http:// ijp.mums.ac.ir
Original Article (Pages: 11743-11749)

Alteration of Platelet Indices in Young Children with Acute Pyelonephritis

Azar Nickavar [1], *Simin Sadeghi- Bojd [2]

[1]Pediatric Nephrology Department, Iran University of Medical Sciences, Tehran, Iran.

[2]Pediatrics Department, Nephrology Division, Zahedan University of Medical Sciences, Zahedan Iran.

Abstract

Background

Platelets have an important contribution in pathogenesis of different infectious and inflammatory disorders. This study was performed to identify the diagnostic value of platelet count (PLT), and platelet indices in children with acute pyelonephritis (APN).

Materials and Methods

In a cross sectional case control study, a total of 91 children with APN and 90 healthy control children were investigated during 2018-2019. About 3 ml EDTA blood was drawn before antibiotic treatment and investigated for white blood count (WBC), Hemoglobin level, mean corpuscular volume (MCV), platelet counts, and platelet indices including mean platelet volume (MPV), platelet distribution width (PDW), and platelet large cell ratio (PLCR) in two groups. Then, the results were compared in two groups.

Results

Mean age at diagnosis of patients was 34.57±30.96 months. Children with APN had significantly higher PLT, along with lower MPV, PDW and PLCR, compared to the normal healthy group. Using the best cutoff points, PLT>452000, and MPV≤7.7 had the highest sensitivity (96.67%) and specificity (92.22%) for diagnosis of APN, respectively. Based on AUC, PLT and platelet indices were accurate diagnostic markers of APN.

Conclusion

Based on the results, PLT and platelet indices were fast and additional tests for diagnosis of children with acute febrile urinary tract infection.

Key Words: Acute pyelonephritis, Children, MPV, Platelet index, Urinary tract infection.

*Please cite this article as: Nickavar A, Sadeghi- Bojd S. Alteration of Platelet Indices in Young Children with Acute Pyelonephritis Int J Pediatr 2020; 8(8): 11743-749. DOI: **10.22038/IJP.2020.47464.3849**

Corresponding Author:

Simin Sadeghi Bojd, Pediatric Nephrologist, Zahedan University of Medical Sciences, Zahedan Iran.

Email: sisadegh@yahoo.com

Received date: Feb.27, 2020; Accepted date: Jun.22, 2020

1- INTRODUCTION

Upper urinary tract infection (UTI) is one of the most common serious bacterial infections in febrile infants and young children, second to otitis media and pharyngitis. Early diagnosis and treatment of febrile UTI have been recommended to prevent its long-term complications, such as renal scars, hypertension, proteinuria, and chronic kidney disease. However, accurate diagnosis and management of acute pyelonephritis (APN) has been a clinical challenge in the absence of specific clinical and laboratory findings in infants and young children (1). It takes about 2-3 days to obtain the responsible organism of UTI by urine culture, with false positive and false-negative results. In addition, urinalysis and inflammatory markers, such as fever, WBC, ESR, and CRP have limited sensitivity and specificity for diagnosis of APN, and do not accurately localize upper or lower UTI (1, 2). Tc-99m DMSA scan has been considered as the gold standard test for determination of renal parenchymal involvement in children with febrile UTI (2). However, it is not available in all medical centers, and increases the risk of irradiation exposure.

Therefore, a sensitive, rapid and noninvasive test with therapeutic implications seems necessary for early diagnosis of APN, especially in suspicious patients (2). Platelets have been considered as acute phase reactant in different inflammatory processes. They are involved in host defense mechanism through induction of phagocytosis, and generation of free cytotoxic radicals with oxidative molecules (2-5). Mean platelet volume (MPV) is a known index of average platelet size, which wasintroduced in 1970 (6). It is a simple, inexpensive, and easy biomarker for evaluation of platelet function and determination the severity of infectious or inflammatory disorders (2, 3, 5, 6). Elevated MPV is an indicator of young platelet population, with increased platelet production and/or destruction (4, 5), which might occur in severe infections. However, decreased MPV value has also been reported in some infectious disorders with less severe conditions (5). PDW is another platelet index, which indicates the heterogeneity of platelet volume, and increases in conditions with platelet destruction and immaturity. Platelet large cell ratio (PLCR) is the proportion of large platelets, which reflects alteration of platelet dimension, with inverse correlation to PLT and direct correlation with MPV and PDW indices (6). According to a few reports about alteration of PLT and platelet indices in children with febrile UTI (3, 4, 6); we performed this study to identify the early diagnostic value of PLT and platelet indices in children with acute febrile UTI.

2- MATERIALS AND METHODS

2-1. Study design and population

A cross-sectional case-control study was conducted in 91 cases with APN, and 90 healthy control children, who were admitted for minor surgeries during 2018-2019. About 3 ml of blood was drawn by venipuncture, and collected in EDTA containing tubes. Complete blood count was done by Sysmex XT 2000i (Roche Diagnostics GmbH, Mannheim, Germany) automated analyzer within 1 hour after blood sampling to minimize variation of platelet size. Urine was obtained at the time of admission in both groups, inoculated on agar plates at 35–37 ^{0}C and examined after 24–48 h to determine the colony count and to identify the bacteria. Data were analyzed according to the reference range of these indices, and compared in two groups.

2-2. Inclusion and exclusion criteria

Inclusion criteria were children aged from 1 month to 8 years, positive urine culture (any growth in suprapubic aspiration, or

$>10^4$ CFU/mL of one organism in a sample obtained by urethral catheterization or $>10^5$ CFU/mL of a single pathogen in midstream clean-voided urine or urine bag collection with pyuria), fever >38.5 ^{0}C, leukocytosis, positive C-reactive protein (CRP), and increased Erythrocyte sedimentation rate (ESR) (2). Patients with mixed urine culture, previous antibiotic treatment, septicemia, renal disorders, Congenital Anomalies of Kidney and Urinary tract (KACUT), chronic kidney disease, anuria, previous UTI, infectious or inflammatory disorders, iron deficiency anemia, malnutrition, collagenosis, platelet dysfunction, drugs, obesity, hypercholesterolemia, hypertension, and diabetes mellitus were excluded from the study.

2-3. Ethical consideration

Informed consent was obtained from all legal guardians at the time of admission. Data were extracted in general and without mentioning the names of patients.

2-4. Data Analyses

All data were analyzed using SPSS software version 24.0 and Med Calc version 15.4. Quantitative and qualitative variables were expressed as mean ± standard deviation (SD), and frequency, respectively. Student-t test and Mann–Whitney U test were used for comparison of continuous variables. In addition, Anova and Kruskall Wallis tests were used for variables with more than 2 categories. Meanwhile, categorical variables were compared between the two groups, using the Chi-square test. Normality of variables were evaluated by Kolmogrov-Smirnov test. Correlation between variables was evaluated by Pearson and Spearman´s tests. P-value of <0.05 was considered statistically significant. Receiver Operating Characteristic (ROC) curves, and area under the curve (AUC) were used to determine the proper cut off of variables with the highest sensitivity, specificity, and accuracy.

3- RESULTS

A total of 181 children (91 patients with APN and 90 normal healthy controls) were enrolled in this study. Mean age at diagnosis of cases had no significant difference between the two groups (p<0.924). The majority of patients were females (92.3%, n=84), as shown in the **Table.1**. However, males outnumbered females in the control group, with a significant difference (p<0.001). Since gender was a confounding variable, a regression model was used for analysis of each dependent variable, as group and gender were two independent variables. All of the patients had pyuria, followed by proteinuria (56%, n=51), positive nitrite test (51.6%, n=47), and microscopic hematuria (27.5%, n=25). Renal pelvic dilatation is shown in 11% of patients by renal ultrasound. Blood culture was positive in 4.4% (n=4) of patients, without severe symptoms of septicemia. E-coli was the most often encountered microorganism (86.8%, n=79), followed by Klebsiella (5.5%, n=5), Enteroccuus (2.2%, n=2), pseudomonas (2.2%, n=2), staph aureus (1.1%, n=1), citrobacter (1.1%, n=1), and proteus (1.1%, n=1). Mean values of quantitative variables are shown in **Table.2**.

Table-1: General characteristics of two groups in Univariate analysis.

Variables (mean ± SD)	With APN	Without APN	P-value
Age (month)	34.57 ± 30.96	35.05 ± 36.82	0.924
Gender (M/F)	7/84(7.7%/92.3%)	74/16(82.2%/17.8%)	< 0.001
WBC (mm3)	16100.00 ± 4848.89	7825.55 ± 1925.38	< 0.001
Hemoglobin (g/dl)	11.12 ± 1.35	11.89 ± 1.50	< 0.001
MCV(fl)	79.66 ±5.49	80.01 ± 6.24	0.696

PLT (140-440.109/L)	$382.10^9 \pm 153.10^9$	$312.10^9 \pm 680.10^9$	< 0.001
MPV (8.5-12.5 fl)	8.31 ± 0.93	8.74 ± 0.82	0.001
PDW (10-17 fl)	9.81 ± 1.49	10.32 ± 1.37	< 0.019
PLCR (17-45%)	14.40 ± 6.12	16.53± 5.67	0.005

WBC: White blood cells, MCV: mean corpuscular volume, PLT: platelet, MPV: mean platelet volume, PDW: platelet distribution width, PLCR: platelet larger cell ratio.

Table-2: Characteristics of quantitative variables in patients with APN.

Variables	Mean ±SD
ESR (mm/h)	62.82 ± 2.53
CRP (mg/dl)	2.59 ± 0.86
Urine PH	6.01 ± 0.08
Urine specific gravity	1013.09 ± 0.71
Leukocyte esterase	1.46 ± 1.13
Na (meq/L)	138.34 ± 0.46
K (meq/L)	4.49 ± 0.05
BUN (mg/dl)	10.96 ± 0.58
Creatinine (mg/dl)	0.59 ± 0.02
Ca (mg/dl)	9.32 ± 0.10
HCO3 (meq/L)	19.08 ± 0.50

APN: acute pyelonephritis, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, BUN: Blood urea nitrogen, SD: standard deviation.

Children with APN had significantly higher WBC and PLT, along with lower MPV, PDW and PLCR, compared to the control group (**Tables 1 and 3**). There was a significantly positive correlation between PLT and ESR. However, all of the platelet indices had significantly negative correlation with ESR (**Table.4**). Using the best cut-off points, sensitivity and specificity of PLT and platelet indices are shown in **Table.5**, suggesting PLT and PLCR as sensitive, but not specific variables for diagnosis of acute febrile UTI. Meanwhile, PDW and MPV were specific, but not sensitive markers for prediction of APN. According to AUC, all of the platelet indices were accurate biomarkers for diagnosis of children with acute febrile UTI. However, WBC count was the most sensitive and specific test for diagnosis of APN, compared to PLT and other indices.

Table-3: Characteristics of two groups in Multivariate analysis (Regression model).

Variables	Gender		Group	
	Regression coefficient	P-value	Regression coefficient	P-value
WBC (mm^3)	-497.88	0.556	7582.48	< 0.001
Hemoglobin (g/dl)	0.383	0.072	-1.540	< 0.001
MCV(fl)	1.418	0.113	-0.274	0.732
PLT (140-440.10^9/L)	6661.41	0.769	74102.10	< 0.001
MPV (8.5-12.5 fl)	-0.097	0.641	-0.407	0.030
PDW (10-17 fl)	-0.756	0.071	-0.975	0.010
PLCR (17-45%)	-3.003	0.058	-2.130	0.137

WBC: White blood cells, MCV: mean corpuscular volume, PLT: platelet, MPV: mean platelet volume, PDW: platelet distribution width, PLCR: platelet larger cell ratio.

Table-4: Correlation of platelet indices with quantitative and qualitative variables.

Variables	P-value	r-correlation
PLT and ESR	0.02	0.239
MPV and ESR	0.02	-0.23
PDW and ESR	0.05	-0.193
PLCR and ESR	0.04	-0.22

PLT: platelet, ESR: erythrocyte sedimentation rate, MPV: mean platelet volume, PDW: platelet distribution width, PLCR: platelet larger cell ratio.

Table-5: Sensitivity, specificity and accuracy of PLT and platelet indices

Variables	Cut of point	Sensitivity	Specificity	AUC	95% CI	SE	P-value
PLT	>452000	96.67	30.77	0.626	0.551-0. 697	0.0419	<0.001
MPV	≤ 7.7	32.97	92.22	0.649	0575-0.719	0.0409	<0.001
PDW	≤ 8.9	37.36	83.33	0.622	0.547-0.693	0.0417	<0.001
PLCR	≤ 17	77.40	45.60	0.625	0.548-0.697	0.0428	0.004
WBC	>10400	97.8	94.4	0.995	0.971-1.000	0.00251	<0.001

AUC: area under the curve, CI: confidence interval, SE: standard error, PLT: platelet, MPV: mean platelet volume, PDW: platelet distribution width, PLCR: platelet larger cell ratio, WBC: White blood cells. .

4- DISCUSSION

Different studies showed conflicting results about PLT, and its indices in patients with infectious and inflammatory diseases. This study was performed to identify alterations of PLT and platelet indices as discriminative indicator of APN. We found higher PLT, in addition to lower MPV, PDW and PLCR in patients with APN, which indicated PLT and its indices as positive and negative acute phase reactants in children with acute febrile UTI, respectively. Different inflammatory biomarkers have been introduced for the early prediction of children with acute febrile UTI. PLT and MPV have been suggested as inflammatory markers in different infectious and inflammatory disorders (3). Alteration of PLT and its indices, as acute phase reactants, might occur in infectious disorders through peripheral destruction or decreased bone marrow production. MPV is an index of average platelet size, which is correlated with platelet activation and bone marrow function following destructive insults (2, 6). We found higher PLT, in addition to lower MPV, PDW and PLCR in patients with APN, which indicated PLT as acute phase reactant, with decreased platelet dimension during an acute febrile UTI. Mild increase of MPV, PDW and PLCR has been reported in mild inflammatory conditions, while PLT and MPV decline in severe inflammatory or infectious disorders (3, 6). Giles et al., found increased MPV values in 3–6% of patients

with infectious disorders, irrespective of localized infection or septicemia (7). Platelet indices were important parameters for diagnosis of septicemia in Guclu et al.'s study. As those with severe septicemia had lower PLT along with higher MPV and PDW. In addition, PDW was a unique parameter for prediction of survivors (8). Mean MPV, PDW and PLCR were significantly higher in patients with severe inflammatory disorders and DIC in Kikuchi et al.'s study, and were considered useful indices for early diagnosis of disseminated intravascular coagulation (DIC) (9). Gao et al. suggested a direct correlation between MPV value and the severity of infection, which was higher in non-survivor septic patients (6). In addition, Aydemir et al., reported significant increase of MPV during the first 3-5 days of gram-positive, gram-negative, and fungal septicemia (10).

Increased MPV has been reported as a positive acute phase reactant in patients with APN, secondary to high serum Interleukin-6 (IL-6) level (2, 3). Catal et al., showed higher MPV in 50% of children with APN, especially in subjects with gram positive compared to gram-negative organisms (4). In a study, Nassaji et al., found higher MPV along with lower PDW in adult patients with APN, compared with the healthy controls, which implies the activation of PLT in this infection (5). PLT and platelet parameters (MPV, PDW) were significantly higher in children with UTI, with a positive correlation with ESR, CRP and IL6 in Zayed et al.'s study. MPV and PDW have 90.1% and 88.6% sensitivity, along with 86.3% and 84.1% specificity for diagnosis of UTI, respectively (11). Srinivasa et al.'s study showed higher MPV and PDW in patients with culture proven UTI, especially with gram-positive organism (12). MPV was a fast and reliable test for diagnosis of febrile UTI and renal scarring in Tekin et al.'s study. It had a better predictive value than CRP, ESR or WBC for diagnosis of APN and renal parenchymal damage, and decreased after appropriate antibiotic treatment (2). Lee et al., reported higher MPV in APN than lower UTI, with a positive correlation with CRP and PDW, and negative relation with PLT. They suggested MPV as an inflammatory marker of UTI, with a lower predictive value than CRP for diagnosis of infection (3). Jung et al., reported transient and lesser changes of MPV, compared to WBC, ESR and CRP in children with APN. MPV had a reverse correlation with PLT and positive relation with WBC and ESR in their study (13). MPV, PDW and PLCR were negative acute phase reactants in our children with acute febrile UTI.

In addition, all of the platelet indices had a reverse correlation with ESR in our study, which suggested a severe disease in patients with higher ESR, higher PLT with lower MPV, PDW and PLCR. MPV had 45% sensitivity and 82% specificity in the previous reports (3). We found PLT as a sensitive test for diagnosis of UTI, higher than urine leukocyte esterase (83%), nitrite (53%), pyuria (73%), and bacteriuria (81%). Meanwhile, MPV and PDW were specific biomarkers for prediction of APN, more than urine leukocyte esterase (78%), pyuria (81%), and bacteriuria (83%) (14). MPV had 81.4% sensitivity and 86.3% specificity for diagnosis of febrile UTI in the other reports, which were higher than WBC, CRP and ESR (2).

5- CONCLUSION

In conclusion, our data suggested PLT as sensitive positive acute phase reactant, and platelet indices including MPV and PDW as specific negative acute phase reactants for prediction of acute febrile UTI. Further evaluations of platelet parameters are recommended for differentiation of upper from lower UTI, and determination the severity of UTI in a larger patient population.

6- CONFLICT OF INTEREST: None.

7- REFERENCES

1. Nickavar A, Safaeian B, Valavi E, Moradpour F.Validity of Neutrophil Gelatinase Associated Lipocaline as a Biomarker for Diagnosis of Children with Acute Pyelonephritis. Urol J. 2016;13(5):2860-2863.

2. Tekin M, Konca C, Gulyuz A, Uckardes F, Turgut M. Is the mean platelet volume a predictive marker for the diagnosis of acute pyelonephritis in children? Clin Exp Nephrol. 2015;19(4):688-93.

3. Lee IR, Shin JI, Park SJ, Oh JY, Kim JH. Mean platelet volume in young children with urinary tract infection. Sci Rep. 2015;15;5:18072.

4. Catal F, Bavbek N, Bayrak O, Uz E, Isik B, Karabel M, Degirmencioglu H, Mete E, Akcay A. Platelet parameters in children with upper urinary tract infection: is there a specific response? Ren Fail. 2008;30(4):377-81.

5. Nassaji M, Ghahremanfard F, Mirmohammadkhani M, Tamadon M, Manoochehri S. Mean platelet volume and other platelet indices in adult patients with acute pyelonephritis. Asian J Pharm Hea Sci. 2014; 4(3): 1097-10.

6. Gao Y, Li Y, Yu X, Guo S, Ji X, Sun T, Lan C, Lavergne V, Ghannoum M, Li L. The impact of various platelet indices as prognostic markers of septic shock. PLoS One. 2014;9(8):e103761.

7. Giles C. The platelet count and mean platelet volume. Br J Haematol. 1981;48(1):31-7.

8. Guclu E, Durmaz Y, Karabay O. Effect of severe sepsis on platelet count and their indices. Afr Health Sci. 2013;13(2):333-8.

9. Kikuchi M, Inagaki T, Nitta M, Imaida K, Shinagawa N, Banno S, Komatsu H, Wakita A. UedaR.Changes in erythrocyte structure andin platelets in elderly patients with disseminatedi ntra vascular coagulation. Nihon Ronen Igakkai Zasshi. 1996;33(11):847-51.

10. Aydemir H, Piskin N, Akduman D, Kokturk F, Aktas E. Platelet and mean platelet volume kinetics in adult patients with sepsis. Platelets. 2015;26(4):331-5.

11. Salem Zayed KM, Abdelhakeem AM, Gafar HS, Eldahshan T. Diagnostic value of platelet parameters versus interleukin-6 in children with urinary tract infection. Egyptian Pediatric Association Gazette. 2016; 64(3):142-8.

12. Srinivasa S., Pragyee Dhingra. Platelet indices in children with urinary tract infection. Int J Contemp Pediatr. 2018; 5(3):953-957.

13. Jung SJ, Lee JH. Hemoglobin level is a more predictive diagnostic marker for acute pyelonephritis than mean platelet volume. Clin Exp Nephrol. 2016; 20(5):823-824.

14. Jeradi KE, Jackson EC. Urinary tract infection. In: Kliegman RM, Geme JW. Nelson textbook of pediatrics. 21th edit. 2789-96.