

# Early Diagnosis of Neonatal Septicemia by using Platelet Indices, CRP and Serum Uric Acid as Markers

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## Abstract

**Introduction:** Neonatal septicemia is a major reason which may lead to an increase in mortality so if diagnosis is made in time and proper management done, it may help in providing adequate antibiotic coverage and preventing the morbidity and mortality of babies.

**Aim and Objective:** The primary objective of this study is to find the prevalence of Thrombocytopenia, Mean Platelet Volume (MPV), Platelet Distribution Width (PDW), Plateletcrit, C-reactive Protein (CRP) and serum uric acid (SUA) level among the cases of culture positive and culture negative sepsis and to determine the etiological agents and the mortality rate.

**Material and methods:** A hospital based observational study was conducted during the period from October 2017- August 2019 in NICU. A total of 208 neonates were taken and were divided into cases having culture proven sepsis (n= 57) , probable sepsis (n=47) who met the inclusion criteria along with normal healthy controls (n=104) which were comparable to the study group. All of neonates were subjected to detailed history including maternal history and signs and symptoms of sepsis. Blood investigation for complete blood count including platelet indices , SUA, CRP and blood culture were sent. Neonates born <34 weeks and those born with congenital anomalies were excluded from the study.

**Result:** Out of 208 neonates 104 were controls, remaining were cases 57 (54.8%) neonates had culture proven sepsis. Thrombocytopenia was seen in 81.7% of cases. Among cases 34 (32.7%) neonates expired. Platelet counts were low in culture proven cases (p<0.01) with similarly significant results in MPV (p<0.01) and CRP (p<0.01) levels. Most common organism isolated in sepsis was Klebsiella pneumoniae (38%).

**Conclusion:** Thrombocytopenia is a common complication associated with neonatal sepsis having a higher mortality rate. MPV, CRP are reliable markers along with PCT, SUA and PDW can be added as an additional tools to detect early onset septicemia.

**Keywords:** Neonatal Septicemia; Gram Positive; Gram Negative; Thrombocytopenia; Serum Uric Acid; Mean Platelet Volume; Platelet Distribution Width; Plateletcrit.

**Abbreviation:** MPV: Mean Platelet Volume; PDW: Platelet Distribution Width; CRP: C-reactive Protein; NICU: Neonatal Intensive Care Unit; J.N.M.C.H; Jawaharlal Nehru Medical College; A.M.U: Aligarh Muslim University; CONS: Coagulase negative staphylococci.

## Introduction

Neonatal sepsis is characterized by signs and symptoms of infections which may be associated with bacteremia presenting mainly during the first month of life [1] and may lead to an increase in deaths of new born [2]. The exact magnitude of neonatal sepsis in India is not known but as per National neonatal prenatal database (2002-2003); 30 cases per 1000 live births had neonatal sepsis which was approximately 19% of the neonatal mortality which occurred in India.

Neonatal septicemia is divided into two types:

**Early onset neonatal sepsis (EOS):** It occurs within 72 hours of birth due to organisms present in the surrounding delivery area or present in the female genital tract.

**Late onset neonatal sepsis (LOS):** It occurs after 72 hours of birth mainly caused by microorganisms which are present in surrounding external environment.

Diagnosis of sepsis in neonates is based on the gold standard that is the blood culture but the results are available after a period of 48-72 hours which are frequently falsely negative. Blood culture positivity occurs in 25-70% cases [3]. So, initiation of antibiotics in suspected neonatal sepsis may lead to unnecessary increase in the antibiotic consumption which subsequently may give rise to high incidence of resistance to them.

MPV measures the size of the platelet present in blood<sup>4</sup>. Neonatal sepsis is frequently associated with elevation in MPV and PDW. In neonates the sensitivity of MPV in diagnosing sepsis is 54% and specificity is 82%<sup>5</sup>. Guclu [4] et al in his study confirmed, there was a significant difference in the values of PDW and MPV among the sepsis cases and control group. Thrombocytopenia is a complication that commonly is present in critically ill patients. Riedler [6] et al reported thrombocytopenia in 80% of sepsis cases were caused by gram negative organisms and 65% by gram positive organisms. In neonatal sepsis damage to the endothelial lining occurs which leads to activation of reticuloendothelial system causing the removal of the platelets, due to this the platelet consumption is more than the platelet production ultimately leading to thrombocytopenia [7]. CRP which is an acute phase reactant is also increased in cases of neonatal sepsis. SUA is an important antioxidants and it neutralizes more than 50% of free radicals and it has a 13% sensitivity and 19% specificity [8]. It has been observed that SUA is significantly lower in neonates with sepsis.

There have been many studies suggesting different parameters for early diagnosis of sepsis but not a definite parameter has been found. An observational study utilizing platelet indices, CRP and SUA levels to determine their prevalence in the patients of culture positive and culture negative sepsis has been conducted.

## Aim

To find the prevalence of Thrombocytopenia, Platelet distribution width, Mean Platelet Volume, serum uric acid and CRP in cases of culture positive and culture negative neonatal sepsis.

## Objectives

### Primary

To assess the efficacy of platelet indices, SUA and CRP level alone and in combination in newborns having sepsis.

### Secondary

To find out etiological agents causing neonatal sepsis and to find out the mortality rate of neonatal septicemia.

## Material and Methods

This study was a hospital based observational study conducted in the Neonatal Intensive Care unit, Department of Pediatrics in collaboration with the Department of Pathology JNMCH AMU, Aligarh from October 2017 – August 2019. Two hundred and eight babies having gestational age 36- 38 weeks with birth

weight >2500g (cases =104; controls=104) were taken up for study. The babies who were up to seven days of age and presented with the signs or symptoms of sepsis were taken as the study population. All neonates with congenital malformations, who received antibiotic prior to blood sampling and less than 34 weeks were excluded from study. The ethical clearance was obtained from the institutional ethics committee, JMNCH, Faculty of Medicine, AMU Aligarh.

## Brief Procedure

A proper consent was taken from the parents of neonates followed by a complete history along with signs of sepsis were properly evaluated. Approximately 6-7 ml of blood was taken and was divided for measurement of CBC, platelet count, PDW and MPV using the Nihon Kohden celltac analyzer. CRP assay and SUA were done by using the serum. Blood culture and sensitivity was done by taking 1-2 ml of blood in blood culture bottle taking all aseptic precautions. Culture was incubated at 37°C and final reports were seen after 5 days.

All cases were further divided into two following groups:

**A) Study group:** Approximately 104 cases of sepsis were taken and divided into: -

1a) *Group A-Proven sepsis (Septicemia)* - Characterized by neonates with clinical sepsis along with laboratory evidence and having a positive blood culture test.

1b) *Group B-Probable sepsis* - Characterized by neonates with clinical sepsis along with laboratory evidence as per IMNCI/WHO criteria<sup>1</sup> but having a negative blood culture test.

**B) Group C - Control /No sepsis:** 104 neonates were taken having no clinical sepsis and normal laboratory parameters.

Reference range for the parameters taken:

### • Platelet count

Thrombocytopenia when platelet count less than  $150 \times 10^3/\mu\text{L}$ .

1. Severe thrombocytopenia less than  $50 \times 10^3/\mu\text{L}$ .
2. Moderate thrombocytopenia  $50-100 \times 10^3/\mu\text{L}$ .
3. Mild thrombocytopenia  $100-150 \times 10^3/\mu\text{L}$ .

### • Platelet indices

1. MPV-  $8.21 \pm 0.65$ . Cut off value taken as 10.4fl.
2. PDW  $17.03 \pm 0.07$ .

### • CRP 0-6 mg/litre.

### • Serum uric acid

Cut off value will be 3.70 g/l.

**Statistical analysis:** The analysis was done using the SPSS software version 25.

## Observations and Results

208 new born were a part of this study. 104 were controls and 104 were sepsis patients among which there were 41 males and 63 females. Gender, mode of delivery and birth weight were compared between septic patients and the control group. (Table 1)

The most common symptom seen in the sepsis patient was that of respiratory distress (82.7%) in form of tachypnea, grunting, retractions, increased work of breathing followed by poor suck (78%), jaundice (72.1%) and lethargy (67.3%). (Table 2)

Blood culture was positive in 57(54.8%) of the sepsis patients and 47(45.2%) had culture negative sepsis. In this study Klebsiella Pneumoniae (54%) was most commonly isolated organism and was followed by Pseudomonas (15%), CONS (9%), Burkholderia (12%), E.coli (6%), Citrobacter (4%), and candida (4%).

In the sepsis patients thrombocytopenia was observed in 81.7% of them and in the control group thrombocytopenia was observed in 9% of patients ( $p < 0.01$ ). Out of the 104 sepsis patients severe thrombocytopenia was seen in 29(27.9%) of them. In the control group the patients with low platelet count had mild thrombocytopenia. In Group A the average platelet count was lower as compared to Group B and also significantly lower than the Group C. The average MPV in Group A was  $11.35 \pm$

1.9 and in Group B was  $10.28 \pm 2.45$  which was significantly higher than the Group C. CRP was also significantly lower in Group C compared to the Group A and B. However there was not much difference seen in the values of Serum uric acid in both Group A and B (Table 3).

Thrombocytopenia showed a 62.4% sensitivity and a 78.9 % specificity in the sepsis patients and when combined with MPV had a sensitivity of 67.2% and a specificity of 85.7 %. When CRP was combined either with MPV or with Uric acid both cases had a sensitivity of (71-78%) with a specificity of (67-69%). (Table 4)

There is a statistically significant positive correlation of MPV with CRP but with thrombocytopenia a negative correlation is seen. SUA with platelet count shows a positive correlation but a negative correlation is seen along with CRP.

We also found that mortality rate in the thrombocytopenic patients was 27 (35.3%) and 58 (64.7%) were discharged. (Table 6)

ROC curve was calculated for the detection of the cut off points of the various parameters. Cut off point of SUA in this study for neonatal septicaemia is 4.65 with a sensitivity of 46% and a specificity of 32%.

The cut-off point of MPV is 10.5fL with a 69% and 47% sensi-

**Table 1. Demographic Comparison between cases and controls.**

Parameters	Grp - A (N=57)	Grp - B (N=47)	Grp - C (N=104)	P value
Gender (No. %)				
Male	12 (21.1%)	29 (61.7%)	53 (50.9%)	0.19
Female	29 (50.8%)	34 (72.3%)	47 (45.2%)	
Mode of delivery	ND = 20 (48.8%)	ND = 35 (55.6%)	ND=57	0.13
	LSCS = 21 (51.2%)	LSCS = 28 (44.4%)	LSCS=43	0.52
Birth weight	$2.76 \pm 0.33$	$2.72 \pm 0.28$	$2.74 \pm 0.24$	0.56

**Table 2. Signs and symptoms indicating sepsis in the cases(N=104).**

Criteria for sepsis	Number	Percentage
Poor suckling	81	78%
Lethargy	70	67.30%
Respiratory Distress	86	82.70%
Jaundice	75	72.10%
Abdominal distension	25	24.10%
Seizures	27	25.90%
Apnea	10	9.60%
Vomiting	40	38.50%
Bleeding	44	42.30%
Hypothermia	30	28.80%
Diarrhea	8	7.69%
Hypoglycemia	34	32.60%
Hyperthermia	15	14.42%

**Table 3. Comparison between the groups based on blood parameters.**

Laboratory parameters	Grp A (N=57) x ± SD	Grp B (N=47) x ± SD	Grp C (N= 100) x ± SD	P Value
Platelets (x10 <sup>3</sup> /μL)	82.5 ± 59	116.12 ± 78.5	262.7 ± 100.2	<0.001
MPV(fl)	11.02 ± 2.37	10.281 ± 2.1	7.503 ± 0.7	<0.001
PDW	18.1 ± 1.85	17.71 ± 1.8	16.57 ± 1.19	<0.001
PCT	0.077 ± 0.046	0.09 ± 0.04	0.12 ± 0.04	<0.001
CRP(mg/dl)	16.63 ± 6.8	11.87 ± 7.02	6.250 ± 1.09	<0.001
SUA	4.15 ± 1.27	5.35 ± 1.35	6.8 ± 0.6	<0.001

**Table 4. Diagnostic validity of laboratory parameters in neonatal septicaemia.**

Cut off point	Sensitivity	Specificity	P value
Thrombocytopenia	62.40%	78.90%	P < 0.02
MPV	65.20%	63.20%	P < 0.008
PDW	63.90%	58%	P < 0.03
CRP	64%	69%	P < 0.04
Serum uric acid	75%	51.20%	P < 0.04

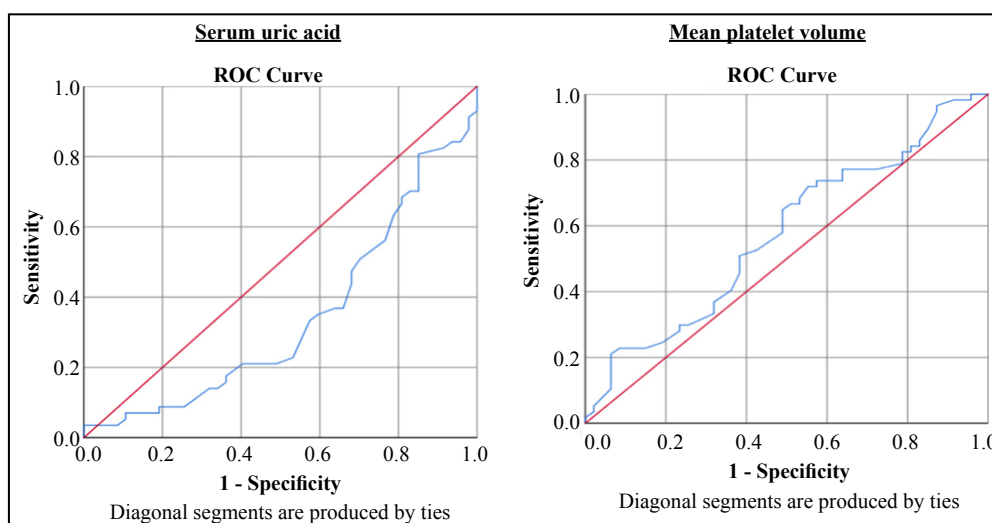
**Table 5. MPV and SUA-correlation seen with birth weight and other parameters.**

Parameters	MPV		Uric acid	
	R	P value	R	P value
Birth weight	0.04	p > 0.5	-0.05	p > 0.5
Platelet count	-0.5	p < 0.01	0.131	p < 0.01
CRP	0.242	p < 0.01	-0.293	p < 0.01

**Table 6. Mortality rates associated with thrombocytopenia.**

Platelet count	Expired	Discharged
Thrombocytopenia (<150000/μL)	27 -35.30%	58 -64.70%
Platelet (>150000/μL)	7 -21%	112 -78.90%

**Figure 1.**



tivity and specificity respectively.

## Discussion

Septicaemia is one of the main causes of neonatal mortality [9]. Hence there is a requirement for an early diagnosis of neonatal sepsis so as to start treatment of the neonate in cases of probable sepsis in order to decrease the occurrence of severe complications. This study aimed to find out the early predictors in form of platelet count, MPV, PDW, Plateletcrit, CRP and SUA for the early diagnosis of neonatal septicaemia.

In this study, presenting clinical features of neonatal sepsis revealed that respiratory distress (82%), poor suck (78%) were the common clinical features. Similar result was seen in another study done by Mustafa which also showed a similar clinical presentation [10]. This study showed a significant decrease in the platelet count, uric acid levels along with an increase in the MPV, CRP, PDW in the cases of neonatal sepsis as compared to the control group. Similar results have been seen in other studies [11-13].

Blood culture was positive in 57(54.8%) of the sepsis patients and 47(45.2%) had culture negative sepsis, but in other studies done by Hisamuddin et al., [11] found that culture proven sepsis was only 30%. Similar high positive blood culture was reported by Heena [14] et al., having a positivity rate of 63%. The number of culture positive results depends on any previous antibiotic treatment, the time when sample is withdrawn and also the extent of bacteraemia in the neonate. In this study *Klebsiella Pneumoniae* (54%) was most commonly isolated organism and was followed by *Pseudomonas* (15%), similar results were also seen in other studies [15]. In our study thrombocytopenia was seen in 85(81.7%) cases of sepsis. Study done by Guida [16] et al., observed thrombocytopenia in 54% of the sepsis cases. Other studies have shown that thrombocytopenia is more severe if caused by gram negative sepsis as compared to infection caused by gram positive sepsis [17]. In this study we observed that in sepsis cases the MPV was higher as compared to the controls. Similarly, Aydin [5] et al., also reported that MPV was high in neonatal sepsis compared to healthy newborn. These findings differed with a study done by Aksoy [18] et al., in which it was observed that in between the septic and control infants MPV did not show significant difference. In this study a statistically negative correlation of MPV is showed with platelet count and statistically positive correlation with CRP. Aydin [5] et al study also had similar correlation results. In this study the cut off of MPV is 10.5 fL to detect sepsis having a 69% sensitivity and a 47% specificity. Septic patients have a higher PDW than controls. Similar results in PDW were also seen in the study by Narayan [19]. Guclu [4] showed statistically that the patient with a PDW higher than 18% had higher risk of death.

There are studies that have shown the association between neonatal sepsis and serum uric acid. It was observed in a study done by Batra [20] et al., on 30 neonates with sepsis, SUA levels were significantly low. Aydin [5] et al also found a lower uric acid level in their study on neonatal sepsis. However, in disagreement to our study Hooman [21] et al., reported otherwise that in septic neonates a higher SUA level served as an additive risk factor. In the current study a positive correlation was observed between SUA and platelet counts and a negative correlation between SUA with CRP and MPV. This study re-

ported the cut off value of SUA in sepsis as 4.65 having a 45% sensitivity but having a low specificity of 32%.

**Limitations:** The newborn population size taken was small. Withdrawal of blood in neonates for investigations is difficult and it may itself lead to contamination and sepsis. The amount of blood required for sampling (total amount 5-6 ml) may lead to iatrogenic anaemia in the babies which can easily be prevented by using micro sampling which requires only 10-20 µl of blood volume.

## Conclusion

It is stated that neonatal infection is a major reason of neonatal thrombocytopenia. Present study concludes that Platelet count and SUA were significantly decreased and CRP and MPV were increased in the septic neonates. Among them SUA has a lower sensitivity. The use of platelet volume indices as a definite parameter to detect infections is still not much in use as proper data regarding cut off values is lacking. Therefore, there is a need to standardize the measurement of platelet volume indices in order to get better results in detection of neonatal septicaemia.

**Recommendation:** By this study we can state that when CRP and MPV is used in combination, it has a higher sensitivity and specificity compared to its individual use in diagnosis of neonatal septicaemia, however the uric acid levels can also be used along with CRP as a supporting tool to help in the detection of sepsis in neonates

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