VALUE OF MEAN PLATELET VOLUME AND SERUM URIC ACID IN DIAGNOSIS OF NEONATAL SEPSIS

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ABSTRACT

Background: Neonatal sepsis (NS) is a potentially life-threatening clinical condition that requires early intervention. The increase in Mean Platelet volume (MPV) could indicate the presence of inflammatory burden in sepsis. Some authors revealed that higher serum Uric Acid (SUA) levels served as an additive risk factor in sepsis.

Aim of the study: The aim of this study was to assess the Value of Mean Platelet Volume and Serum Uric Acid in early diagnosis of Neonatal Sepsis.

Patients and methods: This was a case control study. A total number of 45 participants 30 of them were diagnosed with sepsis and 15 apparently healthy were as control group. They all were assessed and we did the following laboratory to all of them, Complete Blood Count (CBC) with MPV, SUA and C Reactive Protein (CRP).

Results: The percentage of fever was statistically higher among cases group than controls group. The percentage of resp. distress, apnea, convulsions, and skin mottling and bleeding was statistically higher among cases group than controls group. The percentage of poor feeding, jaundice and distention was statistically higher among cases group than controls group. Mean value of CRP was statistically higher among cases group than controls group. Mean value of MPV was statistically higher among cases group than controls group. Mean value of Serum uric acid was statistically lower among cases group than controls group. Regarding Diagnostic accuracy of MPV, Sensitivity was 96.7%, Specificity was 93.3%, PPV was 67.4%, NPV was 50% and accuracy was 66.7%. Regarding Diagnostic accuracy of Uric acid, Sensitivity was 50%, Specificity was 93.3%, PPV was 93.8%, NPV was 48.3% and accuracy was 64.4%.

Conclusion: MPV and SUA could be considered as good diagnostic markers for early diagnosis of sepsis.

Key words: Neonatal Sepsis (NS), Mean Platelet Volume (MPV), Serum Uric Acid (SUA).

I. INTRODUCTION:

Neonatal sepsis (NS) is a potentially life-threatening clinical condition that requires early intervention. Initial symptoms are generally nonspecific and may mimic several other medical conditions. NS is an important cause of mortality and morbidity in neonatal populations (1). There has been constant search of an ideal sepsis biomarker with high sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), so that both the diagnosis and exclusion of neonatal sepsis can be made at the earliest possible and appropriate antibiotics can be started to neonate. Ideal sepsis biomarker will help in guiding us when not to start antibiotics in case of suspect sepsis and total duration of antibiotics course in case of proven sepsis (2).

Several acute phase reactants such as C-reactive protein (CRP) and interleukin-6 (IL-6) have proven helpful in the diagnosis of an ongoing infection, the levels of which increase with the degree of inflammation. However, the rate at which each marker begins to show elevations and the time to normalization differs with every marker (2).
Mean platelet volume (MPV) is a measurement of the average size of platelets found in the blood. The increase in MPV could indicate the presence of inflammatory burden and disease activity in many pathological conditions (3).

Uric acid is an end product of purine catabolism, also it is one of the most important antioxidants in human biological fluids and is responsible for neutralizing > 50% of the free radicals in the human blood. Elevated levels of serum uric acid (SUA) have been shown to be associated with increased cellular damage and mortality of critically ill pediatric patients independent of the underlying disease including inflammation and sepsis (4), there was a large number of studies that investigated the association between neonatal sepsis and SUA. Some authors revealed that higher SUA levels served as an additive risk factor in sepsis (4), however many researchers reported that SUA levels were significantly lower in neonatal patients with sepsis (3, 5).

II. PATIENTS AND METHODS:

2.1. The current study was conducted as Case control study. A total number of 45 participants 30 of them were diagnosed with sepsis and 15 apparently healthy were as control group. They were collected from Neonatology unit, Pediatrics department, Zagazig University Hospitals after obtaining the approval of the institutional review board (IRB) of Zagazig University. 45 divided into 3 groups each of which contains 15 subjects. Group A: Clinically diagnosed NS. Group B: Diagnosed with proven NS. Group C: Apparently healthy control.

2.2. A consent form approved by the committee of human rights in research in Zagazig University was obtained from each participant Parents before the study initiation.

2.3. Patients who were included in this study were full term and preterm neonates in the Neonatology unit, Pediatrics department, Zagazig University Hospitals.

2.4. All patients who had dysmorphic features suggestive of chromosomal anomalies or perinatal asphyxia or any neonates under course of antibiotics prior to appropriate blood sampling were excluded from the study.

2.5. The patients who met the inclusion criteria and were suitable candidates for the study have been subjected to:

1: Complete history taking:
- Obstetric history: death of previous sibling, previous admission to NICU.
- Perinatal history: maternal DM, maternal fever >37, maternal antibiotics and maternal UTI.
- Natal history (PROM, maternal fever).
- Postnatal history: low Apgar score at 1 and 5 min, RD, fever, jaundice.
- Current history: Including most common symptoms of NS in neonates.

2: Thorough clinical examination including assessment of:
- Gestational age.
- Birth weight.
- Clinical signs of sepsis: poor suckling, lethargy, poor Moro reflex, RD, Jaundice…etc.

3: laboratory investigations at the time of diagnosis NS including CBC with differential leucocytic count, MPV, CRP, and serum uric acid measurement.

Sampling:
- Four milliliters of venous blood samples collected aseptically by venipuncture from all participant and distributed as follows :
  - Two ml of whole blood for CBC and MPV.
  - Two ml for serum separation, the separated serum were be used for SUA and CRP assay.

2.6. Statistical analysis:
The collected data were computerized and statistically analyzed using SPSS program (Statistical Package for Social Science) version 24.0. Qualitative data were represented as frequencies and relative percentages. Chi square test was used to calculate difference between qualitative variables. Mann Whitney test was used to calculate difference
between quantitative variables in not normally distributed data in two groups. Paired Wilcoxon test was used to calculate difference between not normally distributed data quantitative variables in the same group pre & post treatment. Spearman’s correlation coefficient was used to calculate correlation between quantitative variables. The threshold of significance is fixed at 5% level (P-value): *P value of >0.05 indicates non-significant results. P value of <0.05 indicates significant results.

III. RESULTS:

There was no statistically significant difference between Cases group and Controls group regarding demographic data (Table 1).

The percentage of distress, apnea, convulsions, and skin mottling and bleeding was statistically higher among cases group than controls group. There was no statistically significant difference between them regarding maternal urinary tract infection (UTI) (Table 2).

The percentage of poor feeding, jaundice and distention was statistically higher among cases group than controls group. There was no statistically significant difference between them regarding vomiting (Table 3).

Mean value of CRP was statistically higher among cases group than controls group (Fig. 1). Mean value of Serum uric acid was statistically lower among cases group than controls group (Fig. 2).

Regarding Diagnostic accuracy of MPV, Sensitivity was 96.7%, Specificity was 93.3%, PPV was 67.4%, NPV was 50% and accuracy was 66.7% Regarding Diagnostic accuracy of Uric acid, Sensitivity was 50%, Specificity was 93.3%, PPV was 93.8%, NPV was 48.3% and accuracy was 64.4% (Table 4, Fig. 3).

Table (1): Comparison between Cases group and Controls group regarding demographic data.

<table>
<thead>
<tr>
<th>Age in Days</th>
<th>Mean ± SD</th>
<th>Cases group</th>
<th>Controls group</th>
<th>t.test</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>4.13± 1.65</td>
<td>4.00± 1.25</td>
<td>0.274</td>
<td>0.785</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>No. 9</td>
<td>30.0%</td>
<td>40.0%</td>
<td>X²</td>
<td>0.502</td>
</tr>
<tr>
<td></td>
<td>% 30.0%</td>
<td>40.0%</td>
<td></td>
<td>0.450</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>No. 21</td>
<td>70.0%</td>
<td>60.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>% 70.0%</td>
<td>60.0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mode of delivery</td>
<td>No. 20</td>
<td>66.7%</td>
<td>53.3%</td>
<td>X²</td>
<td>0.384</td>
</tr>
<tr>
<td></td>
<td>% 66.7%</td>
<td>53.3%</td>
<td></td>
<td>0.756</td>
<td></td>
</tr>
<tr>
<td>vaginal</td>
<td>No. 10</td>
<td>33.3%</td>
<td>46.7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>% 33.3%</td>
<td>46.7%</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Table (2): Comparison between Cases group and Controls group regarding clinical signs of sepsis.

<table>
<thead>
<tr>
<th>resp. diss</th>
<th>Cases group</th>
<th>Controls group</th>
<th>X²</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>No. 18</td>
<td>60.0%</td>
<td>0</td>
<td>15.000</td>
</tr>
<tr>
<td></td>
<td>% 60.0%</td>
<td>0.0%</td>
<td>5.625</td>
<td>0.018</td>
</tr>
<tr>
<td>No</td>
<td>No. 12</td>
<td>40.0%</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>apnea</td>
<td>No. 21</td>
<td>70.0%</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>% 70.0%</td>
<td>100.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>convulsions</td>
<td>Yes</td>
<td>No. 9</td>
<td>30.0%</td>
<td>5.625</td>
</tr>
<tr>
<td></td>
<td>% 30.0%</td>
<td>0.0%</td>
<td>5.625</td>
<td>0.018</td>
</tr>
<tr>
<td>No</td>
<td>No. 21</td>
<td>70.0%</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>skin mottling</td>
<td>Yes</td>
<td>No. 12</td>
<td>40.0%</td>
<td>8.182</td>
</tr>
<tr>
<td></td>
<td>% 40.0%</td>
<td>0.0%</td>
<td>8.182</td>
<td>0.004</td>
</tr>
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</table>
Table (3): Comparison between Cases group and Controls group regarding clinical signs of sepsis continued.

<table>
<thead>
<tr>
<th></th>
<th>Cases group</th>
<th>Controls group</th>
<th>$X^2$</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>No. 8</td>
<td>0</td>
<td>4.865</td>
<td>0.027</td>
</tr>
<tr>
<td></td>
<td>% 60.0%</td>
<td>% 0.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No. 22</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>% 73.3%</td>
<td>% 100.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>maternal uti</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>No. 6</td>
<td>0</td>
<td>3.462</td>
<td>0.063</td>
</tr>
<tr>
<td></td>
<td>% 20.0%</td>
<td>% 0.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No. 22</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>% 73.3%</td>
<td>% 100.0%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure (1): Comparison between Cases group and Controls group regarding CRP.
Figure (2): Comparison between Cases group and Controls group regarding Serum uric acid.

Table (4): Accuracy of MPV and Uric acid in diagnosis of cases

<table>
<thead>
<tr>
<th></th>
<th>Cut off value</th>
<th>AUC</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPV</td>
<td>6.50</td>
<td>0.69</td>
<td>96.7%</td>
<td>93.3%</td>
<td>67.4%</td>
<td>50.0%</td>
<td>66.7%</td>
</tr>
<tr>
<td>Uric acid</td>
<td>3.70</td>
<td>0.60</td>
<td>50.0%</td>
<td>93.3%</td>
<td>93.8%</td>
<td>48.3%</td>
<td>64.4%</td>
</tr>
</tbody>
</table>

Figure (3): ROC Curve for MPV and Uric acid in diagnosis of cases.
IV. DISCUSSION:

Neonatal sepsis has become a global health problem due to its high morbidity and mortality (6).

Worldwide, approximately 0.6 million newborns die from sepsis each year, which accounts for 22% of neonatal deaths. This is a serious challenge for clinicians (7).

The diagnostic criterion for sepsis is blood culture, which usually takes 42–72 hours to obtain a result and has a low sensitivity. These shortcomings often result in delayed and missed diagnoses. As neonatal sepsis is an advanced stage of non-sepsis, early diagnosis and treatment of neonatal infection is an important guarantee to prevent sepsis caused by non-sepsis (8).

For many years, a search has been ongoing to find predictors for neonatal sepsis that identify effectively patients who are at risk of infection (9).

Mean platelet volume (MPV) is a measurement of the average size of platelets found in the blood. The increase in MPV could express either the development of a more invasive infection or the presence of an infection unresponsive to the antibiotic therapy (10).

Serum uric acid (SUA) has important antioxidant properties in vitro, by scavenging free radicals and chelating iron, the latter preventing iron-catalyzed oxidation. There is a strong correlation between the concentration of SUA in biologic fluids and demonstrable antioxidant activity. Indeed, SUA contributes as much as 60% of free-radical scavenging in human serum. Free radicals have been implicated in the pathogenesis of neonatal septicemia (3).

The present work aimed to study the correlation between MPV and SUA and diagnosis of neonatal sepsis.

In the current study, there was no significant difference between both groups concerning age or sex ($p>0.05$).

These findings were comparable with the result of study made by El-Gendy et al. (11) who found there was no significant difference in patients and controls in terms of sex and age.

This study showed that, males predominance among patients with neonatal sepsis was (70%) than females. Male > females.

This was in accordance with that reported by Higazi et al. (12), in their study to evaluate the diagnostic and prognostic performances of urinary interleukin-18 (uIL-18) and serum amyloid A (SAA) in neonatal sepsis parallel to C-reactive protein. They found there is male predominance (60%). This may be correlated to X-linked immune-regulatory genes.

This is in agreement with the previous findings of (13) and explained this due to the fact that male babies receive medical services at a higher rate than female babies in this region.

This is in disagreement with (14) who aimed to determine the role of CD64 expression as a neutrophil surface marker in diagnosis of neonatal sepsis. Their studied population comprised 62 neonates with gestational ages of 26-41 weeks who were to have sepsis and 18 healthy age and sex-matched neonates. They found that no male predominance in NS was seen in their study (male to female ratio 1: 1).

This study showed that, respiratory distress was higher among cases than control.

This comes in agreement with Payashli et al. (15) who found that R.D was the most common clinical presentation (80%) followed by lethargy and hypotonia.

In terms of the clinical manifestations, the percentage of apnea, convulsions, skin mottling and bleeding was statistically higher among cases group than controls group. There was no statistically significant difference between Cases group and Controls group regarding maternal uti. The percentage of poor feeding, jaundice and distention was statistically higher among cases group than controls group.
El-Gendy et al. (11) found that regarding clinical manifestations in the patient group, they found tachypnea (80%), intercostal retraction (65%), lethargy (52.5%), temp instability (45%), hepatomegaly (45%), prolonged capillary refill (35%), bloody stool (5%), lethargy (52.5%), temp instability (45%) and hepatomegaly (45%).

In the present work, the mean count of platelets in the sepsis group was significantly lowered compared with the controls.

This is in agreement with (16) who found that the platelet count was significantly lower in cases than control.

Mondal et al. (17) also found that the platelet count was significantly lower between cases than control.

Thrombocytopenia is one of the most common complications of neonatal sepsis; this may be attributed to bone marrow depression, consumption coagulopathy, platelet sequestration, or a combination of these processes. Thrombocytopenia is considered one of the hematological parameters of severity of neonatal sepsis, but a normal platelet count does not exclude sepsis (18).

In the current study, we found that MPV was significantly higher in patients than controls.

This is in agreement with Shalaby et al. (3) who aimed to determine the role of mean platelet volume (MPV) and serum uric acid (SUA) level in the diagnosis of neonatal sepsis (NS). Case-control study was done on 80 newborns divided into 3 groups: group A (n = 22): clinical NS, group B (n = 18): Proven NS and Group C (n = 40): apparently healthy control. They found Septic neonates showed statistically higher values of MPV than the control group.

This comes in agreement with the study of Aydin et al. (5), who found that MPV in newborns with septicemia was significantly higher than in control group.

Similar results were found by Oncel et al. (19), who studied MPV in neonatal sepsis and found that there was a statistically significant increase with regard to MPV values in patients with sepsis.

This agrees with (20) found that Mean platelet volume showed significant difference between septic neonates and controls (10.2±1.2fL vs.8.0±0.5fL, respectively).

This agrees with (9) who aimed to determine the role of mean platelet volume (MPV) and uric acid (UA) level in the diagnosis of neonatal sepsis. Their study was conducted on 80 newborns divided into two groups: group 1 included 40 newborns diagnosed with neonatal sepsis and group 2 included 40 healthy newborns assigned as controls. They found Septic neonates showed statistically higher values of MPV.

In this study, Mean value of Serum uric acid was statistically lower among cases group than controls group.

This is in agreement with Shalaby et al. (3) who found Septic neonates showed statistically lower levels of SUA than the control group.

This agrees with (9) who found Septic neonates showed statistically lower levels of serum UA.

In this study, regarding Diagnostic accuracy of MPV, Sensitivity was 96.7%, Specificity was 93.3%, PPV was 67.4%, NPV was 50% and accuracy was 66.7%. Regarding Diagnostic accuracy of Uric acid, Sensitivity was 50%, Specificity was 93.3%, PPV was 93.8%, NPV was 48.3% and accuracy was 64.4%.

This was in agreement with Shalaby et al. (3) who revealed that the best cut-off value of MPV to detect sepsis is 10.2 fL with 71% sensitivity and 63% specificity. They also revealed that the best cut-off value of serum UA to detect sepsis is 3.70 mg/dL with 13% sensitivity and 19% specificity.

This is in agreement with Abdel Fadil et al., (21) who found as regards to MPV (had sensitivity, specificity, PPV, & accuracy of 100%) Uric acid (had sensitivity 60%, specificity 90%, PPV 93%, NPV 47%, & accuracy 75%) with other parameters.
V. CONCLUSION:

Conflict of Interest: No conflict of interest.

REFERENCES