### **Original Research Article**

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# Is mean platelet volume the earliest diagnostic marker of neonatal sepsis: a prospective case control study

Ramkumar Pandian<sup>1</sup>\*, Gopal Kugonally<sup>1</sup>, Lakshmipathy S. R.<sup>1</sup>, Sunitha<sup>2</sup>

<sup>1</sup>Department of Pediatrics, <sup>2</sup>Department of Pathology, KC General Hospital, Bangalore, Karnataka, India

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## \*Correspondence: Dr. Ramkumar Pandian.

E-mail: drramkumar4u@gmail.com

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#### **ABSTRACT**

**Background:** Neonatal sepsis is the third leading cause of neonatal mortality after prematurity and intrapartum related complications worldwide. The literature regarding the use of Mean platelet volume as a diagnostic tool in neonatal sepsis is scanty.

**Methods:** Prospective case control study in a district hospital. Neonates > 30 weeks gestation admitted to NICU during the study period were included. Neonates who did not have any risk factors for sepsis and did not have a positive blood culture or elevated CRP were categorized as group 1. Neonates who were admitted with risk factors of sepsis but did not have a positive CRP or blood culture positivity were categorized as group 2. Neonates who were admitted as probable sepsis and subsequently developed blood culture or CRP positivity were categorized as group 3. Septic workup was done for all the subjects at admission and at 72 hours after admission. Newborn with congenital anomalies and who were already on antibiotics prior to admission were excluded from the study. Statistical analysis was done using Statistical Package of Social Sciences (SPSS) version 20.0.

**Results:** Total 240 Neonates were included in the study. Elevation of MPV in neonates with sepsis was seen as early as the first sample whereas CRP elevation was seen only on Day 3. Cut off value for Mean Platelet Volume (MPV) was found to be 10.15fl with sensitivity of 84% and specificity of 74%.

**Conclusions:** MPV can be used as a earliest diagnostic marker for prediction of neonatal sepsis and mortality. It can facilitate early initiation of treatment without any additional exposure.

Keywords: IT ratio, Mean platelet volume, Micro ESR, Neonate, Preterm, Sepsis

#### INTRODUCTION

Neonatal sepsis is characterised by signs and symptoms of infection with or without accompanying bacteremia within the first one month of life. It is the third leading cause of neonatal mortality, only behind prematurity and intrapartum related complications. Mortality ranges from 1% to 5% for sepsis and 9% to 20% for severe sepsis in neonates. While developed nations have a NMR of 4-5(5.82 per 1000 live births in US) as per NCHS 2014 data the NMR of India is 28 per 1000 live births as per Sample registration report 2013. Because of the varied presentations, diagnosis based on clinical symptoms is often obscure. Neonatal sepsis most often go missed at

primary and secondary care, owing to the limitations in availability of the reliable diagnostic measures thereby leading to higher mortality, morbidity and squeal.<sup>2</sup> There is no single laboratory test to detect neonatal sepsis with 100% sensitivity and specificity.<sup>3</sup> Blood culture remains to be the gold standard test to diagnose neonatal sepsis but it takes almost about more than 3 days for the results to come, is relatively expensive and has a low positivity rate.<sup>4</sup> All newborn suspected to have sepsis should undergo a septic screen which include total leucocyte count (TLC), absolute neutrophil count (ANC), immature to mature neutrophil ratio (I:T ratio), micro erythrocyte sedimentation rate (Micro ESR) and C-reactive protein (CRP). The need of the hour is to identify the neonates

who are susceptible to develop sepsis by means of a marker that is cheap, accurate, and easy to perform with quick availability of reports. As early detection of neonatal sepsis as early diagnosis and treatment reduces the morbidity and mortality.<sup>5</sup>

Mean platelet volume is the measurement of average size of platelet volume in blood and routinely available with blood counts. It is a coulter generated parameter. It is used to assess platelet function. Platelet production increases at the onset of sepsis due to accelerated destruction. However Bone marrow is supressed subsequently and thrombocytopenia is seen. It is proven in many studies that the level of MPV is increased in Neonatal sepsis.<sup>6</sup>

While the concentrations of CRP increase at around 24 h after onset of infection, peak between 36 and 50 h and remain elevated throughout infection. It is postulated that PCT starts rising 4h after exposure to bacterial endotoxins, peaking at 6-8 h and remaining elevated up to 24hrs. The timeframe of increase of MPV in comparison with other markers of sepsis have hardly been studied. Aim of the study was to provide information about the early diagnostic value of mean platelet volume and its sensitivity.

#### **METHODS**

It is a prospective case control study done at a district hospital in Bengaluru, Karnataka. Written informed consent was taken from all the parents. Detailed history was taken from parents and thorough clinical examination of the neonates were done. The clinical features of sepsis considered were as follows.

Table 1: Clinical features suggestive of neonatal sepsis.<sup>8</sup>

Clinical features	suggestive of Neonatal sepsis
Respiratory	Rate >60/min, grunting, severe chest indrawing, central cyanosis, poor perfusion, rapid and weak pulse.
Cardiac	Rapid and weak pulse, poor perfusion
Neurological	Convulsions, drowsy, decreased activity, bulging fontannele
Gastrointestinal	Jaundice, poor feeding, abdominal distension
Musculoskeletal	Edema or erythema over bones and joints
Dermatological	Skin pustules, peri umbilical erythema
Temperature	>37.7 C or <35.5 C

All Neonates who were admitted in NICU and fulfilled the inclusion criteria were considered in the study group.

Septic screen was sent and neonates with 2 or more positive parameters were considered to have sepsis.

Table 2: Laboratory parameters for sepsis.<sup>8</sup>

Laboratory parameters for sepsis	Positive for sepsis
Total Leucocyte count	$<5000/\text{mm}^3>30000/\text{mm}^3$
Immature/Total neutrophils	>0.2/20%
Micro ESR	>15mm in first hour
C reactive protein(CRP)	>3mg/dl
Absolute neutrophil count	As per Manroe and Mouzinhos chart

#### Inclusion criteria

 All neonates >30 weeks gestation admitted to neonatal intensive care unit with clinically suspected neonatal sepsis during the study period of 1 year from November 2017-November 2018 were included in the study.

#### Exclusion criteria

- Neonates who were already on antibiotics prior to admission.
- Neonates with congenital anomalies.

Clinically well newborn and those without any symptoms and signs were taken as controls. Demogrpahic data collected included gender, gestational age, birth weight, pre-existing maternal conditions and risk factors of sepsis. Venous blood sampling was done on all the babies under aseptic precautions on two occasions (prior to starting antibiotics and after 72 of admission). 2ml of blood was collected initially for culture followed by 2ml in EDTA and plain vacutainer each.

Plain vacutainer was sent for CRP estimation, which was done by quantitative method and result above 3mg/dl was considered positive. EDTA vacutainer was sent for complete blood count (CBC), differential leucocyte count (DLC), mean platelet volume (MPV), total leucocyte count (TLC) and peripheral smears for estimation of Immature: Total neutrophil (I:T) ratio. MPV was done for all subjects. Neonates with significant growth in blood culture were considered as proven sepsis. Neonates were divided into three groups as described below.

#### Statistical analysis

Statistical analysis was done using Statistical Package of Social Sciences (SPSS) version 20.0 Quantitative data is presented with the help of Mean and Standard deviation. Comparison among the study groups is done with the help of unpaired t test as per results of normality test. Qualitative data is presented with the help of frequency and percentage table. Association among the study groups is assessed with the help of Fisher test, student "t"

test and Chi-Square test. p" value less than 0.05 is taken as significant. Receiver operator curve (ROC) was generated and the area under curve (AUC) was calculated. Sensitivity, specificity, positive predictive value (PPV) and negative predictive values (NPV) were also analysed.

#### **RESULTS**

Total 240 neonates were randomly allocated into three groups via computer generated randomization namely:

Group 1 [No Sepsis (Control)]: 114babies who did not have any risk factors for sepsis and did not have a positive Blood culture or elevated CRP.

Group 2[Probable/ Suspected Sepsis]: 68 babies who were admitted with risk factors of sepsis pending investigations.

Group 3[Proven Sepsis]: 58 babies who were admitted as probable sepsis and subsequently developed Blood culture or CRP positivity.

Table 3: Demographic data of the study population.

Domoguankia nauamatana	Group	1	Grou	р <u>2</u>	Gro	oup 3	р
Demographic parameters	N	Percentage	N	Percentage	N	Percentage	value
Birth weight (kg)							
<2.5kg (%)	21	18.4%	9	13.2%	8	13.8%	0.653
>2.5kg (%)	93	81.6%	59	86.8%	50	86.2%	0.055
Sex							
Male n (%)	66	57.9%	46	67.6%	33	56.9%	0.491
Female n (%)	48	42.1%	22	32.4%	25	43.1%	
Mode of delivery							
Normal vaginal delivery (NVD)	85	74.5%	50	73.6%	43	74.2%	0.568
Lower segment caesariansection (LSCS)	29	25.5%	18	26.4%	15	25.8%	0.508

Table 4: Comparison of hematological parameters on day 1 between groups.

Hematological	Group 1		Group 2		Group 3		p
parameters	Mean	SD	Mean	SD	Mean	SD	value
Total counts	18530	11250	15822	8207	14886	5710	0.001
I:T ratio	0.15	0.01	0.22	0.01	0.29	0.02	0.024
ANC	5226	1842	5465	2108	5921	2432	0.011
Platelet count	188412	69575	204676	87570	216913	110435	0.032
MPV(fl)	10.22	0.59	10.88	1.00	11.21	1.07	0.041
CRP	0.24	0.14	0.75	1.08	0.98	1.30	0.001

Table 5: Comparison of hematological parameters on day 3 between groups.

Hematological	Group 1	Group 1		Group 2		Group 3	
parameters	Mean	SD	Mean	SD	Mean	SD	p value
Total counts	12825	10068	13021	5870	17168	7544	0.001
I:T ratio	0.18	0.01	0.25	0.01	0.27	0.02	0.013
ANC	4786	2162	5297	1067	5832	832	0.027
Platelet count	203181	70291	180985	108790	160572	77907	0.002
MPV(fl)	10.36	0.71	10.75	1.14	10.98	1.00	0.045
CRP	0.25	0.14	1.74	2.60	2.10	3.34	0.001

On day 1 total counts was significantly higher in group 1 compared to group 2 and group 3 as per ANOVA test  $(18530\pm11250~\text{vs.}~15822\pm8207~\text{vs.}~14886\pm5710;$  p=0.001).The immature to total leukocyte ratio (I:T ratio)  $(0.15\pm0.01~\text{vs.}~0.22\pm0.01~\text{vs.}~0.29\pm0.02;~p=0.024),$ 

Absolute Neutrophil Counts (ANC) ( $5226\pm1842$  vs.  $5465\pm2108$  vs.  $5921\pm2432$ ; p=0.011), Platelet Count ( $188412\pm69575$  vs.  $204676\pm87570$  vs.  $216913\pm110435=0.032$ ), MPV ( $10.22\pm0.59$  vs.  $10.88\pm1.00$  vs.  $11.21\pm1.07$ ; p=0.041) and CRP

(0.24 $\pm$ 0.14 vs. 0.75 $\pm$ 1.08 vs. 0.98 $\pm$ 1.30; p=0.001) was significantly lower in Group 1 compared to Group 2 and Group 3 as per ANOVA test (Table 4). In group 2, I:T ratio (0.22 $\pm$ 0.01 vs. 0.25 $\pm$ 0.01; p=0.001) and CRP (0.75 $\pm$ 1.08 vs. 1.74 $\pm$ 2.60; p=0.001) was significantly lower on Day 1 compared to Day 3 as per Student t-test. The MPV (10.88 $\pm$ 1.00 vs. 10.75 $\pm$ 1.14; p=0.243) was comparable between Day 1 and Day 3 as per Student t-

test (Table 4). On day 3, MPV  $(10.36\pm0.71 \text{ vs. } 10.75\pm1.14 \text{ vs. } 10.98\pm1.00; \text{ p=0.045})$  and CRP  $(0.25\pm0.14 \text{ vs. } 1.74\pm2.60 \text{ vs. } 2.10\pm3.34; \text{ p=0.001})$  was significantly lower in Group 1 compared to Group 2 and Group 3 as per ANOVA test (Table 5). MPV  $(10.22\pm0.59 \text{ vs. } 10.36\pm0.71; \text{ p=0.112})$  and CRP  $(0.24\pm0.14 \text{ vs. } 0.25\pm0.14; \text{ p=0.159})$  was comparable between Day 1 and Day 3 as per Student t-test (Table 5).

	Group 3	Group 3					
Hematological parameters	Day 1		Day 3	Day 3			
	Mean	SD	Mean	SD			
Total counts	14886	5710	17168	7544	0.034		
I:T ratio	0.29	0.02	0.27	0.02	0.001		
ANC	5921	2432	5832	832	0.001		
Platelet count	216913	110435	160572	77907	0.001		
MPV (fl)	11.21	1.07	10.98	1.00	0.167		
CRP	0.98	1.30	2.10	3.34	0.002		

Table 6: Comparison of hematological parameters between day 1 and day 3 in group 3.

In group 3, the I:T ratio  $(0.29\pm0.02 \text{ vs. } 0.27\pm0.02;$ p=0.001), ANC (5921±2432 vs. 5832±832; p=0.001) Platelet Count (216913±110435 160572±77907=0.001) and MPV (11.21±1.07 10.98±1.00; p=0.167) was significantly higher on Day 1 compared to Day 3 as per Student t-test (Table 6). This is concordant to the studies of Shaaban HA et al, Shreekrishna PGN et al, Oncel MY et al and Mittal A et al.9-12 Correlation between CRP and MPV in Group 3: There was significant positive correlation between CRP and MPV on Day 1 (r=0.141, p=0.029). Similarly there was significant positive correlation between CRP and MPV on Day 3(r=0.144, p=0.026) (Table 7). This is consistent with the studies of Shaaban HA et al and Oncel MY et al.9,11

#### Time frame for elevation of MPV in group 3

The elevation in MPV in neonates with sepsis was seen as early as the first sample whereas CRP elevation was seen only on Day 3 (Figure 1). Hence the elevation of MPV in the initial samples can guide in providing appropriate antibiotic therapy.

Table 7: Correlation between CRP and MPV in Group 3.

	MPV			
	Day 1		Day 3	
	٠́r'	p value	ʻr'	p value
CRP	0.141	0.029	0.144	0.026

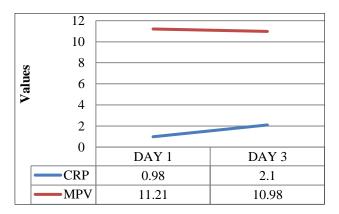


Figure 1: Time frame for elevation of MPV in group 3.

Table 8: Cut off value for MPV in group 3.

Area under the curve							
Toot Possilt Variable(s) Area C4d Errord Asymptotic 95% CI							
Test Result Variable(s)	Area	Std. Error <sup>a</sup>	Asymptotic Sig. <sup>b</sup>	Lower bound	Upper bound		
MPV Day 1	0.727	0.042	0.000	0.645	0.808		
MPV Day 3	0.701	0.043	0.000	0.618	0.785		

a. Under the nonparametric assumption, b. Null hypothesis: true area =0.5

#### Cut-off Value for MPV in Group 3

The cut off value for Mean Platelet Volume (MPV) was found to be 10.15fl with sensitivity of 84% and specificity of 74% (Table 8). Similar observations were noted in the studies of Catal F et al, Aydin B et al, Yao Y et al, Oncel MY et al, Shreekrishna PGN et al, Mittal A et al, Abdulla A et al, Arad ID et al and Shaaban HA et al. 9-16

#### **DISCUSSION**

Sepsis remains to be one of the main causes of neonatal mortality. Early diagnosis and treatment of neonates with suspected sepsis is essential to prevent further complications. our study aimed to determine the role of MPV as an early diagnostic marker of neonatal sepsis. Increased MPV indicates an increased proportion of young platelets in the circulation, because platelets decrease in size as they age, and is suggestive of increased platelet production and/or increased platelet destruction.

In our study, for mean gestational age of neonates, there was no statistically significant difference between the groups as per Chi-Square test (p=0.653). The sex distribution in the groups were comparable and statistically not significant as per Chi-Square test (p=0.491). This is similar to the study of Mittal A et al. <sup>12</sup> The mode of delivery between groups were comparable and statistically not significant as per Chi-square test (p=0.568). This is comparable to the studies of Oncel MY et al and Shreekrishna PGN et al. <sup>10,11</sup>

In our study, in Group 3, the I:T ratio  $(0.29\pm0.02 \text{ vs. } 0.27\pm0.02; p=0.001)$ , ANC  $(5921\pm2432 \text{ vs. } 5832\pm832; p=0.001)$  and Platelet Count  $(216913\pm110435 \text{ vs. } 160572\pm77907=0.001)$  was significantly higher on Day 1 compared to Day 3 as per Student t-test. The total counts  $(14886\pm5710 \text{ vs. } 17168\pm7544; p=0.034)$  and CRP  $(0.98\pm1.30 \text{ vs. } 2.10\pm3.34; p=0.002)$  was significantly lower on Day 1 compared to Day 3 as per Student t-test. The MPV  $(11.21\pm1.07 \text{ vs. } 10.98\pm1.00; p=0.167)$  was comparable between Day 1 and Day 3 as per Student t-test. This is concordant to the studies of Shaaban HA et al, Shreekrishna PGN et al, Oncel MY et al and Mittal A et al.  $^{9-12}$ 

It was observed in our study that the elevation in MPV in neonates with sepsis was seen as early as the first sample whereas CRP elevation was seen only on Day 3. Hence the elevation of MPV in the initial samples can guide in providing appropriate antibiotic therapy. This is in concordance to the studies of Oncel MY et al, Guida J et al and Vander Der Lelie J et al. 11,17,18

#### CONCLUSION

Neonatal sepsis is often accompanied by thrombocytopenia. Although important platelet indices

are readily available while obtaining routine complete blood counts (CBC), they are less studied among neonates although there are data conducted among adults. MPV which is a platelet index obtained from complete blood count can be used an adjuvant marker along with established septic screen to ensure early diagnosis and treatment with no additional expense. However further studies in large scale populations maybe needed.

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Institutional Ethics Committee

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