



Mean platelet volume and serum uric acid in neonatal sepsis: A case-control study



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HIGHLIGHTS

- Mean platelet volume (MPV) reveals the presence of inflammatory burden and disease activity in many diseases. Serum uric acid (SUA) is one of the most important antioxidants in human biological fluids.
- Serum uric acid cutoff point was 3.7 mg/dl, sensitivity was 13%, specificity was 19%, positive predictive value was 19%, negative predictive value was 13% and diagnostic accuracy was 15%.
- This study revealed that MPV showed a statistically significant positive correlation with WBCs and CRP, and a statistically significant negative correlation with gestational age, birth weight and platelet count.
- Cutoff point of MPV was 10.2 fl, sensitivity was 71%, specificity was 63%, positive predictive value was 74%, negative predictive value was 59% and diagnostic accuracy was 68% SUA showed a statistically significant positive correlation with gestational age and birth weight, and significant negative correlation with CRP.

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ABSTRACT

Background: Mean platelet volume (MPV) is a measure of platelet volume. It reveals the presence of inflammatory burden and disease activity in many diseases. Serum uric acid (SUA) 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. For this reason, it was thought that the antioxidant effects of SUA could increase the life expectancy and/or reduce the incidence of malignancy.

Objectives: To determine the role of mean platelet volume (MPV) and serum uric acid (SUA) level in the diagnosis of neonatal sepsis (NS).

Methods: This 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. All patients in the study were subjected to adequate assessment of history, full clinical examination, complete blood count including MPV, C - reactive protein (CRP), blood culture in CRP positive cases, and SUA level at the time of diagnosis of sepsis.

Results: Septic neonates showed statistically higher values of MPV and statistically lower levels of SUA than the control group. The diagnostic cut-off values of MPV and SUA for NS were 10.2 fL, and 3.70 mg/dL, respectively.

Conclusions: MPV could be assessed in the early diagnosis of neonatal sepsis while SUA level has lower sensitivity in neonatal sepsis.

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1. Introduction

Sepsis is recognised as one of the most severe pathologies in newborns and young infants [1] and is responsible for almost one and a half million deaths each year worldwide [2]. Up to 10% of

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infants have infections in the first month of life, the matter which results in 30–50% of total neonatal deaths in developing Countries [2]. And it is considered the single most important cause of death [3] accounting for up to 50% of neonatal mortality [4]. For many years, a search has been ongoing to find predictors for neonatal sepsis that identify effectively patients who are at risk of infection [5]. Mean platelet volume (MPV) is a measurement of the average size of platelets found in the blood [6]. 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 [7]. 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 [8]. Free radicals have been implicated in the pathogenesis of neonatal septicemia [9].

2. Aim

This study aimed to determine the role of mean platelet volume (MPV) and Serum uric acid (SUA) level in the diagnosis of neonatal sepsis.

3. Subject and methods

3.1. Subjects

After approval of the Local Institutional Ethical Committee of Benha University, and obtaining written consents from all parents of patients to participate in this study, this case-control study was carried out on full-term and preterm neonates attending neonatal intensive care unit of Benha University Hospitals, during the period from September 2015 to April 2016. The neonates were classified into three groups: group A (n = 22): diagnosed with clinical neonatal sepsis (NS), 11 males and 11 females their age mean \pm SD (5.41 \pm 2.68) years, group B (n = 18): diagnosed with Proven NS, 8 males and 10 females their age mean \pm SD (4.89 \pm 2.24) days and Group C (n = 40): apparently healthy control, 19 males and 21 females their age mean \pm SD (5.05 \pm 3.4) days. Exclusion criteria: Dysmorphic features suggestive of chromosomal abnormalities, perinatal asphyxia and neonates under a course of antibiotics prior to appropriate blood sampling.

3.2. Methods

All neonates were subjected to the following:

- (1) **Complete history taking from parents:** including obstetric history (death of a previous sibling, previous admission to neonatal intensive care unit, etc.), Prenatal history: diabetes mellitus, maternal fever $>38^\circ\text{C}$, maternal antibiotics, maternal urinary tract infection (UTI). Natal history: premature rupture of membrane (PROM), maternal fever, prolonged second stage of labour, etc., Postnatal History: low Apgar score at 1 and 5 min, aggressive resuscitation, respiratory distress, cyanosis, fever, jaundice. Current history: includes most common symptoms of sepsis in the neonates.
- (2) **Thorough clinical examination** including assessment of gestational age, birth weight measurement, detection of clinical signs of sepsis such as: temperature instability (<37 or $>38.5^\circ\text{C}$), respiratory dysfunction (apnea, intercostal

Table 1
Comparison between studied groups regarding their demographic data.

Demographic Data	Group A	Group B	Group C	Test	P value
	(N = 22)	(N = 18)	(N = 40)		
	NO. %	NO. %	NO. %		
Age/day (mean \pm SD)	5.41 \pm 2.68	4.89 \pm 2.24	5.05 \pm 3.4	F = 0.165	0.848
Gender (NO. %)					
Male	11 (50%)	8 (44.4%)	19 (47.5%)		0.941
Female	11 (50%)	10 (55.6%)	21 (52.5%)	$\chi^2 = 0.123$	

SD = Standard deviation.

retraction, increased oxygen requirement, signs of respiratory distress), circulatory dysfunction (poor peripheral circulation, hypotension, tachycardia, shock, prolonged capillary refill), GIT dysfunction (abdominal distension, bloody stool, feeding intolerance, hepatomegaly, jaundice), neurological dysfunction (irritability, hypotonia, lethargy), hypoglycemia, hyperglycemia, petechiae, bleeding (with thrombocytopenia), or DIC.

- (3) **Laboratory investigations** at the time of diagnosis of sepsis including complete blood cell count with differential leukocytic count & MPV, CRP Quantitative assay, blood culture and serum uric acid measurement.

3.2.1. Sampling

Four millilitres of venous blood samples were collected aseptically by venipuncture from all participants, and distributed as follows:

- a 2 mL whole blood was put in EDTA vacutainer (violet cap) and mixed up & down gently which was used to measure CBC & MPV.
- b 2 plain wasserman tubes without anticoagulant. The plain test tubes were left till coagulation. After coagulation, samples were centrifuged (at 1500 rpm for 15 min). The separated serum was used for the assay of CRP and uric acid.

3.2.2. Laboratory investigations

- 1 CBC was done for all samples using **Sysmex KX-21N** for red blood cell (RBC) count, haemoglobin level, hematocrit value, WBC count (total and differential), platelet count and MPV.

Table 2
Clinical criteria indicating sepsis in the studied neonates (N = 40).

Criteria for sepsis	No.	%
Poor suckling	35	87.5
Lethargy	31	77.5
Poor Moro	31	77.5
RD	33	82.5
Jaundice	36	45.0
Abdominal distension	10	0.25
Seizures	7	17.5
Apnea	5	12.5
Vomiting	28	70
Bleeding	19	47.5
HSM	7	17.5
Hyperthermia	3	7.5
Hypothermia	8	20
Diarrhea	2	5
Sclerema	3	7.5
Purpura	2	5
Umbilical sepsis	5	12.5
Skin infections	2	5

RD: respiratory distress.

Table 3
Comparison between studied groups regarding their laboratory investigations.

Laboratory investigations	Group A (N = 22)	Group B (N = 18)	Group C (N = 40)	F	P value	Post hoc test
	$\bar{X} \pm SD$	$\bar{X} \pm SD$	$\bar{X} \pm SD$			
WBCs ($10^3/\text{cmm}$)	20.2 ± 6.64	15.1 ± 7.01	11.5 ± 4.5	20.1#	0.001**	P1:0.001 P2:0.022 P3:0.023
HB(gm/dl)	11.81 ± 2.15	10.55 ± 2.43	13.8 ± 2.35	14.0	0.001**	P1:0.001 P2:0.001 P3:0.091
ANC ($10^3/\text{cmm}$)	10.7 ± 3.30	9.91 ± 5.65	5.59 ± 1.46	29.0#	0.001**	P1:0.001 P2:0.002 P3:0.717
I/T ratio	0.38 ± 0.13	0.40 ± 0.13	0.02 ± 0.01	55.7#	0.001**	P1:0.001 P2:0.001 P3:0.930
Platelets ($10^3/\text{cmm}$)	231.8 ± 94.0	176.3 ± 96.1	339.0 ± 68.1	27.9	0.001**	P1:0.001** P2:0.001** P3:0.038*
MPV (fl)	10.4 ± 0.71	10.5 ± 0.77	9.46 ± 0.76	17.8	0.001**	P1:0.001 P2:0.001 P3:0.824
Uric acid (mg/dl)	3.95 ± 1.91	2.43 ± 1.36	4.02 ± 1.03	16.2#	0.001**	P1:0.029 P2:0.001 P3:0.002
CRP (mg/l)	44.5 ± 12.6	60.8 ± 14.6	4.09 ± 1.02	61.1#	0.001**	P1:0.001 P2:0.001 P3:0.001

Kruskal-Wallis test.

P1: between group A and C, P2: between group B and C, P3: between group A and B.

* significant, ** highly significant, SD = Standard deviation, Hb = hemoglobin, WBCs = white blood cells, I/T ratio = immature to total neutrophil ratio, ANC = absolute neutrophil count, MPV = mean platelet volume, CRP= C-reactive protein.

2 Quantitative CRP: CRP was measured using human ELISA (sandwich technique) kits provided by Quantiqine, R&D Systems China Co., Ltd. (catalog No. DCRP00). Results were considered positive above 6 mg/l.

3 Uric acid: determined by enzymatic colorimetric test, using the Spinreact kit, Spain catalog No: 41000.

This work has been reported in line with the STROBE criteria [10].

4. Statistical analysis

Data were analysed using SSPS, version 18.0 (Chicago, USA). Quantitative data were expressed as mean ± SD and qualitative data were expressed as frequency and percentage. Independent samples *t*-test of significance was used when comparing two means. The *w*2-test of significance was used to compare proportions between two qualitative parameters. Receiver operating characteristic (ROC) curve analysis was used to find the overall predictivity of parameters and find the best cutoff value for detection, along with sensitivity and specificity. Sensitivity is defined as the probability that a test result will be positive when the disease is present. Specificity is defined as the probability that a test result will be negative when the disease is not present. Positive predictive value (PPV) indicates the probability that the disease is present when the test is positive and negative predictive value (NPV) indicates the probability that the disease is not present when the test is negative.

5. Results

This study showed that there was no statistically significant difference between patient groups (group A and group B) and control group (group C) as regard to sex, and age (Table 1). It was also observed that the most frequent symptoms in our cases were

poor suckling (87.5%), respiratory distress (RD) (82.5%), lethargy and poor Moro reflex (77.5%) (Table 2). According to the laboratory investigations, the WBCs, ANC, I/T ratio, MPV and CRP show statistically significant increase in group A than group C. While platelets, Hb and uric acid show statistically significant decrease in group A than group C. The comparison between group B and group C shows also highly significant increase in WBCs, ANC, I/T ratio, MPV and CRP in group B than group C. While platelets, HB and uric acid show statistically significant decrease in group B than group C. The comparison between group A and group B shows significant increase in WBCs, and decrease in platelets and UA in group B than group C. And highly significant increase in CRP but no significant difference regarding Hb, ANC, I/T ratio and MPV (Table 3). Moreover, 45% of the cases in group B (18 newborns) had positive blood culture as follows: 27.8% of the positive blood cultures were Klebsiella, and 16.7% was coagulase-negative staphylococci (CONS), 11.1% were MRSA, 11.1% were candida, 11.1% were Pseudomonas,

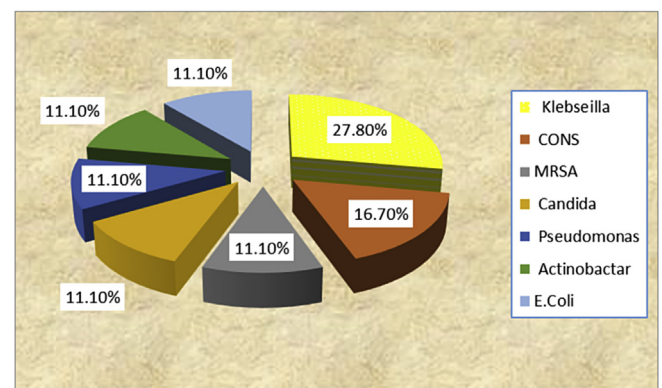


Fig. 1. Microbial results of positive blood culture cases.

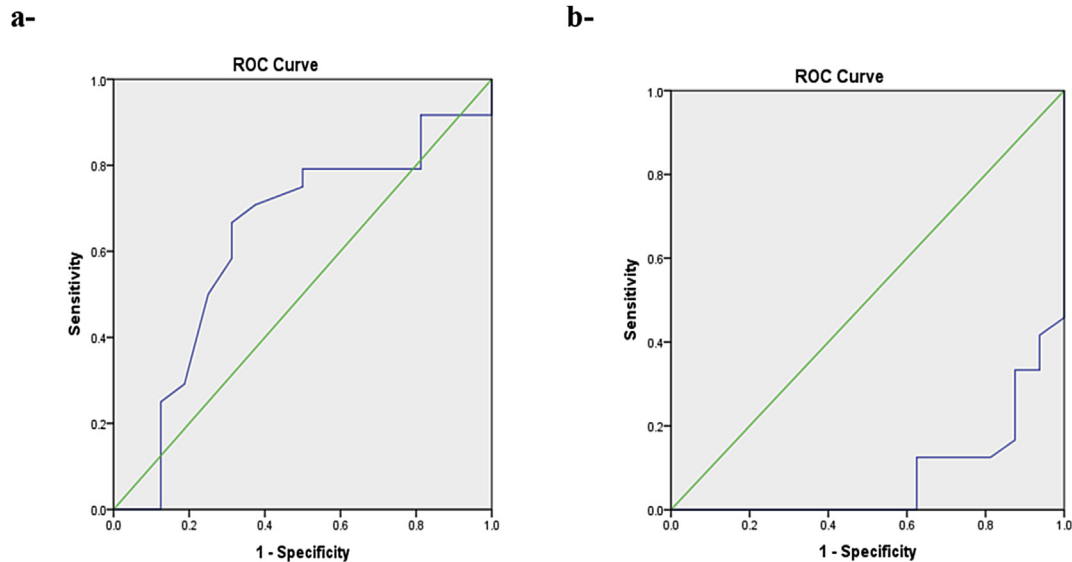


Fig. 2. ROC curve for a-detection of the best cutoff point of MPV in cases of neonatal sepsis. b-detection of the best cutoff point of serum uric acid in cases of neonatal sepsis.

Table 4
Correlation between MPV and uric acid with age, weight and laboratory investigations.

Studied variable	MPV		Uric acid	
	R	P value	R	P value
Gestational age (Weeks)	-0.432	0.001**	0.303	0.006*
Birth weight (kg)	-0.275	0.014*	0.251	0.025*
WBCs	0.239	0.033*	–	–
Platelet count	-0.419	0.001**	0.154	0.343
CRP (mg/l)	0.565	0.001**	-0.339	0.002*

* significant, **highly significant.

11.1% was actinobacteria and 11.1% was *E. coli* (Fig. 1). ROC curve for detection of the best cutoff point of MPV in cases of neonatal sepsis shows that the area under the curve was 0.629. and also the MPV cutoff point was 10.2 fl, sensitivity was 71%, specificity was 63%, positive predictive value was 74%, negative predictive value was 59% and diagnostic accuracy was 68% (Fig. 2a & Table 5). ROC curve for detection of the best cutoff point of serum uric acid in cases of neonatal sepsis shows that the area under the curve was 0.081. Serum uric acid cutoff point was 3.7 mg/dl, sensitivity was 13%, specificity was 19%, positive predictive value was 19%, negative predictive value was 13% and diagnostic accuracy was 15% (Fig. 2b & Table 5). This study revealed that MPV showed a statistically significant positive correlation with WBCs and CRP, and a statistically significant negative correlation with gestational age, birth weight and platelet count. Also, SUA showed a statistically significant positive correlation with gestational age and birth weight, and significant negative correlation with CRP (Table 4).

6. Discussion

It is estimated that four million neonatal deaths occur

Table 5
Diagnostic validity of MPV& serum uric acid in cases of neonatal sepsis.

Cutoff point	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Diagnostic accuracy
MPV 10.2 fl	71	63	74	59	68
Uric acid 3.70 mg/dl	13	19	19	13	15

worldwide every year, and approximately one-third of these are caused by infections. Sepsis and bacterial meningitis continue to be one of the main causes of neonatal mortality, especially among very low birth weight newborn infants [11]. Early diagnosis and treatment of the newborn infant with suspected sepsis are essential to prevent severe and life-threatening complications. Compared with the clear and valuable therapeutic options, the diagnosis of suspected neonatal sepsis is challenging. In preterm infants, the diagnosis of sepsis is more difficult, because of the nonspecific clinical presentation and lack of reliable diagnostic tests [12]. This study aimed to determine the role of mean platelet volume (MPV) and serum uric acid (SUA) level in the diagnosis of neonatal sepsis. In the present study, clinical evaluation of neonates with sepsis revealed that poor suckling (87.5%), respiratory distress (82.5%), lethargy (77.5%) were the most common clinical presentations. This comes in agreement with another study done by Mustafa and his colleagues that described them as the major clinical presentations of sepsis [13]. In this study, there was a significant decrease in haemoglobin level, RBCs count, and platelet count & significant increase in WBCs count, I/T ratio, ANC and MPV in the patient group than in the control group. This agrees with the results of several studies [14,15]. In the current study, CRP was significantly higher in cases than in controls. This comes in agreement with the results of other studies [16–18]. As its one of the acute phase reactants which are synthesised in the liver in response to trauma or invasion of microorganisms [19]. As regards the types of bacteria isolated from blood cultures in the present study, 18 cases had positive culture results (45%) and 22 patients had negative culture results (55%). Similar results have been found in the study of Hisamuddin and his colleagues [16] who found that culture proven sepsis occurred in 30% of cases with sepsis. In addition, Edmond and Zaidi [20] stated that identification of pathogenic organisms in neonates with sepsis syndrome is faced with difficulties. The bacterial load may be low due to mothers receiving antepartum or intrapartum antibiotics and because only small amounts of blood can often be taken from newborns. Contamination rates may also be very high due to the technical difficulties of sterile venipuncture in small babies. There may also be a misinterpretation of the role of coagulase-negative staphylococci (e.g. *S. epidermidis*), as these organisms are both normal skin flora and pathogenic organisms in preterms and infants with indwelling blood vessel catheters. In the present study,

Klebsiella pneumonia was the most common organism isolated in the positive blood cultures followed by CONS (27.8% and 16.7% respectively), and the least common organisms were Actinobacteria (11.1%), Pseudomonas (11.1%), and MRSA (11.1%). This comes in agreement with another study in which the most common organism in positive blood cultures was Klebsiella pneumonia [21]. In the current study, we found that MPV was significantly higher in patients than controls. This comes in agreement with the study of Aydin et al. [22], who found that MPV in newborns with septicemia was significantly higher than in control group. Similar results were found by Oncel et al. [23], 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 disagrees with the study of Aksoy et al. [24], who found that there was no significant difference in MPV between septic and control infants. This disagreement may be due to the difference in the demographic data of the studied group as they focused on MPV in the sepsis of very low birth weight neonates. In the current study, MPV showed significant negative correlation with gestational age, birth weight and platelet count. While it showed statistically significant positive correlation with CRP and WBCs. This comes in agreement with the work of Aydin et al. [22], who found negative correlations between MPV and gestational age ($r = -0.24$, $p = 0.000$), birth weight ($r = -0.27$, $p = 0.000$), platelet count ($r = -0.18$, $p = 0.002$) and uric acid levels ($r = -0.20$, $p = 0.000$). Positive correlations were found between MPV and leukocyte count ($r = 0.11$, $p = 0.04$), and CRP values ($r = 0.32$, $p = 0.000$). Our study revealed that the best cut-off value of MPV to detect sepsis is 10.2 fL with 71% sensitivity and 63% specificity. In our study, we found that serum uric acid was significantly lower in patients than control. There was a large number of studies that investigated the association between neonatal sepsis and free oxygen radicals and antioxidants [25]. However, as far as the authors are concerned, there were three studies that focused on the association between neonatal sepsis and SUA. In their research, which included 30 neonates with sepsis and 20 neonates that did not have sepsis, Batra et al. [26] demonstrated that SUA levels were significantly lower in patients with sepsis. Similarly, Kapoor et al. [27] demonstrated in their research, in which they compared 44 septic newborns with 84 healthy newborns, that the newborns with sepsis had lower SUA levels. Aydin and his colleagues [22] compared 146 cases of NS with 142 healthy newborns and found that the newborns with sepsis had lower SUA levels. In disagreement with our study, Hooman et al. [28] showed that higher SUA levels served as an additive risk factor in sepsis. In the current study, SUA showed statistically significant positive correlation with gestational age and birth weight. While it showed statistically significant negative correlation with CRP. This comes in agreement with the work of Aydin et al. [22], who found positive correlations between SUA levels and gestational age ($r = 0.20$, $p = 0.000$) and birth weight ($r = 0.22$, $p = 0.000$). Uric acid levels were negatively correlated with CRP values ($r = -0.210$, $p = 0.000$). Our study revealed that the best cut-off value of serum UA to detect sepsis is 3.70 mg/dL with 13% sensitivity and 19% specificity.

Limitations: small patient population and possible confounders within the study.

7. Conclusion

Present study concluded that MPV increases significantly in neonates with sepsis while SUA decreases significantly in neonates with sepsis. So, MPV could be a useful early diagnostic marker in neonatal sepsis, while SUA level has lower sensitivity in neonatal sepsis.

Ethical approval

Approval of the Local Institutional Ethical Committee of Benha University, and obtaining written consents from all parents of patients to participate in this study.

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Author contribution

Mohsen M. Shalaby: study design, data collections.
Yasser M. Ismail: data collections, data analysis, writing.
Ahmad A. Sobehi: study design, data collections.
Waleed E. Abdulghany: study design, data collections.
Eman G. Behiry: data collections, data analysis, writing.
Mahmoud A. Abd El-Aziz: data collections, data analysis, writing.

Conflict of interest

No conflict of interest.

Guarantor

Eman G. Behiry.

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