

# Platelet Counts, MPV and PDW in Culture Proven and Probable Neonatal Sepsis and Association of Platelet Counts with Mortality Rate

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## ABSTRACT

**Objective:** To determine frequency of thrombocytopenia and thrombocytosis, the MPV (mean platelet volume) and PDW (platelet distribution width) in patients with probable and culture proven neonatal sepsis and determine any association between platelet counts and mortality rate.

**Study Design:** Descriptive analytical study.

**Place and Duration of Study:** NICU, Fazle Omar Hospital, from January 2011 to December 2012.

**Methodology:** Cases of culture proven and probable neonatal sepsis, admitted in Fazle Omar Hospital, Rabwah, were included in the study. Platelet counts, MPV and PDW of the cases were recorded. Mortality was documented. Frequencies of thrombocytopenia ( $< 150000/\text{mm}^3$ ) and thrombocytosis ( $> 450000/\text{mm}^3$ ) were ascertained. Mortality rates in different groups according to platelet counts were calculated and compared by chi-square test to check association.

**Results:** Four hundred and sixty nine patients were included; 68 (14.5%) of them died. One hundred and thirty six (29%) had culture proven sepsis, and 333 (71%) were categorized as probable sepsis. Thrombocytopenia was present in 116 (24.7%), and thrombocytosis was present in 36 (7.7%) cases. Median platelet count was  $213.0/\text{mm}^3$ . Twenty eight (27.7%) patients with thrombocytopenia, and 40 (12.1%) cases with normal or raised platelet counts died ( $p < 0.001$ ). Median MPV was 9.30, and median PDW was 12.30. MPV and PDW of the patients who died and who were discharged were not significantly different from each other.

**Conclusion:** Thrombocytopenia is a common complication of neonatal sepsis. Those with thrombocytopenia have higher mortality rate. No significant difference was present between PDW and MPV of the cases who survived and died.

**Key Words:** Newborn. Sepsis. Platelet count. Mortality.

## INTRODUCTION

Sepsis in newborn population is one of the leading causes of morbidity and mortality.<sup>1</sup> Hematological changes induced by culture proven and probable neonatal sepsis have been used to make an early diagnosis and to detect complications. Beside other hematological findings, changes in platelet count and platelet indices induced by neonatal sepsis have been the focus of many studies.

Thrombocytopenia is one of the early but non-specific indicator of neonatal sepsis with or without DIC. It can be caused by bacterial, viral, fungal and parasitic infections and other non-infectious causes. The overall prevalence of thrombocytopenia in neonatal age group varies from 1 - 5%, and is reported to be much higher in newborns admitted to intensive care units, i.e. ranging from 22% to 35%. Severe thrombocytopenia ( $\leq 50000/\text{mm}^3$ ) was found to be present in 2.4% patients admitted in

NICU. Bleeding is a major complication of thrombocytopenia but is generally limited to infants with count  $< 30000/\text{mm}^3$ .<sup>2-6</sup> Studies have shown that approximately 50% cases of culture proven of sepsis get thrombocytopenia.<sup>7,8</sup> Changes in other platelet indices, like MPV (mean platelet volume) and PDW (platelet distribution width) have also been examined in relationship to neonatal sepsis in some studies.

Many studies have shown that, in patients suffering from different diseases, the fall in the platelet counts is associated with increased mortality. Patients with different diagnoses were included in these studies. There was a need to ascertain whether thrombocytopenia in the patients of both probable and culture proven neonatal sepsis is associated with increased mortality or not. Thrombocytosis is a frequent finding in infections especially in neonatal age group, but no studies have been conducted to determine whether there is any association between thrombocytosis and mortality among the patients of neonatal sepsis. Variations in MPV and PDW in different diseases have been focus of many studies lately but these indices have not been extensively studied in the cases of probable and culture proven neonatal sepsis.

The purpose of this study was to find out the prevalence of thrombocytopenia and thrombocytosis, the MPV and

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PDW among the cases of probable and culture proven neonatal sepsis, and to ascertain whether any association is present between platelet counts and mortality rate.

## METHODOLOGY

It was a descriptive study conducted at the NICU, Fazle Omar Hospital, Rabwah, Pakistan, from January 2011 to December 2012. Neonatal sepsis was defined as a case, aged from birth to 30 days, presenting with clinical signs and symptoms of sepsis with isolation of pathogen from blood, CSF or urine. Probable sepsis was defined as the case of this age with clinical signs and symptoms of sepsis, without growth of any pathogen from blood, CSF or urine, but with one or more of these criteria; (1) presence of leukocyte count above  $30000/\text{mm}^3$ , or leukocyte count below  $5000/\text{mm}^3$ , or CRP  $> 6\text{ug/ml}$ . (2) Existence of predisposing factors i.e. maternal fever or foul smelling liquors or prolonged rupture of membranes ( $> 12$  hours) or presence of gastric polymorphic leukocytes (5 or more leukocytes/high power field). All neonates admitted at the study place during the study period with the diagnosis of neonatal sepsis or probable sepsis, were included in this study. Patients with congenital heart diseases, congenital anomalies, hypoxic-ischemic encephalopathy and hyaline membrane disease were excluded from the study.

Blood samples of all the patients included in this study were obtained for CBC (by Madonic CA 620 Analyzer), CRP levels and blood cultures. Urine samples of all the patients were sent for routine examination and culture. Patients were assessed for manifestations of meningitis. Lumbar puncture, of the patients showing signs and symptoms of meningitis, was done. Cerebrospinal fluid of these cases was sent for microscopic examination, gram staining, protein and glucose levels, and cultures. Stomach aspirate of those patients who were admitted in first 24 hours of life were sent for microscopic examination. Name, date of admission, age, diagnosis, WBC count, platelet count, MPV, PDW, CRP levels, blood culture reports, urine routine and culture reports, and if applicable, stomach aspirate and CSF reports, and the outcome were recorded on a data form. Thrombocytopenia was defined as platelet count  $< 150000/\text{mm}^3$ . Thrombocytosis was defined as platelet count above  $450000/\text{mm}^3$ . All patients included in this study received appropriate antibiotics. The patients with platelet count  $< 100000/\text{mm}^3$ , received platelet transfusion, if bleeding was present. All patients who had platelet count  $< 50000/\text{mm}^3$  received platelet transfusion even in the absence of bleeding.

Double entry of the data was done by doctors in-charge of the study and a research assistant. Statistical Package for Social Sciences (SPSS) version 20 was

used for data analysis. Kolmogorov-Smirnov test was applied for testing normality. Application of this test showed that the data for platelet counts, MPV, and PDW were not having normal distribution. Differences in continuous variables were compared by using Kruskal-Wallis test. If the result of Kruskal-Wallis test was found to be significant, pairwise comparisons was conducted by Mann-Whitney test. Chi-square test was used to compare frequencies in different groups. A p-value of 0.05 or less was taken as significant among variables and categories.

Ethical and research committee of Fazle Omar Hospital approved the study.

## RESULTS

Four hundred and sixty nine patients were included in this study. Out of these, 68 (14.5%) died, 38 (8.1%) left against medical advice and 363 (77.4%) were discharged. Among the cases included in this study, 136 (29%) were cases of culture proven sepsis, and 333 (71%) were categorized as probable sepsis. Among cases of culture proven sepsis 84 (61.8%) were having gram positive pathogens, and 52 (38.2%) were having gram negative sepsis. None of the cases included in this study had fungal infection on presentation.

Early onset sepsis or probable sepsis (presenting at  $\leq 7$  days age) was present in 315 (67.2%) cases, and late onset sepsis or probable sepsis (presenting at  $> 7$  days age) was present in 154 (32.8%) cases. Thrombocytopenia was present in 116 (24.7%) cases, thrombocytosis was found in 36 (7.7%) cases, and 317 (67.6%) had the normal platelet count. Median platelet count of all the cases included in this study was  $213.0/\text{mm}^3$ . Interquartile range was  $138.0/\text{mm}^2$ . Minimum platelet counts was  $20/\text{mm}^3$ , maximum platelet count was  $1001/\text{mm}^3$ .

Table I shows mortality rate in patients with thrombocytopenia and with normal or raised platelet count. Those patients who left against medical advice were not included in the comparison. This table shows that those cases of culture proven and probable neonatal sepsis who had thrombocytopenia significantly higher mortality as compared with those cases who had normal or increased platelet count ( $p < 0.001$ ). Mortality rate among cases with thrombocytopenia was 27.7% and 12.1% among cases with normal or raised platelet count. Among those with normal platelet count 261 were discharged and 36 (12.1%) died. In the group with thrombocytosis, 29 were discharged and 4 (12.1%) suffered mortality.

Median platelet counts of the cases discharged and expired were  $224.0/\text{mm}^3$  and  $175.0/\text{mm}^3$  respectively. The patients who left against medical advice were having median platelet count of  $163.0/\text{mm}^3$ . Kruskal-

**Table I:** Mortality rates in different groups with or without thrombocytopenia (n = 431).

Group according to platelet count	Total	Expired
Having thrombocytopenia < 1500000/cu mm	101	28 (27.7%)
Those with normal or raised platelet count	330	40 (12.1%)

Chi-square test was significant  $p < 0.001$

**Table II:** Mean ranks of platelet indices in different groups according to outcome.

Platelet indices	Discharged (d)	Left against medical advice (l)	Expired (e)	p-value	Pairwise comparisons		
					dl	de	le
Platelet count n=469	248.63	193.12	185.67	< 0.001	0.018	< 0.001	0.911
MPV n=463	224.58	262.61	255.31	0.080			
PDW n=443	213.73	267.63	242.11	0.024	0.018	0.107	0.301

Kruskal-Wallis test was conducted to evaluate differences among three levels. If Kruskal-Wallis test was significant Mann-Whitney test was used for pairwise comparison.

Wallis test was applied to evaluate differences among the three groups which showed the difference to be significant ( $p < 0.001$ ). Mann-Whitney U test showed significant difference between the platelet counts of the discharged and expired groups ( $p < 0.001$ ). Table II shows median rank values and pairwise comparisons. This table depicts that the platelet counts of the patients who suffered mortality was significantly low as compared with those who were discharged.

Median value for MPV of all the cases included in this study was 9.30 fL. Interquartile range was 1.10. fL Minimum MPV was 6.10 fL and maximum MPV was 12.20 fL. Median MPV of the cases discharged and expired were 9.20 fL and 9.45 fL respectively. Median MPV of the cases who left against medical advice was 9.70 fL. Kruskal-Wallis test found the difference to be insignificant ( $p=0.080$ , Table II).

Median PDW value was 12.30. Interquartile range was 2.10. Minimum value was 4.20, and highest value was 18.20. Median PDW value for the cases discharged and expired were 12.250 and 12.50 respectively. Median PDW for the cases who left against medical advice was 12.90 (Kruskal-Wallis test,  $p=0.024$ ) Mann-Whitney U test was applied for pairwise comparisons and the difference between the PDW values of the cases discharged and expired was found to be non-significant (Table II).

## DISCUSSION

Thrombocytopenia is a common complication in critically ill patients, suffering from different diseases and is associated with increased mortality.<sup>11-14</sup> It is also a common complication of neonatal sepsis. A study by Mannan *et al.* showed that 50% cases of neonatal sepsis had thrombocytopenia.<sup>7</sup> Another study by Guida

*et al.* showed that among very low birth weight neonates with culture proven neonatal sepsis, 54% had thrombocytopenia.<sup>8</sup> According to Guida *et al.*, when compared with cases with gram-positive sepsis, those with gram negative and fungal sepsis had a significantly lower initial platelet count and increased incidence of thrombocytopenia.<sup>8</sup> Charro *et al.* showed that among cases of late onset sepsis, 59.5% cases had thrombocytopenia, and mortality rate was significantly associated with degree of thrombocytopenia.<sup>15</sup> In this study, cases of both probable and culture proven neonatal sepsis were included and 24.7% cases had thrombocytopenia. Many studies have been conducted to assess organism specific response of the platelets in cases of neonatal sepsis. Some studies have shown that cases of gram-negative and fungal sepsis are associated with lower platelet count and more prolonged thrombocytopenia as compared with gram-positive sepsis.<sup>8,15</sup> Manzoni *et al.* showed that there was no significant difference in the incidence of thrombocytopenia among cases of fungal, gram negative, and gram positive sepsis.<sup>16</sup>

Some studies have shown decrease in platelet count with or without intracranial hemorrhage, is associated with higher mortality. Olmez *et al.* showed that a  $\geq 30\%$  decrease in platelet count is associated with increased mortality.<sup>17</sup> Another study by Rastoqi *et al.* concluded that decrease in platelet count among preterm neonates is associated with increased mortality.<sup>18</sup> Besides increased mortality rate, intraventricular hemorrhage  $\geq$  grade 2 occurs more often in neonates with thrombocytopenia but this is independent of severity of thrombocytopenia.<sup>19</sup> This study showed that patients of probable and proven neonatal sepsis with thrombocytopenia significantly suffer more mortality, as shown in Table I.

Thrombocytosis is a common finding in pediatric age group. Essential thrombocytosis is extremely rare. Reactive thrombocytosis is the commonest cause of thrombocytosis in pediatric age group. Many conditions can lead to reactive thrombocytosis. Both viral and bacterial infections can lead to reactive thrombocytosis. Infections of respiratory tract are the commonest cause followed by infections of urinary tract, gastrointestinal tract and meningitis. Besides infections, iron deficiency anemia, hemolytic anemias, bleeding, connective tissue disorders, malignancies, trauma and various drugs can also lead to thrombocytosis. It is more common in neonates, particularly in premature neonates, and in children up to 2 years. Reactive thrombocytosis in children does not require treatment with platelet aggregation inhibitors, even if the platelet count is greater than 1,000,000/ $\mu$ L, unless additional thrombophilic risk factors exist. Therefore, treatment should

be directed to the underlying disease and not to the platelet count.<sup>20,21</sup>

A study conducted by Fouzas *et al.* showed that reactive thrombocytosis is a frequent finding in children with serious bacterial infection and can help in early recognition febrile young infants at risk for serious bacterial infection.<sup>22</sup>

Thrombocytosis was present in 7.7% cases of probable and proven neonatal sepsis in this study. Mortality rates among cases with thrombocytosis and normal platelet counts were same.

MPV and PDW can help to differentiate consumptive from hypoplastic thrombocytopenia. MPV is a measurement of average size of platelets found in blood. This value normally has inverse relationship to platelet count and increases as more young platelets are present in the circulation due to increased destruction of platelets. PDW is an indicator of variation in platelet size.

In newborn children mean value of MPV is  $8.21 \pm 0.65$  and mean PDW is  $17.03 \pm 0.07$ .<sup>23</sup> Neonatal sepsis is frequently associated with elevation in MPV and PDW. Guclu *et al.* showed that there was a significant difference between MPV and PDW of sepsis cases and control group, and patients with PDW higher than 18% had higher risk of death.<sup>24</sup> Guida *et al.* showed statistically significant increase of MPV among cases of neonatal sepsis in very low birth weight babies from baseline values.<sup>8</sup> In this study, there was no significant difference between MPV and PDW of the cases who died and the cases who survived.

## CONCLUSION

Thrombocytopenia is a common complication of culture proven and probable neonatal sepsis. In this study 24.7% had this complication and thrombocytosis was found to be relatively less common (7.7%). Median platelet count of cases who suffered mortality was significantly lower as compared with the platelet counts of those cases who were discharged. The cases with thrombocytopenia suffered more mortality (27.7%) as compared with the cases with normal and higher platelet count. There was no significant difference between MPV and PDW of the cases who died and the cases who survived.

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