The utility of platelet indices in diagnosis of urinary tract infection

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ABSTRACT

Background:
Urinary tract infection (UTI) is one of the most common infections in children and may lead to serious morbidity (such as chronic pyelonephritis and renal scarring) and mortality. Thus, early, appropriate, reliable diagnosis in children is mandatory and prompt antimicrobial treatment is required to minimize renal scarring and progressive kidney damage. When the diagnosis is underestimation may lead to short-term or long-term complication while when the diagnosis is overestimation may lead to use over and unnecessary investigation and work up and invasive procedures for diagnosis even in healthy children.

Aim of the study:
1. The platelet indices could be used as an index for immediate diagnosis and management of UTI even the results of urine culture is not available.
2. What is the relation between the changes in platelet indices with the type of micro-organism (gram +ve or gram -ve) for proper choice of antibacterial therapy?

Methods:
This study (prospective case–control) is done in Karbala teaching hospital for children, Holly Karbala, Iraq. In the period from 1, March to 31, December 2018. The study population consist of 105 children with culture proved UTI and 105 non UTI cases as a control, their age ranging from fifteen days to fourteen years’ old. Children with hematological and non-hematological diseases affecting platelet indices were excluded. Platelet indices were taken including platelet count, mean platelet volume (MPV) and platelet distribution width (PDW) which statistically analyzed.

Results:
A total of 105 children with culture proved UTI, 53 (50.5%) female and 52 (49.5%) male and 105 non UTI cases as control, 58 (55.2%) female and 47 (44.8%) male were enrolled in this study with no significant differences between both groups in demographic variables. Regarding the results of culture, 64 (61%) patients had gram negative rods while the remaining 41 (39%) patients had gram positive cocci and the main causative agent was E. Coli in 49.5% of total cases. The comparison of hematological parameters, revealed that mean hemoglobin level was significantly lower than that of controls, while platelet count, MPV, PDW, white blood cells and (WBC), were significantly higher in UTI cases than controls, in all comparisons, P<0.05. Furthermore, the mean platelet count, MPV, PDW, WBC and C-reactive protein (CRP) is higher with significant value in gram +ve subgroup than that of gram -ve subgroup, in all comparisons, P<0.05, while Hemoglobin level show insignificant variation in both subgroups, P>0.05. Further analysis revealed that count, MPV, PDW, WBC and C-reactive protein (CRP) were good predictors and can differentiate between gram positive and gram negative subgroups with relative difference in validity of these parameters. By comparison of different markers validities, MPV and PDW were better than the platelet counts and CRP with regards to the balance between sensitivity and specificity, where the latter two parameters had lower specificity.

Conclusion:
Platelets indices were good predictors of UTI and can differentiate between types of organism in term of gram positive or gram negative. Platelets counts, MPV, and PDW had good sensitivity, specificity and accuracy in prediction and differentiation.

KEYWORDS: platelet utility, urinary tract infection, platelet indices

http://doi.org/10.36295/ASRO.2020.23945
INTRODUCTION

Urinary tract infection (UTI) regards as a most common infection in children that causing a significant morbidity and mortality. UTI that is accompanying with vesicoureteral reflex (VUR) of high grade may cause chronic pyelonephritis and eventual renal scarring which are components of reflux nephropathy [1]. Early diagnosis and prompt antimicrobial treatment are required to minimize renal scarring and progressive kidney damage[2] Kidney scarring is considered as risk for long term morbidity (hypertension, chronic kidney disease, preeclampsia), though much of this has now been shown to be related to previously presented intrinsic renal disease. Thus a reliable diagnosis of UTI in children is very important. When the diagnosis is underestimation may lead to short-term or long-term complication while when the diagnosis is overestimation may lead to use over and unnecessary investigation and work up and invasive procedures for diagnosis even in healthy children [3]

Clinical presentation and classification
There are 3 major types of UTI are cystitis, pyelonephritis, and asymptomatic bacteriuria. Focal pyelonephritis (“nephronia”) and renal abscesses are not common[4]

Pyelonephritis
Is inflammation of the kidney, typically due to a bacterial infection. Injury to the parenchyma of the kidney is named acute pyelonephritis and the condition may be named pyelitis when the parenchyma of the kidney not involved.

Cystitis
When the inflammation is confined to the bladder is named cystitis which characterized by urgent and frequent micturation with incontinency, dysuria, and bad odor of urine and lower abdominal pain.

Asymptomatic bacteriuria
When the organism is isolated from urine culture but not associated with any manifestations of infection it is named asymptomatic bacteriuria.

Uropathogens
Although UTI may be caused by any pathogen that colonizes the urinary tract (e.g, fungi, parasites, and viruses), most causative agents are bacteria of enteric origin (table 1).

Table 1: Urinary pathogens[5]

<table>
<thead>
<tr>
<th>Species</th>
<th>Organisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram -ve rods</td>
<td>P. aeruginosa, E coli, Citrobacterspp, Klebsiellaspp, Morganellamorganii,</td>
</tr>
<tr>
<td></td>
<td>Proteus mirabilis, Enterobacter cloacae.</td>
</tr>
<tr>
<td>Gram -ve cocci</td>
<td>Neisseria gonorrhoe</td>
</tr>
<tr>
<td>Gram +ve cocci</td>
<td>Streptococcus group B, Enterococcus spp, Staphylococcus Epidermidis,</td>
</tr>
<tr>
<td></td>
<td>Staphylococcus aureus, Streptococcus group D, Strept. Faecalis,</td>
</tr>
<tr>
<td></td>
<td>andStaphylococcus saprophyticus.</td>
</tr>
<tr>
<td>Another type of pathogens</td>
<td>Chlamydia trachomatis, Adenovirus, and Candida spp.</td>
</tr>
</tbody>
</table>

Diagnosis of UTI
When there is a suspension of UTI according to clinical features or depend on the result of urinalysis; a culture of urine is mandatory for confirm diagnosis and to obtain a good treatment[6]

Interpretation of urinalysis
Urinalysis with rapid tests of urine (dipsticks) or gross examination of urine has a significant role in diagnosis of UTI [7]. Also reveals the finding of urinary nitrite (result from dietary nitrates through gram –ve enteric bacteria which present in the urine) and leukocyte esterase (as another marker of pyuria) [8]. A microscopic urine examination is beneficial for detection of leukocytes in urine (a sensitive marker of inflammation when there is infection).

**Urinary cultures interpretation**

Cultures of urine should be done firstly when decide to start antibacterial therapies even a single dose of an appropriate antibiotic can quickly disinfects the urine. Unfortunately the cultures of urine which are the gold standard for diagnosis, needs least 48 hours to get an appropriate and significant results. Urinary catheterization and supra-pubic aspiration (for not toilet trained children), regard as best and appropriate methods for urine collection. A sterile urine adhesive bag culture excludes an infection but a positive result is not useful [9].

**Other investigations**

In addition, laboratory findings of UTI usually show leukocytosis, neutrophilia, and increased erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) levels, as in most of children with suspension of any infection, complete blood count is done as part of other routine investigation, so without added cost can obtain free information about the results of platelet indices[6].

**Platelets**

Platelets (also called thrombocytes) are cytoplasmatic fragments of bone marrow megakaryocytes[10]. In addition to the function as a factor of coagulation, the primary functions of platelets are hemostasis (as a factor to stop the bleeding). Other functions of platelets have a role in the process of inflammatory cascade, as a defense mechanism against microbe, and healing of the wound[11], through following mechanisms;

* have the ability to release small molecules in addition to proteins from their own granules (cytokines, chemokines, β-thromboglobulin, growth factors, etc.), which have a role on the function of the circulating immune cells and vascular wall[12].
* Secrete microbicidal proteins and antibacterial peptides [13].
* Have a role in the movement of leukocyte from the bloodstream to tissues through the vessel wall [11].
* Able to form particles of reactive oxygen (which have the ability to activate platelets through oxidative stress that associated with the inflammation processes)[14].

Thus, platelet indices are potential markers of platelet activation, it was found that platelets significantly contribute to the inflammatory process, so that platelet indices may be used as an index for inflammatory conditions caused by autoimmune conditions or infection [12-13].

**Platelet indices (PI)**

A group of platelet parameters (platelet count, mean platelet volume (MPV) and platelet distribution width (PDW)) that obtained from the complete blood count (automatic). There is much evidence which suggests that platelets may have significant values for diagnosis and prognosis in some disease[14].

**Platelet count** in the blood can be rapidly measured using an automated hematologic analyzer to determine the total number of platelet in a person blood sample, its normally between (155-450) *10^9[15].

**MPV** is the measured platelet volume [16]. Typically, the average mean cell volume is 6.9–10.6 fl in healthy subjects [17]. MPV is a parameter evaluated during the routine blood count (Analyzer-calculated measure of thrombocyte volume) and could be calculated by the following formula, MPV (FL) = [(plateletcrit(%) × plateletcount(×10^3/μl)) × 10^3] [14].

When there is a high MPV that means the diameter of platelets are large, that indicate as a useful marker of;

- **Increased rate of production** (when platelet production is increased, young platelets are bigger and more active, and MPV levels increase).
- **Increased rate of activation of platelet** (shape of platelets transfer from biconcave discs to spherical when there is activation of platelets in addition to formation pseudopod which increase MPV during activation of platelet)[18].

Another role of MPV acts as acute phase reactant (negative or positive) in many inflammatory diseases;

- When there is **inflammation of high-grade** lead to increased MPV levels due to the size of platelets in circulation are large. But sometime in high-grade inflammation MPV may low owing to these large platelets might be consummated and aggregated in the region of inflammation at the site of vascular segments.
- When there is **inflammation of low-grade** lead to decreased MPV levels as in familial Mediterranean fever attacks and rheumatoid arthritis.

[Annals of Tropical Medicine & Public Health](http://doi.org/10.36295/ASRO.2020.23945)
MPV decrease in acute disorders while increase in chronic disorders[19].

**PDW** is a marker of variability in the size of platelets and when there is anisocytosis of platelet there is increased in PDW[20].

PDW is a distribution curve of platelets measured at the level of 20% relative height in a platelet-size distribution curve, with a total curve height of 100% [21]. The PDW value differ largely (the reference range is 9 - 17 % [16].

In spite of the presence many conflicting reports regarding association of platelet volume to platelet numbers as an inflammatory indicator in many diseases that may influenced by a various mechanisms, but about its role in the diagnosis of UTI in children there are no significant and sufficient data[13].

Both of them (platelet counts and mean platelet volume (MPV)) which regards as a marker of inflammation have been studied in relation to the activity of the disease. It has been suggested that the role of this marker is largely influenced by the intensity of inflammation [22].

![Figure 1: Display of the PDW](image)

**PCT** is expressed by percentage which defined as the volume occupied by platelets in the blood and the formula of calculation is \(\text{PCT} = \text{platelet count} \times \text{MPV}/10,000\) [10], so it is directly related to the platelet count and the size of the platelets, and therefore increased and larger platelets lead to an increase PCT. Plateletcrit is also the ratio of the platelet volume to the whole blood volume [23]. The normal range for PCT is 0.17 – 0.35% [17].

**P-LCR (platelet large cell ratio)** is defined as the % of large platelets with a given volume more than 12 fL. A side from two flexible discriminators which delimit the volume distribution curve, there is additionally a fixed discriminator at 12 fL (Fig.2). Also it’s expressed in % (the share platelets more than 12 fL in the total platelet number) and the range 15–35% is regard as standard range. Microerythrocytes, platelet aggregates, and giant platelets are expressed by increase of this parameter [10].

![Figure: 2 Display of the P-LCR](image)

Platelet indices as a value for diagnosis and prognosis

In general the disease severity can be evaluated by measurement of the platelet indices and that means the changes in the platelet indices to the potential etiologies that resulted in this changes. When and during production of platelet, there is a variation of volume of platelet that released which lead to increases MPV and PDW, that mean there is increase production of platelets from bone marrow which rapidly releases into circulation[21]. At the same time as the result of the excessive platelets consumption, there is decrease of platelet counts and PCT[24].

http://doi.org/10.36295/ASRO.2020.23945
When there is an inflammatory process, the platelets have additional and important function in inflammation that is recently discovered. The important and significant roles of platelets in the pathogenesis of many inflammatory conditions have been demonstrated in various studies [25]. There is association between the changes in platelet indices with the activation of the coagulation system, trauma, infection, thrombotic diseases, and systemic inflammatory reactions demonstrated by many research [25]. Platelet indices also regard as a marker of diagnosis in many inflammatory diseases, such as rheumatoid arthritis, inflammatory bowel diseases, atherosclerosis, and ankylosing spondylitis [23-25].

**Aim of the study:**

1. The platelet indices could be used as an index for immediate diagnosis and management of UTI even the results of urine culture is not available.
2. What is the relation between the changes in platelet indices with the type of micro-organism (gram +ve or gram -ve) for proper choice of antibacterial therapy.

**PATIENTS AND METHODS**

**Study design**

This study (prospective case–control) is done in Karbala teaching hospital for children, holy Karbala, Iraq. In the period from 1, March 2018 to 31, December 2018.

**Sample and sampling technique**

The study population consists of 105 children with culture proved UTI, and 105 non UTI cases as control seen in Karbala teaching hospital for children. The studied patients were ranged from fifteen days to fourteen years old.

An oral consent was taken from the parents of participants and older children, with short explanation on the objectives of study.

**Data collection**

The information was taken through specific questionnaire arranged for this study and filled through direct interviews with the parents and children. The structural form of questioner consists of demographic characteristics (name, age, and gender), date of presentation, current presenting features, constitutional symptoms, background disease, and history of medication used. The results of urinalysis, urine C/S, automated CBC (Hemoglobin concentration, WBC count, RBC count, platelet count, MPV and PDW), blood film, iron study, serum ferritin levels and C-reactive protein (CRP) were collected. The presenting symptoms include one or more of the following: fever, vomiting, sweating + rigor, loin / abdominal pain, irritability, malaise, dripping, urgency, frequency, enuresis, change in color of urine, burning micturition, jaundice, and diarrhea. According to clinical presentation and a good history diagnosis of UTI done which proved by urine analysis abnormality and significant result of urine culture.

**Urine samples**

Was done according to the guideline depending on age of the patient:

- For patients who were not toilet trained, urine was collected using a urine catheter.
- For older children fresh midstream urine sample was obtained.

Urine sample is then submitted to urinalysis and urine culture/sensitivity. Urinalysis includes direct microscopic examination which is useful to determine whether there are white blood cells in the urine, which is a sensitive indicator of inflammation associated with infection. The finding of more than 5 white blood cells per high power field considered abnormal, also the finding of 5 red blood cells or more per high power field in the sample is considered suggestive for UTI, and in addition any amount of bacteria in the urine may suggest UTI in asymptomatic patient.

**Blood samples**

A five milliliter of blood sample (venous)is aspirated and sent for:

- CBC parameters (Hemoglobin concentration, WBC count, RBC count, platelet count, MPV and PDW) and blood film.
- Iron study and serum ferritin levels were also requested in selected patients for exclusion of hematological disorders.
C-reactive protein (CRP) was assayed (reference range <0.5mg/L). The automated cell counter (CELL-DYN Ruby software version 2.0 analyzer S/N: 35863BG) was used to measure platelet indices (platelet count, MPV and PDW), in our institute. The reference ranges at our institute were (155-450*10^3 for platelet count, 6.9-10.6 fl for MPV and 11-16 for PDW).

**Statistical analysis**

Data were entered and analyzed using the statistical package for social sciences version 25, descriptive statistics presented as mean, standard deviation (SD), frequencies and proportions. Chi-squared test used to compare frequencies while t test used to compare two means. Receiver operating characteristics (ROC) curve used to assess the validity of the studied indices in differentiation between gram positive and gram negative UTI, are under the curve (AUC) was calculated and compared. The interpretation of AUC depends on the standard cutoff points as followed: Significance was considered when P value equal to 0.05 or below.

![AUC](image)

**RESULTS**

There were 105 UTI patients and 105 controls enrolled in this study, the baseline demographic characteristics of them are shown below in (Table 2) and there were no statistically significant differences between both groups (P>0.05).

<table>
<thead>
<tr>
<th>Variable</th>
<th>UTI group (N=105)</th>
<th>Control (N=105)</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Age (year)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; One year</td>
<td>21</td>
<td>20.0</td>
<td>18</td>
</tr>
<tr>
<td>1 – 5</td>
<td>43</td>
<td>41.0</td>
<td>51</td>
</tr>
<tr>
<td>6 – 10</td>
<td>28</td>
<td>26.6</td>
<td>28</td>
</tr>
<tr>
<td>&gt; 10</td>
<td>13</td>
<td>12.4</td>
<td>8</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>4.0 (1.5 – 8)</td>
<td>4.0 (2 - 6)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>52</td>
<td>49.5</td>
<td>47</td>
</tr>
<tr>
<td>Female</td>
<td>53</td>
<td>50.5</td>
<td>58</td>
</tr>
<tr>
<td>Circumcised *</td>
<td>Yes</td>
<td>50</td>
<td>96.2</td>
</tr>
<tr>
<td>No</td>
<td>2</td>
<td>3.8</td>
<td>2</td>
</tr>
</tbody>
</table>

*Percentage calculated out of 52 male cases and 47 male controls, IQR (interquartile range)

Regarding the methods of urine collection, it was mainly midstream 65.7% and 71.4%, in UTI cases and control, respectively, followed by urine catheter, while the least frequently used was adhesive urine bag in only one case and 2 controls with insignificant difference (P>0.05) as shown in (Table 3).
Table 3: Distribution of Urine collection methods among the studied group

<table>
<thead>
<tr>
<th>Methods of urine collection</th>
<th>UTI group (N=105)</th>
<th>Control (N=105)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Urine collection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine catheter</td>
<td>35</td>
<td>33.3</td>
</tr>
<tr>
<td>Midstream</td>
<td>69</td>
<td>65.7</td>
</tr>
<tr>
<td>Adhesive urine bag</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>P. value = 0.522</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

General urine examination revealed that presence of urine albumin was significantly more frequent in UTI group than controls (15.2% vs. 6.7%), respectively, additionally presence of pus cells was significantly more frequent in UTI cases (P<0.05). Red blood cells did not significantly different between both groups, P>0.05 (Table 4).

Table 4: Distribution of General Urine findings of the studied group

<table>
<thead>
<tr>
<th>Variable</th>
<th>UTI group (N=105)</th>
<th>Control (N=105)</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Urine albumin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nil</td>
<td>89</td>
<td>84.8</td>
<td>100</td>
</tr>
<tr>
<td>Trace/ 1 +, 2 +</td>
<td>16</td>
<td>15.2</td>
<td>5</td>
</tr>
<tr>
<td>Pus cells</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5</td>
<td>4</td>
<td>3.8</td>
<td>104</td>
</tr>
<tr>
<td>5-10</td>
<td>34</td>
<td>32.4</td>
<td>1</td>
</tr>
<tr>
<td>&gt;10</td>
<td>67</td>
<td>63.8</td>
<td>0</td>
</tr>
<tr>
<td>Red blood cells</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nil</td>
<td>94</td>
<td>89.5</td>
<td>101</td>
</tr>
<tr>
<td>5-6 cell</td>
<td>11</td>
<td>10.5</td>
<td>4</td>
</tr>
</tbody>
</table>

The comparison of hematological parameters revealed that mean hemoglobin level was significantly lower than that of controls while platelet count, MPV, PDW, WBC, and the neutrophil count were significantly higher in UTI cases than controls, in all comparisons, P<0.05 (Table 5).

Table 5: Study of compares between hematological parameters and C-reactive protein

<table>
<thead>
<tr>
<th>Parameters</th>
<th>UTI group (N =105)</th>
<th>Controls (N = 105)</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb</td>
<td>Mean 12.66</td>
<td>SD 1.02</td>
<td>Mean 13.01</td>
</tr>
<tr>
<td>Platelet count</td>
<td>349.88</td>
<td>71.7</td>
<td>307.26</td>
</tr>
<tr>
<td>MPV</td>
<td>10.71</td>
<td>1.44</td>
<td>8.97</td>
</tr>
<tr>
<td>PDW</td>
<td>14.37</td>
<td>2.64</td>
<td>10.62</td>
</tr>
<tr>
<td>WBC</td>
<td>12.99</td>
<td>6.08</td>
<td>9.29</td>
</tr>
<tr>
<td>Neutrophil</td>
<td>0.57</td>
<td>0.18</td>
<td>0.47</td>
</tr>
<tr>
<td>CRP</td>
<td>5.18</td>
<td>4.47</td>
<td>3.77</td>
</tr>
</tbody>
</table>

Regarding the results of culture, shows that 64 (61%) patients had gram negative rods while the 41(39%) patients had gram positive cocci.

On the other hand, the main causative agent was E. Coli in 49.5%, Staphylococcus in 27.9%, Enterococcus in 11.4%, Proteus and Pseudomonas aeruginosa were less frequently reported among the patients, 7.6% and 3.8%, respectively.

The mean platelet count, MPV, PDW, WBC and CRP are more significantly in gram +ve subgroup than that of gram -ve subgroup, in all comparisons, P<0.05. Hemoglobin level was not significantly different between both subgroups, P>0.05 (Table 6).
Table 6: Study of compares between hematological parameters and C-reactive protein of UTI cases according to the type of bacterial growth.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Gram positive cocci (n=41)</th>
<th>Gram negative rods (n=64)</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Hb</td>
<td>12.75</td>
<td>0.91</td>
<td>12.60</td>
</tr>
<tr>
<td>PLT</td>
<td>427.92</td>
<td>122.2</td>
<td>299.10</td>
</tr>
<tr>
<td>MPV</td>
<td>11.54</td>
<td>1.66</td>
<td>10.16</td>
</tr>
<tr>
<td>PDW</td>
<td>16.13</td>
<td>2.69</td>
<td>13.24</td>
</tr>
<tr>
<td>WBC</td>
<td>14.92</td>
<td>6.49</td>
<td>11.75</td>
</tr>
<tr>
<td>CRP</td>
<td>7.09</td>
<td>5.57</td>
<td>3.95</td>
</tr>
</tbody>
</table>

Further analysis was performed to assess the validity of the studied parameters in differentiation between gram positive and gram negative subgroups, using receiver operating characteristics (ROC) curve, (Figure 4), which revealed that platelet count, MPV, PDW, and C-reactive protein were good predictors and can differentiate between gram positive and gram negative subgroups with relative difference in validity parameters; platelet count showed an area under the curve (AUC) of 0.892, sensitivity of 83.4%, specificity (79.6%) and accuracy of 82.5%, (P. value = 0.003), MPV had AUC of 0.895 and sensitivity, specificity and accuracy of 84.3%, 80.1% and 83.2%, respectively, (P. value = 0.002), PDW showed corresponding values of 81.2%, 82.3% and 82.8%, respectively, with an AUC of 0.903, (P. value < 0.001), the CRP was also able in differentiation with an AUC of 0.813, sensitivity (85.1%), specificity (78.7%) and accuracy of 82.9%.

Hemoglobin level failed to be a predictor and was unable to differentiate between the two subgroups (AUC = 0.565, P. value > 0.05).

By comparison of different markers validities, MPV and PDW were better than the platelet count and CRP with regards to the balance between sensitivity and specificity, where the latter two parameters had lower specificity as shown in (Table 7).

![Figure 3: Receiver operating characteristics (ROC) curve for the validity of platelet indices and C-reactive protein in differentiation of gram positive and gram negative bacteria](http://example.com/figure3.png)

Table 7: Results of assessment of validity of different markers

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Area Under the Curve</th>
<th>P. value</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb</td>
<td>0.565</td>
<td>0.36</td>
<td>58.30</td>
<td>64.70</td>
<td>62.5</td>
</tr>
<tr>
<td>PLT</td>
<td>0.892</td>
<td>0.003</td>
<td>83.40</td>
<td>79.60</td>
<td>82.5</td>
</tr>
<tr>
<td>MPV</td>
<td>0.895</td>
<td>0.002</td>
<td>84.30</td>
<td>80.10</td>
<td>83.2</td>
</tr>
<tr>
<td>PDW</td>
<td>0.903</td>
<td>&lt;0.001</td>
<td>81.20</td>
<td>82.30</td>
<td>82.8</td>
</tr>
<tr>
<td>CRP</td>
<td>0.813</td>
<td>0.011</td>
<td>85.10</td>
<td>78.70</td>
<td>82.9</td>
</tr>
</tbody>
</table>

**DISCUSSION**

Urinary tract infection (UTI) is a common problem in infants and children, in many countries different complications could be seriously associated with UTI and can lead to kidney damage, therefore, diagnosis sometime be difficult particularly in young pediatric group and infancy and hence it is important to have an accurate diagnosis of UTI, an effective and early treatment and make the relevant investigations to discover the presence of alterations in the kidney or the urinary tract [26].
Alteration in the platelets morphology and indices could be a promising marker for early detection of UTI and prevention of adverse sequel of this infection [26].

The present study determined the validity of platelets indices in diagnosis of UTI and differentiation of the type of bacterial infection as gram positive or negative, this an important point in the treatment plan as it widely proved that the treatment modality, surly, depend on the type of bacterial infection, culture and sensitivity, therefore, finding of a predictor index will have a significant role in the management of UTI cases in pediatric age group.

The general urine examination revealed that albuminuria was significantly more frequent in UTI cases than controls 15.2% vs. 6.7% (P<0.05), this can be considered as transient proteinuria which is not unusual in children with acute febrile illness [27].

Also pus cells were significantly more reported in UTI cases with 5 or more cells per HPF, in vast majority of the cases (96.2%), compared to only one control child, these findings were not unexpected due as the general urine examination is one of the diagnostic tools of UTI [28]and logically it appears positive, all the included cases already have UTI, while the pus cells reported among one of the controls group was incidentally, and could be attributed to other cause other than UTI, however, this child sent for further investigations, and diagnosed as a case of renal stone which is an important cause of sterile pyuria and parents advised for follow up and further consultation.

The comparison of hematological parameters revealed that mean hemoglobin level was significantly lower than that of controls. Despite the mean value of hemoglobin reported in the present study was within the normal levels of hemoglobin in this age group, however, some patients had lower values and they were anemic when compared with hemoglobin range values of the controls. It is postulated that anemia and lower hemoglobin levels could be associated with infection or anemia of chronic disease, however, a very recent study by Dhabangi A et al published in 2019 found that urinary tract infections were infrequent among previously transfused children with recurrent anemia [27].

The present study found that the platelets count, MPV, and PDW levels were significantly higher in UTI cases than controls, in all comparisons P<0.05, however, the mean platelets count of UTI cases in the current study was within normal range but it still higher than control and this significant difference due to thrombocytosis in some UTI cases.

Platelets participated as a part of the immune system naturally, during inflammatory process the platelets count might elevated due to inflammation and the activation of platelets may cause some morphological changes which in turn leads to increase in the MPV and PDW which have an important role in the acute phase [29]. On the other hand, there is an evidence that MPV level increased due to increase in the thrombopoietin production which is activated and induced by interleukin 6 [27].

These findings agreed with that reported in a recent Indian study were conducted by Srinivasa and Dhingra in 2018 [6].

The findings of earlier study conducted by Tekin et al. who found that in patients with UTI there was a thrombocytosis and increased levels of MPV and PDW, specially with gram positive organism which consistent with the findings of the present study [29].

An earlier study conducted by Gofrit et al. in 2006 was also documented thrombocytosis in children with UTI [30].

Zayed et al assessed in 2016 the validity of platelets parameters and compared them with interleukin-6 in UTI Egyptian children and found that in children with UTI there is a significant association between platelet indices, C-reactive protein, and ESRwith interleukin-6 [31].

In the present study, the mean platelet count, MPV, PDW, WBC and CRP is more significantly in gram +ve than that of gram -ve subgroup, P<0.05. These findings indicated an association between gram +ve agents and the elevated levels of these parameters, this could be attributed to that gram +ve and gram -ve bacteria induce different patterns of cytokine production in human mononuclear cells (Gram +ve bacteria preferentially stimulate monocytic interleukin-12 production while gram-ve bacteria are potent inducers of IL-10 which are secreted in response to bacterial products from monocytes/macrophages that have a significant effects on the immune system. Cytotoxicity and gamma interferon secretion by NK cells and T cells are activated by IL-12, while these functions are inhibited by IL-10)[32].
Other explanation for thrombocytopenia is a result of increased platelet destruction by anti-body-mediated binding, uptake, and activation which occurs in association with gram -ve infection. Also other factor that plays a role in thrombocytopenia is cell-free extracts containing lipopolysaccharide (component of the cell wall of gram -ve organisms) as shown in experimental models [33], in compares to other studies

Catal et al. found that the platelet counts and MPV values are more significantly in patients with UTI and specifically more in gram +ve infections than gram -ve infections [34].

Zayed et al found that MPV and PDWbut not platelet counts are more significantly more in children with UTI due to gram +ve infections than gram -ve infections[31].

Moreover, in the present study, the validity of mean platelet count, MPV, PDW, WBC and CRP in differentiation between gram positive and gram negative subgroups was assessed using the ROC curve analysis which revealed that elevated MPV, PDW, and platelets were significant predictors and were able to differentiate between gram positive and gram negative agents. Nonetheless, there were relative variation in the validities of these parameters, in term of sensitivity, specificity and accuracy with other studies, but generally, they were good sensitive, specific and accurate. From other point of view, by comparing the area under the curve (AUC) that generated by the ROC curve, the higher AUC was produced by PDW, followed by MPV, platelets count and then CRP, it is worth mentioned that the higher AUC indicated better performance of the test. Regarding the hemoglobin, it was unable to differentiate between gram positive and negative subgroups with an AUC of only 0.565 (AUC below 0.6 indicates poor performance and failed predictor).

Interestingly, Bartges JW. found that the sensitivity and specificity based on the clinical history reported to be 50% and 80%, respectively, therefore, immediate therapy, without additional diagnostic testing, is thus an enticing option and is quite conventional in many countries [35].

Srinivasa and Dhingra tested the validity of Hb, CRP, Platelets count, MPV and PDW and found higher sensitivity, specificity and accuracy produced by these parameters except Hb, and the higher AUC was produced by MPV (0.990), followed by PDW (0.910) and CRP (0.910) and the MPV had a sensitivity and specificity of 97.1% each [6].

Gofrit et al. found that the thrombocytosis accompanying urinary tract infection suggests obstruction or abscess and with a sensitivity, specificity, and accuracy of 76.5%, 77%, and 76.5%[30].

Zayed et al assessed that sensitivity of MPV (90.1%) and PDW (88.6%) and specificity of MPV (86.3%) and PDW (84.1%) for diagnosis of patients with UTI [31].

A previous study conducted by Lee et al. assessed the value of MPV and PDW in children with lower UTI and compared them to a group of children with acute pyelonephritis and authors also used the ROC curve to assess the validity of MPV, ESR, CRP, and WBCs, they found that MPV had lower AUC than CRP but it was higher than that of WBC and ESR then concluded that MPV acting as acute phase inflammatory reactant in UTI [36].

Regarding the causative agent, gram negative rods were found in (61%) of the UTI cases, while 39% had gram positive cocci. On the other hand, the main causative agent was E. Coli in 49.5%, Staphylococcus saprophyticus in 27.9%, Enterococcus in 11.4%, Proteus and Pseudomonas aeruginosa were less frequently reported among the patients, 7.6% and 3.8%, respectively. Usually UTIscaused by ascending infections, the fecal flora is a source of bacteria, which a rise to colonize the perineum throught the urethra enter the bladder. Bacteria that is characterized by P fimbriae are significantly higherfor causingof UTI in term of pyelonephritis, between 76-94% of pyelonephritogenic strains of E. colihave P fimbriae, compared with 19-23% of cystitis strains [4]. In these findings the present study consistent with the results obtained in previous studies and what was reported in literatures regarding the causative agents of UTI among pediatric age group;

Farajnia et al. found that E. coli was responsible for almost 76% of UTI cases followed by Klebsiellaspp in (11.7%), Staphylococcus saprophyticus in (6.4%), and Pseudomonas aeruginosa in (2.2%) [39], however, type of causative bacteria varies in different countries and populations and there were some variations among different studies, but almost all studies and literatures proved that E. coli was the most common causative agent of UTI followed by gram positive cocci[37].

Moreover, Gofrit et al. found that the most frequently isolated bacteria in the study group were E coli (28%), Proteus mirabilis (16%), Staphylococcus aureus (12%), and Pseudomonas aeruginosa and Streptococcus species each in (7.4%)[30].
CONCLUSIONS AND RECOMMENDATIONS

Conclusions:
1. Platelets indices were good predictors of UTI and can differentiate between types of organism in term of gram positive or negative.
2. MPV, PDW and platelets counts had good sensitivity, specificity and accuracy in prediction and differentiation.
3. C-reactive protein appeared to be good predictor of UTI and can differentiate between types of microorganism. Hemoglobin level failed to predict or differentiate between subgroups of microorganism

RECOMMENDATIONS:
1. Using platelets indices as predictor of UTI and to differentiate between types of microorganism could help in early detection and diagnosis of UTI and monitoring of treatment.
2. Further studies with multiple centers and longer duration are highly suggested and it preferred to compare these indices before and after treatment to get more precise results.

REFERENCE: