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Mean platelet volume in preterm infants as a predictor of late-onset neonatal sepsis: a retrospective comparative study

Leah Leibovitch ,[1] Hagar Zohar,[2,3] Ayelet Gavri-Beker,[1] Abigail Goshen,[4] Tzipora Strauss[1]

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[1]Neonatology, Sheba Medical Center, Tel Hashomer, Israel
[2]Sheba Medical Center, Tel Hashomer, Israel
[3]Faculty of Medicine, Ariel University, Ariel, Israel
[4]Sheba Longevity Center, Sheba Medical Center, Tel Hashomer, Israel

Correspondence to
Dr Leah Leibovitch; leah.leibovitch@sheba.health.gov.il

ABSTRACT

Background Neonatal sepsis remains a primary cause of morbidity and mortality among newborns. Rapid and accurate diagnosis poses a significant challenge—the non-specific clinical presentation of neonatal sepsis relies heavily on various laboratory indices for early detection and subsequent management. One such indicator under investigation is the mean platelet volume (MPV), which may serve as a predictive marker. This study aims to evaluate the association between the MPV and late-onset sepsis in preterm infants.

Methods This retrospective study included 63 newborns born at Sheba Medical Center from 2016 to 2020 with late-onset sepsis as evidenced by positive blood cultures, and 63 newborns in the control group. We analysed blood count data at three intervals: preinfection, intrainfection and postinfection. Electronic medical records provided supplemental data. Each septic neonate was paired with a non-septic control.

Results Our results revealed a significant elevation of MPV in septic newborns compared with non-septic controls during the days prior to the infection (9.323 and 8.876, respectively, p=0.043) and persisted up to 2 weeks postinfection (9.39 vs 8.714, p=0.025).
The MPV and the MPV-to-total platelet (PLT) count ratio exhibited significant predictive capabilities in receiver operating characteristics analysis (–0.60 and –0.57, respectively).

Conclusions High MPV in combination with PLT decrement might be predictive for the diagnosis of late-onset sepsis. Future studies should be conducted in order to better understand the underlying pathophysiology and the potential clinical applications of these findings.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ High mean platelet volume (MPV) can be indicative of early-onset sepsis in newborns.

WHAT THIS STUDY ADDS

⇒ A significant increase in MPV days before the infection may indicate the evolution of an infection.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ A high MPV should serve as a warning sign for a developing infection, and close monitoring of the infant for signs of infection is suggested, for early detection and management.

BACKGROUND

Bacteraemia in neonates is a major cause of morbidity and mortality.[1]

Despite advancements in medicine, the rapid and precise identification of neonatal sepsis through clinical evaluation and laboratory investigations still poses a significant challenge. It is imperative to detect bacteraemia and sepsis as early as possible, as delayed diagnosis and/or late commencement of antibiotic therapy can cause severe complications, including multisystem failure and death. The clinical manifestations of neonatal infections are often indistinct and could mimic various newborn conditions. Clinical signs such as apathy, compromised perfusion, respiratory distress and haemodynamic instability increase the suspicion of sepsis. The recent advances in technological utilities that facilitate the identification of sepsis-related genes, mRNA, proteins and metabolites in biological samples (such as integration of AI software and OMIC technology), are being considered tools for early sepsis detection, however, these utilities are still under investigation.[2]

Systemic inflammatory responses can be triggered by blood infections leading to multiorgan failure affecting, among others, the brain, lungs, kidneys and haematopoietic system. Haematological abnormalities such as leucocytosis, leucopenia and thrombocytopaenia are common during infections and serve as indicators of disease severity. Another established marker is the elevation of C reactive protein (CRP) levels, usually observed from around the second day of infection.[3]

Neonatal sepsis is broadly categorised into early sepsis, caused by organisms acquired perinatally, and late-onset sepsis (LOS), which appears after three calendar days from birth in hospitalised neonates (defined by 'Identifying Healthcare Associated

Table 1 Clinical characteristics

	No sepsis No=63	Sepsis No=63	Independent t-test p value
Sex			
Male	28 (44.44%)	34 (53.97%)	0.373
Female	35 (55.55%)	29 (46.03%)	
Mode of delivery			
Vaginal delivery	20 (31.74%)	18 (28.57%)	0.846
Caesarean section	43 (68.25%)	45 (71.42%)	
Gestational age (SD)	31.67 (0.47)	31.13 (2.92)	0.897
Birth weight (g), SD	1259.51 (516.31)	1168.10 (540.15)	0.337
Apgar score 1 min	5.44 (2.54)	6.46 (2.25)	0.02
Apgar score 5 min	8.95 (1.27)	8.29 (2.06)	0.03
Days at hospital	57.11 (38.13)	71.61 (36.44)	0.039
Premature complications			
IVH	1	4	0.174
BPD	22	24	0.714
ROP	1	5	0.096
NEC	3	5	0.469

BPD, bronchopulmonary dysplasia; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; ROP, retinopathy of prematurity.

Infection, January 2024), usually, due to postnatal hospital-acquired organisms.[4] While early sepsis incidence has declined due to antibiotic administration during childbirth, late sepsis episodes have risen. Preterm neonates or those with low birth weight are 3–10 times more susceptible to sepsis than full-term, normal-weight infants.[5 6]

Thrombocytopaenia in neonates, defined as platelet counts below 150x10^9/L, is frequently perceived as an indicator of severity during sepsis.[7] This finding is often concurrent with early infection signs and might worsen rapidly, with the platelet count nadir typically noted between 24 and 48 hours.[8]

The half-life of platelets in the blood circulation is 7–10 days. Newly released platelets are comparatively large relative to 'older' platelets. The average size and maturity of circulating platelets are expressed as mean platelet volume (MPV), which is calculated as the plateletcrit divided by the total platelet count (TPC) and is part of a complete blood count (CBC).[9–12] The average volume of the platelets in the blood circulation is between 7 and 9 fL.[13] A high MPV value indicates an increased production of platelets by the bone marrow to compensate for destroyed platelets. Platelet volume in the blood offers a more comprehensive picture of platelet functionality when compared with platelet count.

There are several studies that have demonstrated the use of a high MPV as a predictor of mortality in early sepsis.[14–18] There is one case–control study that suggests a relationship between MPV and LOS in preterm infants.[19]

Our study aims to evaluate the association between MPV and LOS in preterm infants.

METHODS

This is a retrospective comparative study. The study group includes 63 newborns and premature babies born at the Sheba Medical Center between 2016 and 2020 with LOS and positive blood cultures. The control group includes 63 newborns without infection, born in the same year, matched in terms of gestational age and birth weight.

The following patients were excluded from the study: Newborns born with congenital thrombocytopaenia (platelet count less than 150x10^9/L), congenital CMV and other viral infections, IUGR infants were excluded only if they had thrombocytopaenia at birth and infants lacking data in the electronic medical record (EMR) and/or lack of blood counts at the relevant times.

Blood cultures, CBC and CRP were taken when there were clinical signs or a high index of suspicion of sepsis ('intrainfection'). The CBC was analysed within 2 hours of collection. For the infants with positive blood culture a successive blood culture, CBC and CRP were taken. In our department routine, CBC is taken every 7–10 days with additional blood tests conducted based on clinical condition. We retrospectively examined the MPV values in the CBCs taken within 7 days before the sepsis ('preinfection'), and during the first week following sepsis, as well as 10–14 days postsepsis ('postinfection'). In the control group, we analysed the MPV values from CBCs taken around the same age as the sepsis event that occurred in the matched pairs. The values were then compared between the two groups.

For each newborn, data from EMR were collected including spontaneous delivery or caesarean section,

Table 2 Laboratory results preinfection and postinfection

	Sepsis No=63	No sepsis No=63	Independent t-test P value
Week before the infection (preinfection)			
WCC (×10^9/µL)	12.714	12.097	0.681
Hgb (g/L)	130.63	139.04	0.171
Platelet (×10^9/µL)	255.984	272.541	0.553
MPV (fL)	9.323	8.876	0.043
During the infection (intrainfection)			
WCC (×10^9/µL)	13.97	13.674	0.858
Hgb (g/L)	121.6	132.10	0.854
Platelet (×10^9/µL)	190.29	368.774	<0.001
MPV (fL)	9.825	9.234	0.011
CRP (mg/dL)	48.05	–	
1–7 days after the infection (postinfection)			
WCC (×10^9/µL)	16.07	15.020	0.554
Hgb (g/L)	110.4	114.17	0.453
Platelet (×10^9/µL)	190.86	379.472	<0.001
MPV (fL)	10.19	9.408	0.003
CRP (mg/dL)	15.83	–	
10–14 days after the infection (postinfection)			
WCC (×10^9/µL)	10.61	9.302	0.210
Hgb (g/L)	102.3	107.42	0.236
Platelet (×10^9/µL)	318.93	365.756	0.158
MPV (fL)	9.39	8.714	0.025

Mann-Whitney U test.
CRP, C reactive protein; Hgb, haemoglobin; MPV, mean platelets volume; WCC, white cell count.

date of birth, gestational age, prolonged/premature prolonged rupture of membranes (PROM) and Apgar score. In addition, neonatal parameters were collected including the day of infection, CBC results, blood cultures, CRP and premature complications (severe retinopathy of prematurity (grades 3–5 or plus disease), severe intraventricular haemorrhage (IVH grades III or IV), bronchopulmonary dysplasia (defined as O2 therapy at 28 days) and necrotising enterocolitis (NEC—Bell's criteria 2 or 3).

We declare that neither patients nor the public were involved in the design, conduct, reporting or dissemination of our research.

Statistical analysis

The data collection was carried out with the approval of the hospital ethics committee.

Data are presented as mean±SD using a χ^2 test. The comparison between continuous variables that are normally distributed was made using the t-test and for continuous variables that are not normally distributed the Mann-Whitney U test was performed. When there were more than two groups to compare, we used the analysis of variance test.

The platelet indices (MPV, TPC) collected before infection in both study groups were evaluated by the receiver operating characteristics (ROC) curve with the help of the pROC statistical package in the R software.

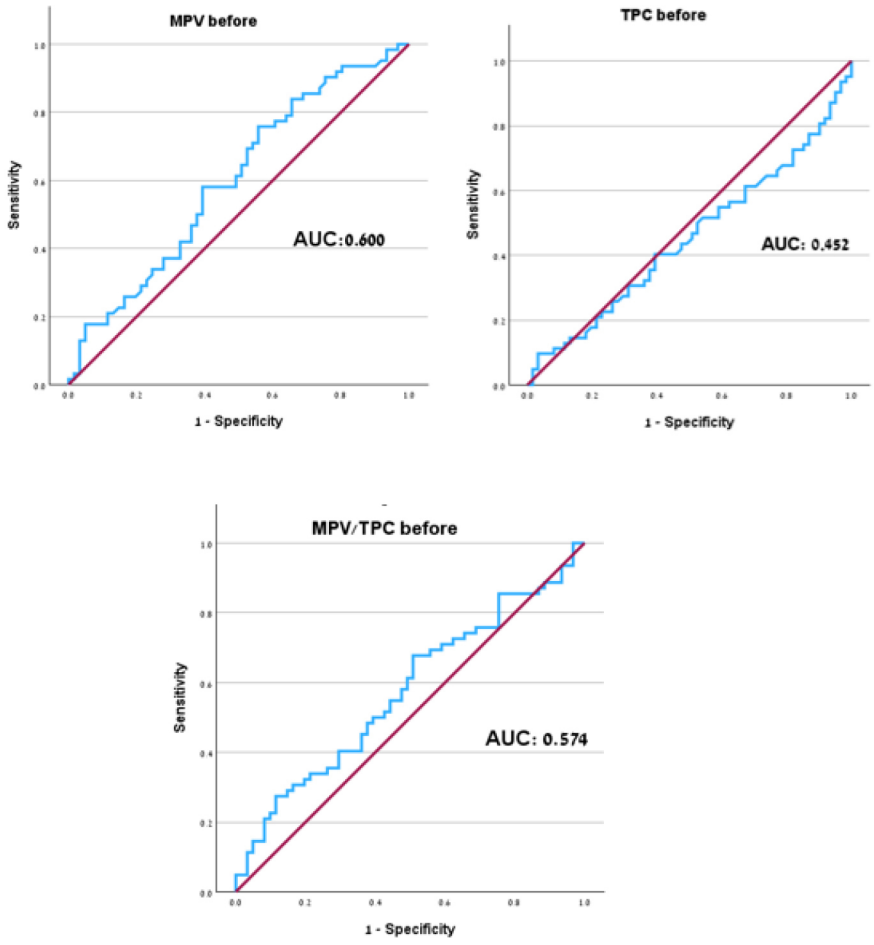
Statistical significance was defined as p<0.05. All statistical analyses were performed using software for statistical processing (IBM SPSS).

RESULTS

In this study, 126 newborns were enrolled, 63 of whom were diagnosed with late-onset sepsis, and 63 in the control group. The demographics of the study population are shown in table 1. There were no statistically significant differences between the sepsis and control groups.

There were no differences between the study and control groups regarding gestational age, birth weight, gender and mode of delivery. The number of hospitalisation days of the sepsis group was significantly greater than the control group (71.61 vs 57.11 days, respectively, p=0.039). There were no differences between the groups regarding premature complications.

Among the positive blood cultures, 28 (44.4%) were gram-negative bacteria, 32 (50.8%) were gram-positive bacteria (CONS) and 3 (4.8%) were fungi. The average age of LOS was 18 days. In the sepsis group, there were four cases of IVH and five cases of NEC, in one case, the



Test variables	AUC	Std. Error	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
MPV	0.600	0.051	0.500	0.700
TPC	0.452	0.052	0.350	0.554
MPV/TPC	0.574	0.052	0.472	0.675

Figure 1 ROC values of MPV, TPC, CRP and the ratio between MPV to TPC. AUC, area under the curve; CRP, C reactive protein; MPV, mean platelets volume; ROC, receiver operating characteristics; TPC, total platelet count.

sepsis occurred on the same day as the IVH. In the other three, the intervals were 3, 11 and 12 days apart from the IVH. For NEC, in one case, the sepsis occurred on the same day of the NEC, and in the four others, the interval was 8, 14, 18 and 25 days apart.

As shown in table 2, a significantly higher MPV in the sepsis group was noted during the week before the infection (9.323 fL vs 8.876 fL p=0.043) as well as during the infection, and up to 14 days postinfection, and it might be explained by the platelets life span.

The platelet count was significantly lower during the infection and the week after.

In the sepsis group, we had 18 (28.6%) infants defined as IUGR and 6 (9.5%) in the control group, however, they did not have thrombocytopaenia after birth.

Only in one case we found a thrombocytopaenia of 44x10^9/L and MPV 10.5 in a CBC taken a few days before the IVH occurred. The patient had platelet transfusions due to thrombocytopaenia and on the

day of sepsis, his platelet count was 117x10^9/L with an MPV of 12.6.

In figure 1, the ROC analysis shows an area under the curve of 0.60 for MPV in predicting the LOS. Using Youden's index[20 21] to determine the optimal threshold value for identifying LOS during the week before infection, the calculated threshold for MPV was 8.495. This value represents a potential cut-off point for distinguishing newborns likely to develop LOS based on their MPV levels during the preinfection period (sensitivity 81.7% and specificity 51.2%).

DISCUSSION

In this study, we have shown that MPV may be considered a predictor for LOS in preterm infants.

Recently, Guney Varal *et al*[19] published a case study that defined MPV as a potential early predictor of LOS in preterm infants. He showed that MPV could play a role in the early detection of sepsis as a result of the concurrent inflammatory response.

During systemic inflammation, the expression of P-selectin on the platelet surface enhances the adhesion of platelets to leucocytes, and their subsequent aggregation, in addition to promoting the expression of tissue factor by monocytes. In septic neonates, the interaction of platelets with the activated endothelium leads to platelet consumption and thrombus formation, resulting in thrombocytopaenia.[22]

Thrombocytopaenia is a well-known marker for sepsis, with a significant reduction in platelet count corresponding with the severity of the disease. In sepsis, proinflammatory and anti-inflammatory cytokines that foster thrombus formation lead to the exhaustion of fibrinolytic and fibrinogenic agents, causing an increased destruction of platelets.[23]

Platelet consumption and destruction in sepsis lead to increased production of young platelets by the bone marrow, which are not only larger but also more functionally active. An increase in MPV is consequently observed, serving as an early indication for the onset of sepsis.

According to the publication by Wiedmeier *et al*, average MPV values increased during the first two postnatal weeks, peaking at 9.5 fL, thereafter gradually decreasing with a plateau mean value of 8.5 fL.[24]

In our ROC analysis, the cut-off of 8.495 for MPV indicates the likelihood of LOS with a sensitivity of 81.7%. These newborns should be supervised with a high index of suspicion for LOS development.

Interestingly, the elevated MPV in the septic group persisted in the subsequent CBCs up to 2 weeks after the septic event. This might be explained by the platelet's half-life of 7–10 days.

Forest *et al* showed that CRP is an acute phase reactant in sepsis[25] and can be elevated on the day of the event or later, as was shown in our data too, whereas the early elevated levels of MPV might serve as an early predictor of LOS even a week prior to the event.

While the study presents compelling evidence for the utility of MPV as an early marker for LOS, it is not without its limitations.

The retrospective nature of the study might introduce potential biases. Furthermore, while the results are promising, larger multicentre studies are required to validate these findings and ascertain the generalised applicability of the MPV threshold identified.

CONCLUSION

The combination of a PLT decrement and a high MPV might be predictive in diagnosing LOS and could be considered for incorporation into clinical practice. As platelet count and MPV are routinely reported in the CBC, they represent a potential low cost and easily available option, further increasing their utility.

Future studies should be conducted for understanding the underlying pathophysiology and the potential clinical applications of these findings.

Contributors LL: conception and design of the work and responsible for the overall content as guarantor. HZ: collecting the data, analysis and interpretation of data for the work; drafting the work. ANG-B: reviewing it critically for important intellectual content. AG: statistical analysis and interpretation of data for the work. TS: conception and design of the work, reviewing it critically for important intellectual content.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

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ORCID iD

Leah Leibovitch http://orcid.org/0000-0001-5576-5092

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