

## New Insight for Early Diagnosis of Neonatal Sepsis

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### Abstract

**Background:** Mean platelet volume MPV that is included in CBC, will be larger with platelet destruction problems as in Neonatal sepsis NS or when the body is producing increased numbers of platelets. Also, NS is associated with increased production of reactive oxygen species that will lead to consumption of specific antioxidant molecules like uric acid.

The aim of the work: to determine the role of MPV and uric acid levels in the early diagnosis of NS.

**Methods:** This study was carried out in NICUs of El-Minia University Hospital between September 2016 and February 2018. A total of 140 newborns involved in this study, the neonates were divided into three groups: clinical NS group I (n=50), culture-proven group II (n=50), NS, & healthy controls group III. CBC with differential, C reactive protein, uric acid levels, and blood culture was done to all three groups.

**Results:** patients in group II had the highest C-reactive protein CRP levels, lowest platelet counts, and uric acid level when compared to groups I and III. MPV values were higher in group I and group II when compared to group III (p=0.001), although there was no difference between groups I and II. Area under curve values for CRP, MPV, and uric acid were 0.92 (p=0.001), 0.76 (p=0.001) and 0.28 (p=0.001), respectively. Sensitivity and specificity of MPV in NS were 100% and 100% respectively. When combined with CRP its sensitivity and specificity is 96% and 100 % respectively.

**Conclusion:** The combined use of CRP and MPV should be considered in the early diagnosis of NS, but uric acid levels may only be utilized as an additional tool to support the diagnosis. MPV is shown to be more sensitive and specific than CRP and uric acid in diagnosing neonatal sepsis.

**Keywords:** Neonatal Sepsis; Mean Platelet Volume; Uric Acid; Thrombocytopenia

**List of abbreviations:** MPV: Mean Platelet Volume; NS: Neonatal Sepsis; CRP: C-Reactive Protein; CBC: Complete Blood Count; UA: Uric Acid; PPV: Positive Predictive Value; NPV: Negative Predictive Value; NICU: Neonatal Intensive Care Unit; MPV/PDW: Mean Platelet Volume/Platelet Distribution Width; GIT: Gastrointestinal Tract; ITP: Immune Thrombocytopenic Purpura

### Background

Neonatal sepsis still one of the leading causes of morbidity and mortality in both term and preterm infants [1]. Clinically suspected sepsis is one of the commonest diagnoses in NICU, because the symptoms and signs of neonatal sepsis are nonspecific and are observed with inflammatory syndromes of noninfectious origin that mimic those of neonatal sepsis [2,3]. So rapidly identifying neonates with clinical suspicion of sepsis and initiating antimicrobial therapy still remain the most important challenge for clinicians.

Thrombocytopenia due to platelet destruction is an early laboratory sign of NS but also, non-specific sign [4-6]. Moreover, clinical response to antimicrobial therapy cannot be judged by platelet counts which remain depressed for days to weeks after sepsis [7].

MPV is higher with platelets destruction as is seen in immune thrombocytopenic purpura (ITP), inflammatory bowel diseases and in NS [4,6,8].

NS is also associated with excessive production of reactive oxygen species that consume body antioxidant activity; therefore, low blood levels of specific antioxidant molecules like uric acid can provide evidence of oxidative stress of sepsis [9].

However, while much is known about neonatal sepsis, MPV & antioxidant activity are not well studied.

### The aim of the work

To determine the role of MPV and uric acid levels in the diagnosis of Neonatal Sepsis.

### Methods

This case-control study had been carried out in NICU of El-Minia University Hospital between September 2016 and March 2018. Patients enrolled in the study are newborns either full term or preterm, from both sexes, with clinical symptoms and signs of sepsis within the 1st month of life, laboratory data showing sepsis (leukocytosis or leukopenia, elevated immature to total neutrophil ratio, thrombocytopenia and increased CRP ± +ve blood culture. Patients excluded from the study are Newborns undergoing a course of antibiotics prior to blood sampling, newborns undergoing surgery in the previous week, chromosomal abnormality, lack of consent from the parents, inadequate sampling of all tests.

The subjects were classified into three groups: group I (n = 50): clinical NS; group II (n = 50): culture proven NS; and group III (n = 40): sex, gestational age, birth weight, mode of delivery and five minutes Apgar score matched healthy stable control.

Clinical NS group I included patients with two or more of the following clinical findings: either respiratory dysfunction (tachypnea with respiratory rate > 60 breaths/min, intercostal or sub costal retractions, apnea, or central cyanosis); or circulatory dysfunction (poor peripheral circulation, hypotension, tachycardia, shock and prolonged capillary refill >3 seconds); or GIT dysfunction (abdominal distension, bloody stool, feeding intolerance, hepatomegaly and jaundice; neurological dysfunction (irritability, convulsion, hypotonia and lethargy; hematological dysfunction (bleeding tendency); renal dysfunction: oliguria, unstable temperature (<36.5 °C or >37.5 °C on two occasions within 12 h) ± laboratory findings [leukocytosis (>20,000/mm<sup>3</sup>) or leukopenia (<5,000/mm<sup>3</sup>); immature/total neutrophil count >0.2; thrombocytopenia (<150,000/mm<sup>3</sup>)], but with negative blood culture.

The normal neonatal values in CBC include the followings; WBC count 5000-20,000/mm<sup>3</sup>, Thrombocytopenia is considered if less than 150000/mm<sup>3</sup>, with platelet count in the 1st wk ranges between 84-478 × 109/L, while after the 1st wk equal that of the adult and ranges between 150-400 × 109/L. Serum CRP levels were measured by nephelometry and considered high if the value exceeded 4.05 mg/L; while the Area under curve values for CRP showed the diagnostic cutoff value is 9.5 mg/dL. MPV ranges between 8.67 ± 1.03/ fL, and the uric acid serum level ranges between 3.5-5 mg/dl [9,10].

Two mL of fresh venous blood were collected from peripheral veins of neonates by sterile venipuncture in a sterile vacutainer tube containing K2 EDTA as an anticoagulant for CBC with differential at time of sepsis evaluation.

Platelet count and MPV were determined using a Beckman Coulter hematology analyzer. Serum uric acid levels were detected using the spectrophotometric method. The Bactec microbial detection system (BACTEC™ 9120) was used to detect positive blood cultures.

The study was carried out according to the principles of declarations of Helsinki, and its appendices and was approved the hospital ethical review board in El Minia university hospital (code 75a, March 2015) [10]. Written informed consents from patients' caregivers were obtained for the use of their study-related information and for participation in the ongoing research.

### Results

Table 1&2 Comparison of Demographic data between the three groups:

		Group I (Clinical sepsis) N = 50	Group II (Culture-proven NS) N = 50	Group III (Control group) N = 40	P - value
Mode of Delivery	NVD	14 (56%)	19 (76%)	12 (60%)	0.301
	CS	11 (44%)	6 (24%)	8 (40%)	
Gender		13 (52%)	17 (68%)	10 (50%)	0.389
		12 (48%)	8 (32%)	10 (50%)	
Prematurity		11 (44%)	14 (56%)	6 (30%)	0.218
		14 (56%)	11 (44%)	14 (70%)	

Table 1: Comparison between case (group I & II) and control groups according to Demographic data

Data	Group I (No = 50)	Group II (No = 50)	Group III (No = 40)	P - value
Birth weight in (gram)	1020 – 3200	1010 – 3920	1050 – 3440	0.299 NS
	2176.2 ± 663	2151.2 ± 858.6	2357.5 ± 697.3	
Gestational age in (week)	31 – 40	30 – 40	30 – 40	0.617 NS
	36.1 ± 3	34.9 ± 3.4	36.4 ± 3.5	

Table 2: Comparison between groups according to birth weight and gestational age

No statistical differences in demographic data were detected among the 3 groups as regards to type of delivery, gender, gestational age, birth weight and rate of prematurity as demonstrated in (Table 1 and 2). However, the postnatal hospitalization age was greater in the sepsis groups than that of the controls as shown in (Table 3).

Data	Group I (n=50)	Group II (n=50)	Group III (n=40)	P-value
Post natal hospitalization age (days)	5.5 (1-60)	2.0 (1-28)	5.0 (1-38)	0.01*

\* P- value < 0.05 means there is significant difference between groups

Table 3: Comparison between groups according to postnatal hospitalization age

Table 4 frequency of clinical criteria indicating sepsis in the studied neonates: shows that the commonest clinical signs of studied groups were poor suckling (42 %), lethargy (30%), poor Moro reflex (14%), respiratory distress (8%) and Jaundice (6%).

Criteria of Sepsis	Number (50)	Percentage (%)
Poor suckling	21	42 %
Lethargy	15	30 %
Poor Moro reflex	7	14 %
Respiratory distress	4	8 %
Jaundice	3	6 %

Table 4: Frequency of clinical criteria indicating sepsis in the studied Neonates

Table 5 Comparison of laboratory findings between the three groups: The patients in Group II had the highest CRP levels ( $124.3 \pm 71.5$ mg/L), lowest platelet counts ( $171.3 \pm 45$ /mm<sup>3</sup>) and lowest uric acid levels ( $1.9 \pm 0.7$  mg/dl) when compared to Group I and Group III (p < 0.05 for all comparisons).

Leukocytic count, ANC, and MPV values were higher in Group I and Group II in comparison with Group III (P < 0.05), although there was no difference between Group I and Group II for these parameters (P > 0.05).

Data	Group I (no = 50)	Group II (no = 50)	Group III (no = 40)	P - value	
Leucocytes in (mm <sup>3</sup> )	Range	11.5 – 30.6	3.9 – 19.3	3.9 – 12.4	< 0.001*
	Mean ± SD	17.6 ± 5.6	14.5 ± 3.9	8.4 ± 2.8	
ANC in (mm <sup>3</sup> )	Range	5 – 15	1.4 – 9.8	1.3 – 7.5	< 0.001*
	Mean ± SD	9.1 ± 3.2	7.5 ± 1.7	4.5 ± 1.9	
Platelet in(mm <sup>3</sup> )	Range	159 – 597	117 – 313	150 – 436	< 0.001*
	Mean ± SD	275.3 ± 107.3	171.3 ± 45	281.2 ± 72.7	
MPV in (fl)	Range	10.5 – 15.5	10.5 – 22.1	7.7 – 10.1	< 0.001*
	Mean ± SD	11.7 ± 1.3	12.2 ± 2.5	8.5 ± 0.5	
CRP in (mg/ l)	Range	12 – 96	12 – 384	1 – 24	< 0.001*
	Mean ± SD	45.8 ± 21.9	124.3 ± 71.5	5.7 ± 6.7	
Uric acid in (mg/dl)	Range	1.3 – 11.6	0.9 – 3.7	2 – 6.7	< 0.001*
	Mean ± SD	3.7 ± 2.3	1.9 ± 0.7	4 ± 1.5	

\* P- value < 0.05 means there is significant difference between groups

Table 5: Comparison between groups according to laboratory parameter

Table 6 Predictive values of CRP, MPV and uric acid levels

	Sensitivity(%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy(%)
CRP	96%	95%	98%	90%	99%
MPV	100%	100%	100%	100%	100%
Uric acid	60%	90%	93%	47%	75%
CRP+ MPV	96%	100%	100%	90.9%	98%
CRP+ Uric acid	62%	95%	97%	50%	78.5%

CRP: C-reactive protein; MPV: Mean platelet volume; NPV: Negative predictive value;

PPV: Positive predictive value

Table 6: Predictive values of CRP, MPV and uric acid levels

Table 7 Results of Microbial Cultures in group II: showing that the highest frequency was Pseudomonas and Klebsiella in 12 cases for each (24% of each sp) followed by E- coli and Candida; 8 cases of each (16% of each), Streptococci was reported in 6 cases (12%) and Staphylococci was reported in 4 cases (8%).

Microorganism		Number	Percent
Gram -ve bacteria	Pseudomonas spp.	6	24%
	Klebsiella spp.	6	24%
	E- coli spp.	4	16%
	Total	16	64%
Gram + ve bacteria	Streptococci spp.	3	12%
	Staphylococci spp.	2	8%
	Total	5	20%
Fungi	Candida spp.	4	16%
Total		25	100

Table 7: Percentage of microorganism in group II

Figures:

Figure 1 Comparison between the three groups in MPV (highest in group II)

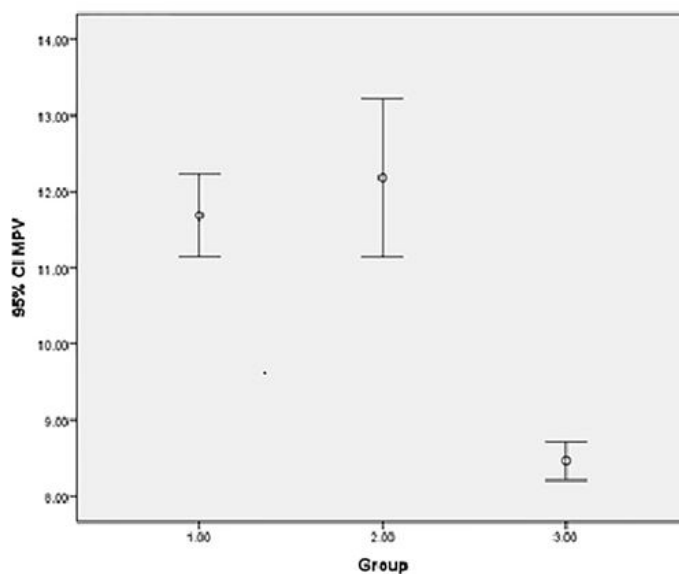


Figure 1: Comparison between the three groups in MPV (highest in group II)

Figure 2 Correlation between MPV and uric acid: There is weak negative Correlation between MPV and uric acid this correlation is not significant

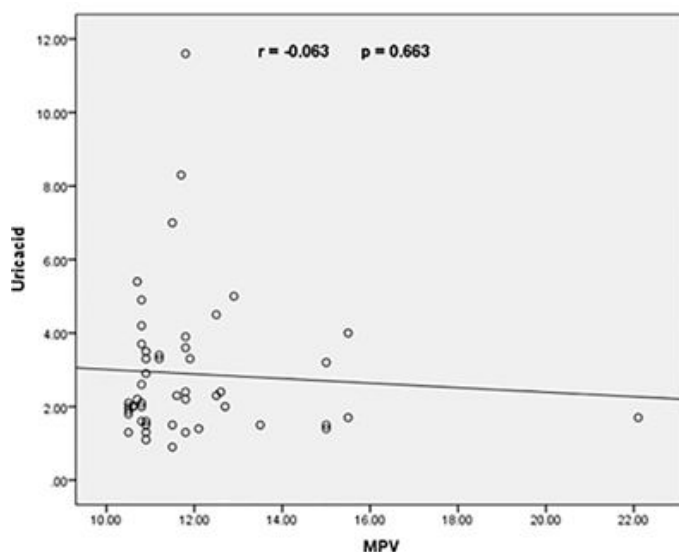


Figure 2: Correlation between MPV and uric acid

**Figure 3 Correlation between MPV and CRP:** There is a fair positive Correlation between MPV and CRP this correlation is not significant

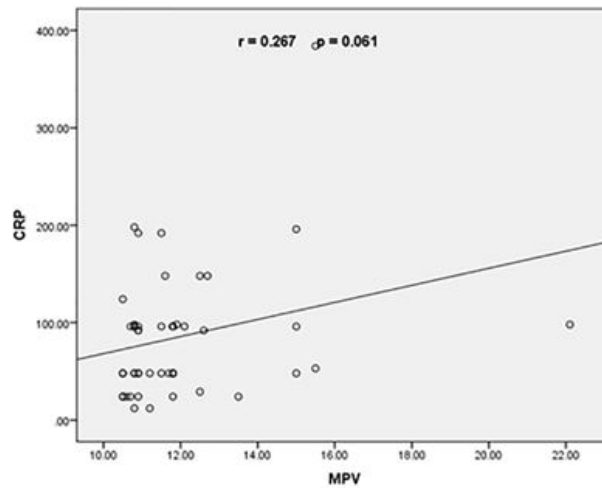


Figure 3: Correlation between MPV and CRP

**Figure 4 Correlation between uric acid and CRP:** There is weak negative Correlation between uric acid and CRP this correlation is not significant

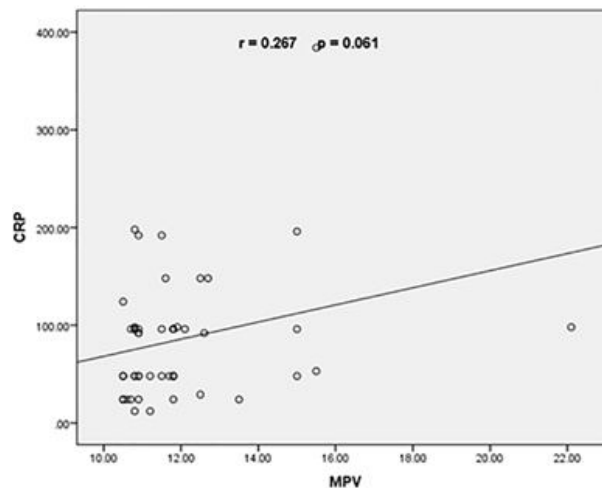


Figure 4: Correlation between uric acid and CRP

**Figure 5 ROC curve for MPV as a predictor for diagnosis of sepsis:** MPV (using the cutoff value of 10.4 fl) had a sensitivity of 100% and specificity of 100% with a PPV of 100%, NPV of 100% and accuracy of 100%.

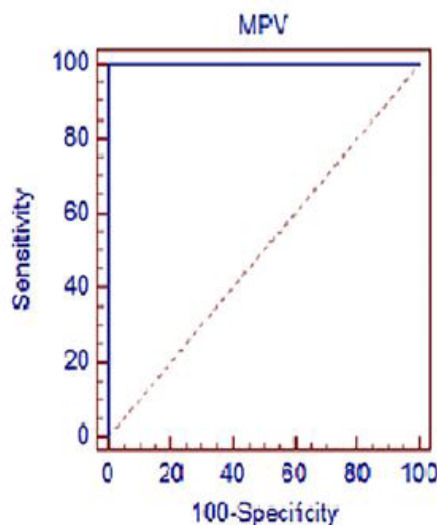


Figure 5: ROC curve for MPV as a predictor for diagnosis of sepsis

**Figure 6 ROC curve for uric acid as a predictor for diagnosis of sepsis:** Uric acid level (using the cutoff value of 3.5mg/dl) had a sensitivity of 60% and specificity of 90% with a PPV of 93%, NPV of 47% and accuracy of 75%.

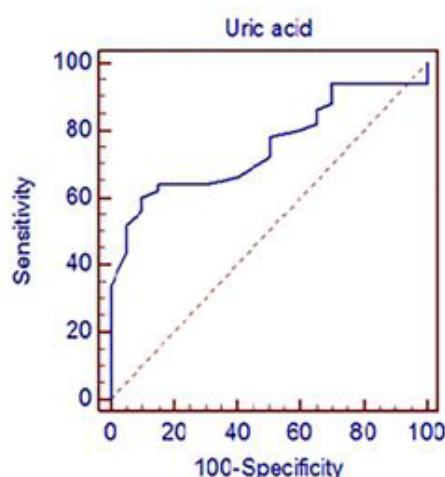


Figure 6: ROC curve for uric acid as a predictor for diagnosis of sepsis

## Discussion

Sepsis becomes a growing problem in NICUs due to resistant microorganisms and higher resistance to commonly used antimicrobial agents [12].

Sepsis neonatorum is the term used to describe any systemic bacterial infection documented by a positive blood culture in the first month of life. Bacterial sepsis in the neonate is a clinical syndrome characterized by systemic signs of infection accompanied by bacteremia [13].

Although a large number of studies have focused on the relationship between NS and thrombocytopenia, there are few studies investigating the association between NS and platelet kinetics [5]. It has been demonstrated that MPV values increase as a result of raised platelet production and/or increased platelet destruction in sepsis [5].

In my study, it was revealed that MPV was higher in group 1 (clinical NS) (mean =  $11.7 \pm 1.3$ ) and group 2 (culture proven NS) (mean =  $12.2 \pm 2.5$ ) than group 3 (healthy control) (mean =  $8.5 \pm 2.5$ ). This is in agreement with Patrick *et al.*, 1990 who evaluated 156 newborns and showed that MPV was considerably higher in patients with bacteremia compared to those without NS and O'Connor *et al.*, 1993 [14,15].

A study conducted by Guida *et al.*, 2003 on patients with culture-positive sepsis and a birth weight of less than 1,500 g, pointed out that 54% sepsis episodes were associated with thrombocytopenia and 61% were associated with an elevation in MPV [5]. Also our study goes in agreement with O'Connor *et al.*, 1993, and Catal F *et al.*, 2014 [15,16].

Some authors concluded that high MPV in the first hours of life might reflect the presence of a risk factor for the development of NEC, bronchopulmonary dysplasia and intraventricular hemorrhage in extremely preterm infants and others indicate that higher MPV values were not associated with the development of sepsis as in a large study by Merza *et al.*, 2014 [17,18].

In my study thrombocytopenia was well documented with all types of sepsis, but was more pronounced with fungal sepsis; this is in agreement with Kaufman *et al.*, 2004 [19]. Benjamin *et al.*, 2000 also have demonstrated that fungal sepsis is associated with a higher degree of thrombocytopenia [20]. Also, it is well reported with gram negative sepsis as in a study by Scheifele *et al.*, 1985 and in sepsis caused by necrotizing enterocolitis [21,22].

In explanation of this phenomenon, some authors explained that bacteria-platelet interactions are characterized by the binding of bacteria to platelets either directly through a bacterial surface protein or indirectly by a plasma-bridging molecule that links bacterial and platelet surface receptors [23].

As regards to serum uric acid level; Batra *et al.*, 2000, & Kapoor *et al.*, 2006 agreed with our finding of lower serum uric acid levels in NS [24,25].

In a trial of explanation of this finding, some authors said that when come in contact with vascular endothelial cells, inflammatory mediators are rapidly released, this release setting into motion a rapid cascade of events. Free oxygen radicals that are generated during this cascade of events cause tissue damage by damaging DNA, denaturing proteins, and causing peroxidation of cell membrane lipids [26]. Total antioxidant capacity (TAC), including uric acid level which is a non-enzymatic antioxidant, will be consumed in correlation with severity of NS [24,25]. While in another study by Chia *et al.*, 2006 & Hooman *et al.*, 2010 found higher uric acid levels & consider it as an additive risk factor in critically ill children with sepsis [27,28].

The cutoff value of CRP in my study was 9.5 mg/l, with a sensitivity of 96% and specificity of 95% with a PPV of 98%, NPV of 90% and accuracy of 99%. Adib & his colleagues found CRP cutoff value of 12 mg/l & had a sensitivity of 45% and specificity of 95% with a PPV of 30%, NPV of 30%, whereas Abdollahi et al., 2012 found sensitivity of 49% and specificity of 100% with a PPV of 100% and NPV of 58% when using the cutoff value of 8 mg/l and lastly Ng et al., 2004 found that a combination of CD64 and CRP revealed sensitivity of 100% and specificity of 80% with a PPV of 90% and NPV of 100% [29-31].

## Conclusion

The use of the MPV and uric acid level as diagnostic markers for NS is advantageous because the measurement is quantitative and enables comparison of results among different centers, noninvasive utility, and the MPV can be done by CBC routinely without additional sampling.

## Recommendations

We can conclude that the combined use of CRP and MPV should be considered in the early diagnosis of NS; however uric acid levels may only be utilized as an additional tool to support diagnosis.

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