 compared to mild and moderate groups. While there was no significant difference between groups as regarding to CO2, ALT, AST, sodium, potassium, calcium or C reactive protein.

In another study (13)**,** Significantly elevated HbA1c, BUN, creatinine and significantly lower PH and HCO3 were observed in severe DKA as compared to moderate DKA ($p \leq 0.05$).

Similarly, *other researchers* (14)**,** found that acidosis and decreased bicarbonates were significantly associated with the degree of severity of DKA (p values of 0.012,< 0 .001 and < 0.001 respectively). The severity of DKA showed significant association with acidosis. However, they noticed

that there was a significant relationship between hypokalemia and severity of DKA.

In the current study, children with severe DKA group had statistically significant higher frequency of pyuria, complication, and longer duration of hospital stay compared to mild and moderate groups.

Similarly, other researchers (6)**,** reported that the mean length of hospital stay was longer for patients with severe dehydration

In the present study, NLR was statistically higher in severe DKA compared to moderate and mild disease, NLR was significantly higher in patients with hypertension compared to normotensive patients. NLR was significantly higher in patients with pyuria compared to patients with normal urine.

This agreed with a previous study (15)**,** which reported that serum NLR levels of T1DM patients are significantly higher than that of normal controls and if DKA occurs, the NLR levels increase further and increase with the severity of DKA.

In the current study, there was a significant positive correlation between NLR and (heart rate, systolic and diastolic blood pressure, HbA1c, urea, creatinine, length of hospital stay) and there was a significant negative correlation between NLR and (PH and HCO3).

Our results were in agreement with Cheng et al., (15)**,** who reported that serum NLR was positively correlated with SBP, BUN, CREA, HbA1c, and WBC and negatively correlated with AST, ALT, and ALB.

In the same way, a recent study (16)**,** reported that the levels of NLR were positively correlated with the circulating levels of creatinine (r=0.5; P=0.008)

In the present study, ROC analysis was done to assess the performance of NLR to detect severe DKA; AUC was 0.843 (95% confidence interval: 0.767-0.920), p<0.001. At a cutoff point ≥ 5.5, the sensitivity was 68.5% and specificity was 94.9%.

Similarly, other researchers (16)**,** observed that T1DM patients with DKA had significantly higher serum NLR levels than those without DKA (9.71±8.85vs 2.30 ±1.05; P=0.035). Furthermore, in ROC curve analysis; The most influential indicator for DKA patients was NLR (AUC 0.85; 95%CI: 0.7–1;p <0.005). The statistical threshold value of the NLR in predicting DKA was 2.05, with a sensitivity of 100% and a specificity of 50%.

In another study (7)**,** the diagnostic ability of HbA1c, C peptide, WBCs, monocytes, and NLR in predicting DKA was analyzed by the ROC curve. The AUCs and cut-off values were calculated according to their specificity and sensitivity as predictive factors. The most influential indicators for DKA patients were WBCs (AUC 0.800; 95% CI: 0.723–0.877, p < 0.000), monocytes (AUC 0.815; 95% CI: 0.742–0.887, p < 0.000), NLR

(AUC = 0.903; 95% CI: 0.854–0.952, $p < 0.000$), and, to a lesser extent, C peptide (AUC = 0.690; 95% CI: 0.591–0.789, $p = 0.001$), as opposed to HbA1c. The statistical threshold value of the NLR in predicting DKA was 1.84, with a sensitivity of 80.2% and a specificity of 80%.

Previously, other researchers (17), considered the NLR as a possible marker of the underlying severity of acute systemic inflammation in uninfected DKA patients.

Aside from the obvious effect of hemoconcentration on the NLR, the potential relationship between hyperglycemia and an increased NLR has been addressed in previous studies (18)**.** One possible explanation is that WBCs that are activated by advanced glycation end-products produce pro-inflammatory cytokines. Another explanation is the fact that, in DKA, acute hyperglycemia promotes the accumulation of reactive oxygen species (ROS) which can damage peripheral blood lymphocytes' DNA. This in turn may cause the apoptosis of lymphocytes and affect their proliferation (7)**.**

There were some limitations in the present study. Firstly, the sample size was relatively small, which could limit the power of the analyses. Secondly, our patients are only from one hospital, so that selection bias cannot be ruled out. The source of pyuria cannot be determined from our data and pyuria may reflect inflammation elsewhere along the urinary tract. Although BP was recorded throughout DKA treatment for all patients in this analysis, the frequency of measurements varied among study sites and there was no formal protocol to verify abnormal BP measurements. Our current data may therefore underestimate the frequency of hypertension during DKA. Additionally, only one measurement of CBC and subsequent NLR calculation were used in the analysis: those upon admission. As such, there was no monitoring of the dynamic trend of the NLR. We look forward to additional multicenter studies with large samples.

Conclusion

Hypertension and pyuria was frequent in children with DKA as 17% had hypertension, 15% had mild pyuria, 8% had moderate pyuria and 7% had severe pyuria. Pyuria and hypertension were associated with severe DKA. NLR was statistically higher in severe DKA, in patients with hypertension and in patients with pyuria. There was a significant positive correlation between NLR and (heart rate, systolic and diastolic blood pressure, HbA1c, urea, creatinine, length of hospital stay) and there was a significant negative correlation between NLR and (PH and HCO3). At a cutoff point $\geq$ 5.5, NLR could predict cases with severe DKA with sensitivity 68.5% and specificity 94.9%. NLR is an easy, cheap and quick test which showed a good predictive poor of cases with severe DKA. So, future studies showed assess the role of NLR in follow up of patients with T1DM and patients with DKA.

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