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The predictability of mean platelet volume as a biomarker of pyelonephritis among pediatrics with urinary tract infection

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ABSTRACT

Introduction: Delayed diagnosis of acute pyelonephritis and its differentiation from cystitis can lead to irreversible complications in renal tissue, hypertension and even renal failure.
Objectives: The present study aimed to evaluate the diagnostic value of platelet volume in acute pyelonephritis.
Patients and Methods: This cross-sectional study was conducted on 110 children with febrile acute urinary tract infection (UTI) referred to our educational hospital in Qom, Iran. Individuals with inclusion criteria were examined for mean platelet volume (MPV), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood cell (WBC) and platelet counts. Additionally, Tc 99m-dimercaptosuccinic acid scan (DMSA scan) was used as the gold standard for differentiation of cystitis from acute pyelonephritis. Urine culture was also used to confirm diagnosis of UTI.
Results: The mean age of the participants was two years with a range of two months to 13 years. The MPV ($P=0.001$), CRP ($P=0.001$), ESR ($P=0.001$), platelet ($P=0.013$) and WBC count ($P=0.001$) were significantly higher in the pyelonephritis group compared to cystitis group. We showed that MPV has similar potency in differentiating pyelonephritis from cystitis compared to other inflammatory markers; however CRP was more accurate than other markers. The cut-off point for MPV was estimated 7.8 fl, with sensitivity of 91%, specificity of 92.7%, and positive predictive value of 92.6%.
Conclusion: The high level of ESR is a risk factor to develop pyelonephritis. MPV as an inflammatory marker is similar to that of other inflammatory markers in segregating pyelonephritis in children, although further studies are needed to confirm the results of this study.

Original

Implication for health policy/practice/research/medical education:
In a cross-sectional study on 110 children with febrile acute urinary tract infection, we found mean platelet volume is an inflammatory marker similar to the other inflammatory markers in segregating pyelonephritis.
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Introduction

Urinary tract infection (UTI) is one of the most common infections in infancy and childhood that affects urinary system and appears in two lower (cystitis) and upper (pyelonephritis) forms (1-4). Cystitis is associated with symptoms such as dysuria, urine frequency or urgency, whereas symptoms of pyelonephritis include fever and abdominal pain. The above symptoms are typically vague or indistinctable and impartible at early ages (1, 5). There are four main steps in the clinical management of UTI in childhood; diagnosis of UTI, determination of the site of the infection, search for the cause of the UTI and treatment (4). The most commonly reported causes leading to these infections are Escherichia coli (1,2). Urine culture to confirm the presence of infection is usually taken before starting treatment and 48 hours after treatment.

Antibiotics are used as the treatment and in case of antibiotic resistance or prolonged treatment, intravenous route may be prescribed or further diagnostic tests may be required (6). Acute pyelonephritis is an infection that affects the renal parenchyma and is usually associated with systemic symptoms of inflammation. It is one of the

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most important diseases in childhood (7,8) and accounts for an important risk factor of renal scar and other adverse effects (8,9). Therefore, accurate diagnosis can have an effective role in preventing subsequent adverse effects. The primary diagnosis of acute pyelonephritis is by urine test and clinical symptoms. Clinical symptoms such as fever, abdominal pain, flank pain, anorexia, and inflammatory factors including white blood cells (WBCs), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) can be used for diagnosis of type of UTI, although they are not always reliable (10,11). Therefore, a reliable and practical method is necessary for this purpose since the proper classification of patients into acute pyelonephritis versus cystitis is of significant importance. Numerous studies have suggested the importance and the role of platelets as an indicator of inflammation. Multiple inflammatory factors such as cytokines and coagulation factors are secreted by platelets (12). Mean platelet volume (MPV) has a significant relationship with its function, while high volume may indicate increased function and significant inflammation (13). MPV, along with other diagnostic criteria for acute pyelonephritis, seems to be useful as an inflammatory marker in acute pyelonephritis.

Objectives

The aim of this study was to evaluate the diagnostic value of MPV for differentiation of pyelonephritis from cystitis in children with primary clinical symptoms of UTI.

Patients and Methods

Study design

This study is a cross-sectional. The statistical population of this study was children with UTI admitted to the Hazrat Maasomeh hospital in Qom (Iran). Data (MPV, CRP, ESR and WBC) was measured and recorded for each patient separately after taking informed consent from their legal guardians. Children with UTI symptoms and the following diagnostic criteria (pyuria; mean WBC ≥ 5/high-power field, temperature (fever) of 38°C (100.4°F) or above, positive urine cultures (pure growth of >105 organisms/mL), were included in the study. Tc 99m-dimercaptosuccinic acid scan (DMSA) scans were used to classify individuals into two groups of pyelonephritis and cystitis. Then, according to DMSA scan, scar tissues were classified into two groups; acute pyelonephritis and cystitis. Children with history of UTI or under antibiotic therapy, kidney scars and urinary anomalies, except those with vesicoureteral reflux (VUR) were excluded from the study. Data were measured at baseline four days to one week after routine antibiotic therapy.

Accordingly, Tc 99m-dimercaptosuccinic acid (DSMA) scan results were categorized as follows: no renal lesion (cystitis), very mild lesion (<5%), mild lesion (5%-10%), moderate lesion (10%-30%) and severe renal lesion (>30%). To collect the data, a demographic checklist of children as well as blood test were used to check blood markers such as platelet count, MPV, WBC, ESR and CRP. Standard calibrated meters and scales were used to measure height and weight. Urine culture was used to diagnose the UTI. Blood samples were collected before and after 48 hours antibiotic therapy in both groups and were evaluated in about one hour. The reference used for the average platelet volume was determined by cell counter Sysmex.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of Qom University of Medical Sciences approved this study. The institutional ethical committee at Qom University of Medical Sciences approved all study protocols (IR.MUQ.REC.1398.001), which was conducted with the financial support of Qom University of Medical Sciences. Accordingly, written informed consent was taken from all participants before any intervention.

Statistical analysis

According to the sample size formula for receiver operating characteristic (ROC) analysis, considering 0.05 for type one error, power of 0.8, 0.7 for area under the curve (AUC), minimum of 47 individuals were estimated in each group. To increase the accuracy of the sample, a minimum sample size of 110 was considered. Due to the similarity of population and confounding factors, like pain in the two groups, individuals were selected from a medical center with the most referral and easy access. For statistical analysis, stepwise multiple logistic regression analysis was applied to describe the data collected from descriptive statistics and to analyze the factors associated with acute pyelonephritis by adjusting the effect of other variables. The effect size and correlation with odds ratio were also presented. This model was also used to investigate the relationship between independent variables and pyelonephritis. ROC analysis was used to estimate the optimal cut-off point, platelet volume, as well as to compare AUC, to predict acute pyelonephritis. Indices including sensitivity, specificity, positive predictive value, negative predictive value, cut-off point, associated criterion and area under ROC were reported too. Values close to one for each of the above indices indicate the best value and diagnostic power. The above analysis was performed with R 3.5.3 software with a significance level of less than 0.05.

Results

Regarding weight of the patients, there was no statistical difference between the two groups of pyelonephritis and cystitis (t=-1.306, 0.194). The mean age of the pyelonephritis group is six months lower than cystitis group, although this difference was not statistically significant (t=-1.733, 0.086) (Table 1). Frequency of microorganism in the culture can be observed in Figure

Table 1. The results of age and weight differences between pyelonephritis and cystitis groups

Variable	DMSA	Mean	Std. Deviation	t	*P* value
Age	Pyelonephritis	32.7091	29.38	-1.733	0.086
	Cystitis	44.3636	40.30		
Weight	Pyelonephritis	13.1473	7.04	-1.306	0.194
	Cystitis	15.3891	10.60		

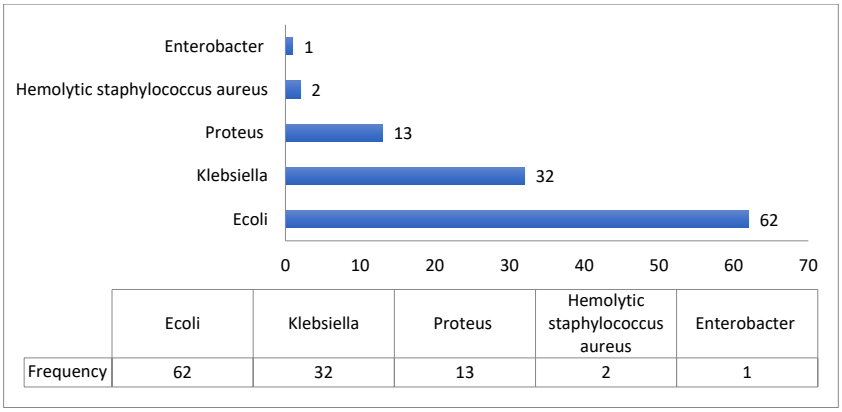

Figure 1. Frequency of microorganism in the culture.

1, in which the most common microorganism was *E. coli* in 62 cultures.

In Table 2, the effect size of each variable on the response was reported as a single variable and the variables with $P<0.2$ were entered into the controlled model to test estimation bias. In the first adjusted model, ESR variable was more likely to prevent cystitis development (OR = 0.730) means with increase one unit in the ESR, the chance to develop cystitis decreased. In contrast, with increase one unit of ESR, the chance to develop pyelonephritis increases by 1.3 times. ESR increase is a risk factor to develop pyelonephritis. PLT and WBC increment had no association with pyelonephritis or cystitis because the odds ratio was obtained about 1 (neither risk factor nor preventive factor).

ROC test results were shown in Figure 2A-E. Figure 2A shows the optimal cut-off point for the MPV was 8.7 fl. Indeed, if the patients' test is positive for MPV (MPV>8.7 fl), they are 92.6% likely to have pyelonephritis. ROC results show that, based on MPV values above 8.7 fl, almost 91% of the individuals with positive DMSA are classified in the pyelonephritis group, while 9% of the individuals are mistakenly classified as false negative. Furthermore, 92.6% of the individuals with negative DMSA will be classified in the healthy group and 7.4% in the false positive group. As Figure 2B indicates, the PLT count had not statistically ability to classify individuals in pyelonephritis or cystitis group ($P=0.06$ with AUC of 0.6 closing to null hypothesis). Based on platelets, a sensitivity and specificity of 29.09 and 96.36%, respectively were considered for the values above 465 000/μL to classify the individuals into pyelonephritis or cystitis group. Figure 2C shows that the optimal cut-off point for CRP is 31 (mg/L). If an individual has a CRP test above 31, it will be 96.5% likely to have pyelonephritis. Zero percent of people are mistakenly classified as false negative. Additionally, 96.4% of people with negative DMSA will be classified in the healthy group and 3.6% in the false positive group. Figure 2D presents the optimal cut-off point for ESR as 36 mL/h. Therefore, the sensitivity and specificity of test

Table 2. The logistic regression results to examine the association between WBC count and dimercaptosuccinic acid (DMSA)

Binary outcome (DMSA)	B	Standard error	Wald	*P* value	Odds ratio (OR)	95% CI for OR	
						Lower	Upper
MPV	-0.168	1.180	0.020	0.887	0.845	0.084	8.545
PLT	0.000	0.000	6.631	0.010	1.000	1.000	1.000
CRP	-0.062	0.060	1.050	0.305	0.940	0.835	1.058
ESR	-0.315	0.076	17.161	>0.001	0.730	0.629	0.847
WBC	-0.001	0.000	4.716	0.030	0.999	0.999	1.000

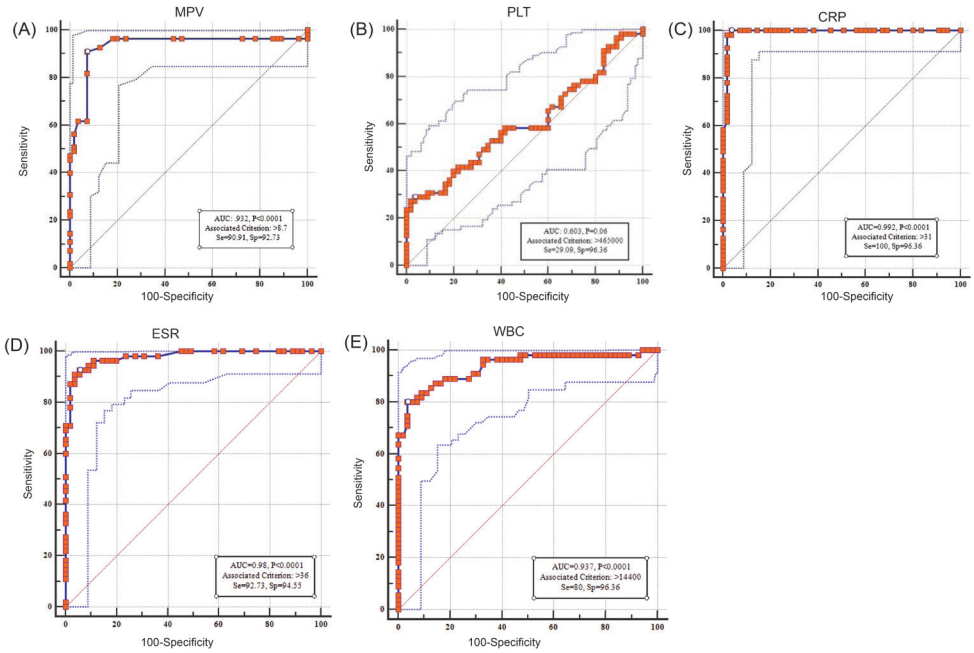

Figure 2. The ROC regression results for prediction of pyelonephritis via (A) MPV, (B) PLT, (C) CRP, (D) ESR, (E) WBC.

were estimated as 93% and 94%, respectively. This in turn will be classified by about 5.5% of individuals in the false positive group. The positive ESR above 36 mL/h indicates that a patient is 94.4% likely to have pyelonephritis. Figure 2E shows the optimal cut-off point for WBC as 14 400/μL. The individuals having WBC >14 400/μL, will be 95.65% likely to have pyelonephritis.

Discussion

Acute pyelonephritis may be difficult to diagnose in childhood, however its differentiation from cystitis can prevent further unpleasant consequences such as renal parenchymal damage, which is of great importance. This study was aimed to evaluate the role of MPV as a biomarker in predicting pyelonephritis in children with UTI. The results of other studies showed that MPV is significantly higher in the pyelonephritis group than in the cystitis group (7,8). Considering DMSA as the gold standard of pyelonephritis, MPV had acceptable sensitivity and positive predictive value for the classification of individuals in the pyelonephritis group. The optimal cut-off point for classification of individuals by MPV was 8.7fl (7). ESR, MPV, CRP and WBC count were, respectively the indicators of pyelonephritis. Nevertheless, there was no statistically significant difference between the diagnostic values of the above biomarkers. It should be noted that the diagnostic value of PLT count for pyelonephritis was not significant (7-9,13). Limited studies indicated the MPV diagnostic potential for acute pyelonephritis. In these studies, the value of MPV parameters, CRP, WBC and ESR were significantly higher in the pyelonephritis group than those in the cystitis group. In this study, we showed that MPV has similar potency in differentiating pyelonephritis from cystitis compared to other inflammatory markers.

In a similar study by Tekin et al (7), sensitivity and positive predictive value of MPV for the diagnosis of acute pyelonephritis in children were estimated less than the value of the present study (SE = 81.4, PPV = 83.3). The optimal cut-off point was also >8.2fl (7). However, in our study, MPV along with CRP and ESR was estimated as an inflammatory marker in the diagnosis of pyelonephritis. According to the study by Lee et al (8), the optimal cutoff point for MPV to diagnose acute pyelonephritis from the cystitis was >7.4 fl with a sensitivity of 45.2%, which was less than our value and the study by Tekin et al (7). We showed that the estimated mean for MPV in the two groups of pyelonephritis and cystitis was similar to the study by Tekin et al (7). Therefore, by comparing these studies, it seems that while MPV potency may decrease in the early ages. However, it is unclear whether this decrease is also true for other inflammatory markers. In the study by Lee et al, the same CRP and MPV potency was estimated for the diagnosis of pyelonephritis (8). Considering the age as a variable, it seems that the mentioned studies did not use a proper index (median rather than mean) for the diagnosis of pyelonephritis. In our study, the mean age index was used instead of the median one. Therefore, different factors such as age, time of diagnosis and differences in the frequency of the type of infection observed may contribute to this difference (8, 9).

MPV was estimated to be significantly different based on, disease duration and stage of tissue injury, and was also higher in infection with gram-negative bacteria (8). Due to the statistical difference between

MPV and other inflammatory factors, MPV can be used as a rapid and inexpensive diagnostic maker of acute pyelonephritis in children, especially in the elderly children. However, further studies based on different age groups are needed to be performed to compare the homogeneity of the cut-off points. Other studies have reported serum procalcitonin, IL-1 beta, IL-6 and IL-8 as diagnostic factors for pyelonephritis. This may be due to the association between interleukins and MPV (13, 14). Some studies have reported a positive relation between MPV and thrombopoietin in coronary artery disease (10, 11). Inflammatory cytokines, such as IL-6, increases in pyelonephritis, related to renal scar (12).

MPV level is likely to increase due to the increased thrombopoietin induced by IL-6. Numerous studies have reported inefficiencies of CRP, WBC, ESR, and interleukins in differentiating pyelonephritis from cystitis (15-17). The study by Gökçe et al (16) also showed no significant difference in the MPV values between patients with upper and lower UTIs. It has been shown that the type of infection can be effective in observing different outcomes; therefore, it is possible to make more precise and reliable decisions about the role of MPV to differentiate pyelonephritis from cystitis (18).

Conclusion

In our study, we showed, CRP, ESR, and WBC counts are quite sensitive to detection and localization of UTI. One of the limitations of the present study was the inability to evaluate and compare the age and gender subtypes due to the reduced study ability, as well as the lack of perception about the time of infection and the stage of the disease, which can affect the results. It is recommended that future studies should be designed and implemented with regard to different age groups in order to compare the potential of changing the optimal cut-off points and the predictive power of the target markers. We showed that MPV has similar potency in differentiating pyelonephritis from cystitis, compared to other inflammatory markers. Although the above results can be applied clinically for the same sex and gender groups, further studies can be effective to confirm the findings of the present study.

Limitations of the study

Our study was conducted with a limited number of patients and was single-center. We suggest more investigation on this subject.

Authors' contribution

MRR, MAS and KE were the principal investigators of the study. MAS, PS, MRR, MAS and KE were included in preparing the concept and design. MAS and SA revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

The authors declare that they do not have any conflict of interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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