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Original article

Mean platelet volume (MPV) and plasma lactate level in the diagnosis and prognosis of neonatal bacteremia

Marwa Abd EL-Rasoul EL-Ashry [1], Ghada Ahmed Saleh [2], Yara Raafat Hosny [*1], Noha Alaa Eldin Fahim [1]

1- Clinical Pathology Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt.
2- Pediatrics Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt.

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ABSTRACT

Background: Neonatal sepsis is a life-threatening clinical condition. It is associated with high morbidity and mortality if not treated properly. Blood culture remains the gold standard method for diagnosis of sepsis, but it takes at least 24 hours for presumptive diagnosis. Owing to the fact that neonates are vulnerable and can deteriorate easily, rapid diagnosis and management is a must. **Aim of the work:** Determination of the role of mean platelet volume (MPV) and plasma lactate level in the diagnosis and prognosis of neonatal bacteremia. **Methods:** Study included 108 clinically septic neonates aged 0-28 days. All neonates were subjected to blood culture, complete blood picture (for MPV evaluation), C-reactive protein (CRP) and blood lactic acid (BLA) level. **Results:** The current study showed that there was a significant difference between cases and controls as regards MPV, CRP, and lactate with higher mean and median values among cases with *p* value 0.001, 0.003, and 0.021 respectively. High blood lactic acid level was found to be highly significant in non-survived neonates when compared to the survived ones with *p* value 0.001. **Conclusion*:*** Mean platelet volume and BLA tests are simple, rapid, and inexpensive methods to diagnose neonatal bacteremia. The available evidence confirms significantly higher MPV, and BLA in neonates with bacteremia compared to neonates with non-bacteremia causes of sepsis. Therefore, in clinical practice, MPV and BLA could be used as indicators for the early diagnosis of sepsis, while BLA can be used as well as a predictor of mortality.

Introduction

Neonatal sepsis is a clinical syndrome characterized by signs and symptoms of infection with or without bacteremia, caused by various organisms invading the blood stream, which may be, bacterial, viral, fungal, or protozoal, whereas in bacterial sepsis, bacteremia is a cardinal feature [1].

Globally, sepsis is considered to be the major cause of high morbidity and mortality among neonates, despite the efforts done in health care units. Around 40% of under –five deaths worldwide occurs in the neonatal period, owing to 3.1 million newborn deaths annually [2].

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* *Corresponding author:* Yara Rafaat Hosny
E-mail address: yararaafat57357@gmail.com

Unfortunately, the symptoms and signs of neonatal sepsis are subtle and non-specific, so rapid diagnosis and management become a challenge every health care worker faces [3]. Blood culture and sepsis screening tests (elevated C-reactive protein (CRP), elevated total leukocytic count, and thrombocytopenia) are the most common used methods routinely. Although blood culture is the gold standard method for diagnosis of bacterial sepsis, at least 24 hours are needed for preliminary diagnosis. So a rapid and reliable diagnostic tests are needed [3, 4].

Thrombocytopenia is a common hematological abnormality in neonates with bacteremia. The auto-analyzers readily provide platelet indices along with platelet counts without any additional cost. However, these indices are not given proper attention. One of the important platelet indices available for clinical utility is the mean platelet volume (MPV), which is defined by the arithmetic mean of platelets [3].

Lactic acid is the metabolite of the anaerobic oxidation of sugar (glycolysis) and is generated by many organs as the brain, skeletal muscles and red blood cells [5]. There have been a few studies conducted on the influence of blood lactic acid (BLA) detection on neonatal bacterial sepsis diagnosis [6].

The present study aimed at determination of the role of MPV and plasma lactate level in the diagnosis and prognosis of neonatal bacterial sepsis.

Material and Methods

Study design

This study is a prospective cohort study, which was conducted at the Central Microbiology Laboratory of Ain Shams University Hospitals during the period between December 2019-june 2020. After The approval of the Ethical Committee of Ain Shams University (00017585, 2020), an informed consent was obtained from the legal guardian of each patient before enrollment.

Study population

Hundred and eight (108) clinically suspected neonates to have neonatal sepsis enrolled in the present study. Neonates presented with sepsis early on the first 7 days were considered early onset sepsis, and after 7 days were considered late onset sepsis They were subjected to blood culture, complete blood picture (for MPV evaluation), CRP and BLA level. They were further categorized into 54 cases (confirmed positive blood culture) and 54 controls (confirmed negative blood culture).

Inclusion criteria of the enrolled neonates included: neonates with age ranging 0-28 days. Neonates experienced signs of sepsis which were: temperature >37.5°C or <35.5 °C, lethargy, poor suckling, and respiratory rate >60/min [7].

Exclusion criteria included: any blood culture positive for skin contaminants and previously confirmed cases for neonatal sepsis.

All the cases were subjected to the following:

1. ***Detailed medical history with special emphasis on:***
   - Maternal history: presence of fever, urinary tract infection, mode of delivery, and odor of amniotic fluid.
   - Neonatal history: gestational age, sex, tolerance of feeding, and presence of fever.
2. ***Thorough clinical examination, laying stress on:***
   - Weight and length.
   - Gestational age
   - Vital signs including temperature and heart rate
   - Complete systemic examination including: Neurological examination including neonatal reflexes (suckling and Moro reflexes), lethargy, irritability, and crying. Cardiac examination (heart rate, blood pressure). Chest (respiratory rate, air entry, adventitious sounds, apnea, signs of respiratory distress). Abdominal (laxity, distention, umbilical cord, and intestinal sounds). Skin examination (pallor, mottling, and presence of septic focus).
3. ***Laboratory investigations:***

Four blood samples were collected simultaneously under complete aseptic conditions and were used for the following investigations:

- Blood culture: One millilitre of venous blood was added to BACT/ALERT blood bottle and incubated in BACT/ALERT 3D 60 blood culture instrument **(Biomerieux, France)**. Upon positive signal, subculture was done on two blood agar plates (aerobic and anaerobic), MacConkey agar and Chocolate agar plates.

Any recovered isolate was identified to the species level using Vitek2C system (Biomerieux, France).

- Complete Blood Count (CBC): The blood samples were collected on ethylene diamine tetra acetic acid EDTA (K_2EDTA) vacutainer with proper mixing to measure mean platelet volume (MPV) in femtoliter (fl) using: Coulter LH 780 Haematology Analyzer **(Beckman Coulter, U.S)**, Sysmex XT-1800i Haematology Analyzer **(Sysmex, Japan)**, and ABX Micros ES 60 **(Horiba, Japan).**
- C-reactive protein: Gel activated plain tubes were used to measure CRP after clotting of blood within 4 hours to ensure good results, samples were centrifuged at 1000 xg for 15 minutes and sera were separated then the test was performed on AU680 Beckman Coulter analyzer **(Beckman coulter, U.S)**.
- Lactate level using a heparinised blood sample was measured on ABL 800 Flex analyser **(Radiometer, Germany).**

Data management and statistical analysis

The collected data was revised, coded, tabulated and introduced to a PC using Statistical package for Social Science **(IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp).** Data was presented and suitable analysis was done according to the type of data obtained for each parameter.

Results

The present study was conducted on 108 neonates with suspected sepsis. They were 52 (48%) males and 56 (52%) females. One blood culture bottle was collected from each neonate and submitted for routine culture in the central microbiology laboratory Ain Shams University, and simultaneously a blood sample was collected for MPV, CRP, and lactate testing.The enrolled neonates were categorized according to their blood culture results. Neonates with positive blood culture (54 neonates, 50%) were considered cases, while neonates with negative blood culture (54 neonates, 50%) were considered controls.

As regards the descriptive data in our study, about 60% of cases were late onset sepsis; half of cases were males (50%), Gram-negative cases represented 61.1% of cases and mortality was reported in about third of cases didn't survive (37%). As for the control group about 37% of controls were late onset sepsis; about 46% of controls were males. While mortality rate constituted 25% of controls. There was no significant difference noted between cases and controls as regard gender and mortality, however a significant difference was found between cases and controls as regard age of onset of sepsis with *p* value (0.021), 59.3% of cases had late onset sepsis compared to 37% only of controls. The descriptive data of both the cases and controls groups along with their statistical significance are summarized in **table (1)**.

As for the laboratory data, the results summarized in **table (2)** show that there was a significant difference between cases and controls as regard MPV, CRP and lactate with higher mean and median values among cases with *p* -values 0.001, 0.003, 0.021 respectively.

Regarding the correlations between laboratory data and mortality rate among cases group, we found no significant correlations between EOS, and LOS cases as per type of organism, laboratory data and mortality rate except for the CRP with higher mean CRP between LOS compared to EOS (83.14±71.6 vs. 34.8±26) with *p* value 0.017. There is no significant difference between male, and female cases as regards the laboratory data (MPV, CRP, and lactate), and mortality. As for the control group, no significant correlations were noted between EOS, and LOS controls as regards lab data and mortality except for the MPV with higher mean in LOS control group (9.03± 1.17 Vs. 8.14± 1.27) with *p* value 0.014.

Regarding the difference in the lab data among the survived group and non-survived group, data shows no significant difference between survived and non-survived cases except for lactate level with a higher mean among the non-survived cases group (4.49± 1.79 Vs. 2.21± 0.95) with *p* value 0.001 **(Table 3)**.

As for the control group, data summarized in **table (4)** show that there is unexpected high significant correlation between non-survived and survived controls as regards CRP, and lactate levels with a higher mean among non-survived cases (60.6 ±49.5 Vs. 23.5± 24.3), and *p* -value 0.006, and 0.001 respectively

After adjustment of all parameters, it was shown that both MPV and lactate were the independent factors associated with gram positive culture (Odds ratio (OR) =8.6, p <0.001 and OR=1.76, p<0.05, respectively). On the other hand,

MPV, CRP and lactate were the independent factors associated with gram negative culture (Odds ratio (OR) =1.87, $p<0.05$ O R=1.01, $p<0.05$ and OR=1.56, $p<0.05$, respectively) **(Tables 5, 6)**.

Table 1. Comparison between cases and controls as regard age, gender and mortality.

		Group				*p*	Sig
		Control		Case			
		N	%	N	%		
Age	Early onset sepsis	34	63.0%	22	40.7%	0.021*	S
	Late onset sepsis	20	37.0%	32	59.3%		
Gender	Male	25	46.3%	27	50.0%	0.7*	NS
	Female	29	53.7%	27	50.0%		
Mortality	Alive	40	74.1%	34	63.0%	0.21*	NS
	Dead	14	25.9%	20	37.0%		

*Chi-square tests

Table 2. Comparison between cases and controls as regard laboratory data.

	Group									*p*	Sig
	Control					Case					
	Mean	±SD	Median	IQR		Mean	±SD	Median	IQR		
MPV/FL	8.47	1.30	8.45	9.50	7.30	11.15	1.13	11.15	12.00	10.50	0.001*	HS
CRP	33.14	36.16	20.80	35.00	11.00	63.47	61.99	38.50	88.80	19.90	0.003**	HS
Lactate	2.34	1.15	1.95	2.80	1.60	3.03	1.70	2.30	3.90	1.90	0.021**	S

*Student T test
**Mann-Whitney

Table 3. Comparison between survived, and non-survived cases as regards laboratory data.

	Mortality									*p*	Sig
	Alive					Dead					
	Mean	±SD	Median	IQR		Mean	±SD	Median	IQR		
MPV/FL	11.19	1.04	11.25	11.90	10.60	11.08	1.30	10.90	12.50	10.45	0.738	NS
CRP	49.46	47.15	29.20	81.90	14.50	87.30	76.87	57.05	174.50	29.75	0.089	NS
Lactate	2.21	0.95	2.10	2.40	1.50	4.49	1.79	4.70	5.80	2.90	0.001	HS

*Student T test
**Mann-Whitney
‡Chi-Square Tests

Table 4. Comparison between survived, and non-survived controls as regards laboratory data.

	Mortality										***p***	**Sig**
	Alive					**Dead**						
	Mean	**±SD**	**Median**	**IQR**		**Mean**	**±SD**	**Median**	**IQR**			
MPV/FL	8.64	1.36	8.65	9.85	7.45	7.97	.97	8.20	8.60	7.20	0.095	NS
CRP	23.53	24.37	16.85	27.70	10.70	60.60	49.53	44.60	100.40	19.00	0.006	HS
Lactate	1.82	.45	1.80	2.05	1.50	3.83	1.25	3.55	4.70	2.80	0.001	HS

*Student T test
**Mann-Whitney

Table 5. Logistic regression for studying independent factors associated with Gram-positive culture cases.

	Odds ratio(OR)	***p***	**Sig.**	**95% Confidence interval for (OR)**	
				Lower	**Upper**
Early onset sepsis*	1.752	0.419	NS	.450	6.819
Gender (female)**	1.026	0.969	NS	.275	3.822
MPV/FL	8.699	**0.0001**	**HS**	3.416	22.152
CRP	1.015	0.061	NS	.999	1.032
Lactate	1.677	**0.041**	**S**	1.022	2.753

*Reference (Late onset sepsis)
**Reference (Male)

Table 6. Logistic regression for studying independent factors associated with Gram negative blood culture cases.

	Odds ratio(OR)	***p***	**Sig.**	**95% Confidence interval for (OR)**	
				Lower	**Upper**
Early onset sepsis*	2.955	0.128	NS	.731	11.935
Gender(female)**	1.281	0.700	NS	.363	4.521
MPV/FL	1.876	**0.043**	**S**	1.021	3.449
CRP	1.015	**0.040**	**S**	1.001	1.030
Lactate	1.563	**0.048**	**S**	1.005	2.433

*Reference (Late onset sepsis)
**Reference (Male)

Discussion

Sepsis is a non-specific inflammatory defense mechanism, where every organ and system in the body can be involved [8]. Neonatal sepsis remains a global health problem due to its significant contribution to morbidity and mortality.

The prognosis and outcome of neonatal sepsis depend on early diagnosis and proper management [9].

Neonatal sepsis is commonly diagnosed by a combination of clinical signs, nonspecific laboratory tests, and microbiologically confirmed by positive blood culture [10]. Thus, there is an eager need of a biomarker that can point out sepsis in an early stage so that appropriate management plan can be started and antibiotics can be initiated [11].

So our study aimed at determination of the role of MPV and plasma lactate level in the diagnosis and prognosis of neonatal bacterial sepsis.

As regards the gender, our results showed that among the cases group, males and females were equal in number, while in the control group the males constituted around 46%. So, our study showed that there was no significant difference between the case and control groups as regards to gender. Our results are in line with **El Mashad and her colleagues** from Egypt, who conducted a study on 40 neonates, and also found no statistical difference [9].

Similarly, **Tamelytė and others** from Lithuanian University of Health Sciences reported that there was no significant difference between the case and control groups when it comes to gender **[**12].

Regarding age of onset of sepsis, our study showed that there was a significant difference between the two groups with 59.3% of cases had late onset sepsis compared to 37% only of the controls with *p*-value 0.021, this outcome was closely similar to a study conducted at Zekai Tahir Burak Maternity Teaching Hospital situated in Ankara. They conducted the study on 100 septic neonates [13].

In contrast, another study was conducted on 40 septic neonates in Egypt, reported no significant difference as regards age between the culture positive septic neonates and culture negative septic neonates (age/day 5.41 ± 2.68 versus 4.89 ± 2.24 respectively). The difference between our reported results and this study may be attributed to difference in number of neonates allocated in each group as our study had more candidates than the reported number in this study [14].

In our study, regarding the type of organism recovered, in the cases group blood culture that yielded a Gram-negative organisms represented 61.1% of the cases. These results are in line with another studies that reported about 67.5% 66.6%, 54.3%, and 66.1% of culture positive cases yielded Gram-negative organisms respectively [1, 9, 13, 14].

However, another study from Indonesia conducted by **Rohadi** reported that among the cases group, the blood culture that yielded Gram- positive organisms over numbered the Gram negative ones. This may be attributed to lower gestational age and lower birth weight found in the culture proven sepsis group, lower number of cases group and difference in geographic distribution [10].

In our study, the mean MPV among cases showed a higher level of 11.15 ±1.13 FL with a median of 11.15, while in the control group the mean MPV among control group was 8.4 ±1.3 FL with a median of 8.45.

These results conclude a highly significant difference between cases and controls when it comes to MPV.

These results are in agreement with the subgroup comparison of the cases group, done to investigate any changes in mean platelet volume between bacteremic septic neonates and non-bacteremic septic neonates. The results of the study revealed that mean baseline level of MPV was significantly higher in septic neonates with positive blood culture compared to the group of septic neonates with negative blood culture (8.82 ± 0.8 FL versus 8.44± 0.5 FL respectively) [13].

Similarly, a prospective cohort (case control) study conducted in the neonatal division of Department of Pediatrics at Medical collage Jodhpur on 196 neonates to evaluate the significance of platelet indices with existing sepsis screen as a marker of neonatal sepsis, showed that mean MPV value was 11.82 ± 1.69 FL in cases versus 9.75± 1.45 FL in controls, which was significantly higher in case group than in control group [11].

Another study conducted on 107 neonates to evaluate the MPV among the culture proven bacterial sepsis, and clinical bacterial sepsis, reported that MPV is again higher in the proven bacterial group (10.51± 1.124 FL versus 10.27±0.8 FL respectively) [7]

Although in the study conducted by **EL Mashad and her colleagues** to determine the role of MPV and uric acid (UA) level in the diagnosis of neonatal sepsis, the control group was healthy neonates, but similarly their study came up with the same conclusion that there was a significant increase in MPV in the septic group compared with the

control group (8.62±1.01 FL Versus 8.28±0.91 FL respectively) [9].

On the contrary, another study showed that there was no significant difference in MPV value between septic neonates with positive blood culture and septic neonates with negative blood culture. However, the study showed a significant difference in MPV between the culture proven septic group and the control group of healthy neonates. This may be owed to the small study population [14].

Regarding difference of MPV between the EOS and LOS patients, our study showed no statistical significance of MPV value between the EOS and LOS cases group, which is in contrast to a study conducted by **Choudhary et al.** that showed that MPV increase is frequently seen in late onset septic cases group [11].

This may be explained by the fact that in our study we used the age of 7 days as the discriminating age between the EOS and LOS, while in the other study they divided the groups using cutoff age 3 days [11].

Regards the CRP results, in our study the results showed that its mean was 63.4±61.99 mg/dl with a median of 38.5 among the cases group, compared to the control group with the mean 33.1 ±36.1 mg/dl with a median of 20.8, and this confirmed the significant difference between cases and controls as regard CRP with higher mean and median values among cases.

The results obtained from our study were in accordance with those obtained by **Oncel et al.** where their mean baseline level of CRP was significantly higher in septic neonates with positive blood culture compared the group of septic neonates with negative blood culture [13].

Also, another study showed that there was significant difference in CRP value between septic neonates with positive blood culture and septic neonates with negative blood culture (60.8 ± 14.6 versus 44.5 ± 12.6) [14].

Although, **Tamelyte et al.** performed their study on older age group but not surprisingly, all sepsis/bacteremia patients demonstrated significantly higher CRP level, when compared with the sepsis/non bacteremia patients [12]

When comparing CRP between the EOS and LOS case group, CRP found to be higher in the LOS cases group in our study.

This result is in line with another study that confirmed serum level of CRP was higher in patients with LOS than patients with EOS [13].

Regarding the plasma lactate, we concluded from our study that the mean lactate level in cases group was 3±1.7 mmol/L with a median of 2.3 compared to its level in the control group with a mean of 2.34 ± 1.1 mmol/L with a median of 1.95, which was statistically significant.

Our results were closely similar to a study carried by **Kim and his colleagues,** to examine the utility of lactate at an emergency department for diagnosing serious bacterial infection (SBI), they measured BLA level between bacteremic septic neonates and non-bacteremic septic neonates. The results confirmed that BLA was higher in bacteremic group compared to the non-bacteremic one [15].

When comparing BLA level in survived neonates versus the non survived ones in the present study, results showed that the non-survived group had BLA level higher than the survived group (4.49 ±1.79 versus 2.21±0.95).

Despite, the fact that studies on the role of BLA in diagnosis and prognosis of neonatal bacteremia were scarce, but their results were in agreement with ours.

This comes in agreement with a retrospective study that was conducted to evaluate the relationship between the BLA level, serum procalcitonin (PCT), CRP and the severity and prognosis of neonatal sepsis. Patients were divided into the non-survival group and the survival group. The BLA level of the non-survival group were significantly greater than those of the survival group [6].

Similarly, Another prospective cohort study was conducted in the levels 2 and 3 of neonatal care unit, Department of Child Health, Dr. Sardjito General Hospital, Yogyakarta, 40 septic neonates were enrolled in this study, and were divided into either the high or low lactate clearance groups. All neonates were followed up until they were discharged from the hospital, as to whether they survived or died. Results showed that the mortality rate was 48% in neonates with low lactate clearance (high BLA level) compared to 7% mortality rate in neonates with high lactate clearance (low BLA level) [16].

Another study was conducted in the Emergency Ward of a tertiary hospital catering to

the urban slum population of east Delhi, India, assessing the role of serial plasma lactate estimates and its clearance in predicting mortality in septic children in the emergency room, they divided the candidates into surviving (104 child) and non-surviving group (45 child). Blood lactic acid was measured at the time of admission. Despite the different selection of the age group enrolled in their study as they selected infants aged 1 month to 12 years, BLA was significantly higher in non-survived group (3.3±1.65), compared to non-survived group (5.4 ±3.3) [17].

Conclusion

In conclusion, the MPV and BLA tests performed in this study are simple, rapid, and inexpensive methods to diagnose neonatal bacteremia. The available evidence confirms significantly higher MPV, and BLA in neonates with bacteremia compared to neonates with non-bacteremia causes of sepsis. Therefore, in clinical practice, MPV and BLA could be used as indicators for the early diagnosis of sepsis, while blood lactic acid can be used as well as a predictor of mortality.

Conflicts of interest: none.

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