Type of the Paper (Article)

The Role of Mean Platelet Volume and Serum Uric Acid in the diagnosis of Neonatal Sepsis at Fayoum University Hospitals

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Abstract:

Introduction: Mean Platelet Volume (MPV) is a measure of platelet size; larger platelets contain more granules. It reflects the inflammatory burden and disease activity in various illnesses. Uric acid (UA) is a significant antioxidant in human biological fluids, responsible for neutralizing more than half of the free radicals in the bloodstream. Its antioxidant properties have been associated with potential longevity and reduced cancer risk.

Aim of the study: This study aimed to explore the diagnostic potential of serum uric acid (SUA) and mean platelet volume (MPV) in neonatal sepsis. The study encompassed both full-term and preterm infants and received approval from the Ethics Committee of Fayoum University's Faculty of Medicine.

Subjects and Methods: Conducted between July 2018 and January 2019, this study took place at Fayoum University Hospitals' neonatal intensive care unit and involved 100 infants, including 54 males and 46 females. The infants were divided into two groups: Group 1 comprised 50 newborns diagnosed with neonatal sepsis based on clinical and laboratory criteria, while Group 2 consisted of 50 healthy neonates without any clinical or laboratory evidence of sepsis.

Results: Septic neonates demonstrated significantly higher MPV levels and statistically lower serum UA levels. The area under the curve values for MPV and UA were 0.654 ($P = 0.01$) and 0.69 ($P = 0.001$), respectively. The diagnostic cut-off values for MPV and UA in newborn sepsis were determined to be 11.2 fl and 2.6 mg/dl, respectively.

Conclusions: MPV and UA levels merit assessment in the early stages of diagnosing neonatal sepsis.

Keywords: MPV; newborn; sepsis; uric acid.

1. Introduction

Sepsis in neonates is a widespread and potentially fatal disorder, characterized as a systemic inflammatory reaction triggered by an infection, whether diagnosed or suspected, occurring within the first four weeks of life [1]. Up to 10% of newborns may contract an infection during their first month of life, accounting for 30–50% of all neonatal deaths in developing nations [2]. It is considered the leading cause of death, responsible for up to 50% of neonatal fatalities [3].

Mean Platelet Volume (MPV) is used to determine the average size of platelets in blood [4]. An increase in MPV may indicate the onset of a more severe illness or the presence of an antibiotic-resistant infection [5]. Neonates with sepsis typically exhibit elevated MPV levels and decreased platelet volumes [6].

Serum uric acid (SUA) levels in biological fluids are closely linked to measured antioxidant properties. Furthermore, SUA may neutralize up to 60% of the free radicals present in human serum [7]. Neonatal sepsis has been associated with an increase in free radicals [8].

2. Subjects and Methods

2.1. Subjects

From July 2018 to January 2019, one hundred infants (54 males and 33 females) were studied in the neonatal intensive care unit of Fayoum University Hospital.

Inclusion criteria

Newborns (including full-term and preterm) showing signs and symptoms of neonatal sepsis were classified as NS using the Griffin score and confirmed by blood cultures [9].

Exclusion criteria

Any neonate requiring surgery, having serious congenital problems, lacking sepsis, or whose parents did not provide consent.

2.2. Methods

All neonates underwent the following:

Full history taking

a. Pre-natal history

To identify maternal neonatal infection risk factors, such as maternal urinary tract infection, premature rupture of membrane (PROM) (up to 18 hr.), vaginal hemorrhage, maternal fever (greater than 38°C), maternal antimicrobial drug usage, and chorioamnionitis.

b. Peri-natal history

To identify risk factors for neonatal sepsis, such as gestational age, delivery mode, and Apgar score.

c. Post-natal history:

To identify the most common symptoms of neonatal sepsis.

Clinical examination

a. General examination

Gestational age was assessed using the new Ballard score. The reflexes specific to newborns, such as Moro's reflex, suckling, and grasping were considered. The skull circumference, weight, and length were measured. Apgar scores were recorded at one and five minutes [10].

b. Local examination

The symptoms of gastrointestinal disorders include bloody stools, hepatomegaly, food intolerance, jaundice, and abdominal distension were identified.

Lethargy, hypotonia, and irritability were signs of neurological conditions. Circulatory impairment manifests as prolonged capillary refill, tachycardia, shock, hypotension, and inadequate peripheral circulation were identified. Respiratory dysfunction was characterized by apnea, intercostal retraction, increased oxygen requirement, and signs of respiratory distress.

Routine investigations

a. Complete blood count (CBC) with differential leukocyte count and MPV. CBC at the time of diagnosis included differential white blood cell count with detection of I/T ratio and differential platelet count and MPV.

b. Quantitative C-reactive protein (CRP) expression levels in serum were assessed using a slide latex agglutination method (Rapitex CRP kit). A titer greater than 6 mg/L was considered positive.

c. Blood samples were taken at the onset of sepsis. Aerobic and anaerobic cultures were performed on MacConkey agar and blood agar plates with 10% carbon dioxide. Isolated colonies were further identified by examining colony morphology, Gram-stained smears, biochemical, and enzymatic reactions. True bacteremia was considered when blood culture was positive within 72

hours. If no growth was observed, the sample was incubated for up to 10 days on solid medium, with subcultures every other day. Blood cultures were considered negative if no growth occurred after 10 days of incubation. Among the 50 neonates with NS, 16 had positive cultures (+ve) and 34 had negative cultures (–ve).

d. For the serum uric acid measurement, blood samples were aseptically obtained from both controls and patients via venipuncture. The blood was allowed to clot before centrifugation for 10 minutes at 5000 rpm. The sera were isolated and stored at –20°C until testing.

2.3. Statistical Method

Data were collected, processed, and statistically analyzed using an IBM personal computer running the Statistical Package for Social Science (SPSS) version 20 and appropriate statistics.

Descriptive statistics: Quantitative data were presented as mean, standard deviation (SD), and range. Numbers and percentages were used to represent qualitative data.

Analytical statistics: Were used to determine the potential correlation between the examined variables and the targeted condition. The Chi-square test ($\chi 2$) was used to investigate the correlation between two qualitative variables. Mann-Whitney significance test (non-parametric): Used to compare two sets that are not normally distributed and have quantitative variables [11]. Student t-test: A statistical test used to compare two sets containing quantitative variables. Pearson correlation (r): A test used to assess the relationship between two quantitative variables [12]. A p-value of 0.05 was considered statistically significant. A p-value of 0.001 was considered statistically highly significant.

3. Results

The demographic statistics for the study groups are shown in **Table 1.** There was no statistically meaningful distinction among study groups in terms of median age, $p = 0.791$. Moreover, the case's median body weight was substantially lower than the control's (2.3 vs. 2.87 kg), $p = 0.001$. In terms of gender, there was no meaningful distinction between case and control ($p = 0.422$).

Table 1: Demographic data of control subjects and psoriasis patients.

Variable		Case (n=50)	Control (n=50)	*P-value*
Age (days)		2 (1-28)	3 (1-29)	0.791#
Weight (kg)		2.3 (1-3.41)	2.87 (1.21-4.55)	0.001#*
Gender	Male	29 (58%)	25 (50)	0.422##
	Female	21 (42%)	25 (50)	

*#Mann Whitney-U test ## Chi-squared test *Significant.*

Table 2 didn't reveal any meaningful difference between the study groups regarding gestational age, *p* =0.075. However, there was a statistically meaningful difference between case and control concerning the mode of delivery as the vaginal is minor in the case than control, *p* =0.032. Regarding PROM, it was meaningfully higher in the case than control, *p* =0.021.

Table 2: History related to delivery.

Variable		Case (n=50)	Control (n=50)	*P-value*#
Gestational age	Full term	32 (64%)	40 (80%)	0.075
	Pre-term	18 (36%)	10 (20%)	
Mode of delivery	Vaginal	11 (22%)	21 (42%)	0.032*
	C.S	39 (78%)	29 (58%)	
PROM	Yes	11 (22%)	3 (6%)	0.021*
	No	39 (78%)	47 (94%)	

*# Chi-squared test *Significant.*

Table 3 revealed that there was no meaningful difference in RBS between case and control, *p* =0.213. In terms of median TLC, there was a statistically meaningful difference between case and control, with the case having a greater median TLC than control, *p* =0.002. In terms of median PLT count, the case was substantially lower than

the control. In addition, there was a statistically meaningful difference in the median Griffin score between the case and control, with the case being higher than the control, p =0.0001.

Table 3: Laboratory data in studied groups.

Variable	Case (n=50)	Control (n=50)	*P-value#*
RBS (mg/dl)	84.5 (44-193)	92 (58-171)	0.213#
TLC/1000	13.6 (5.5-65)	9.88 (5.6-593)	0.002#*
PLT/1000	185 (51-520)	250.5 (56-669)	0.007#*
Griffin score	4 (2-8)	0 (0-1)	<0.0001#*

*#Mann Whitney-U test, *Significant.*

Table 4 demonstrates a meaningful difference between the case and control in terms of shift to the left, with the case being greater than the control, $p = 0.0001$. CRP was substantially greater in the case than in the control, $p = 0.0001$.

Table 4: Septic work-up.

Variable		Case (n=50)	Control (n=50)	*P-value#*
Shift	**Yes**	33 (66%)	3 (6%)	<0.0001*
	No	17 (34%)	47 (94%)	
CRP	**Positive**	49 (98%)	0 (0%)	<0.0001*
	Negative	1 (2%)	50 (100%)	
Blood culture	**Positive**	16 (32%)		
	Negative	34 (68%)		

*# Chi-squared test *Significant*

According to **Table 5**, the median MPV differed meaningfully (p <0.0001) among the case and control groups. Furthermore, the case's median UA was meaningfully less than that of the control (p <0.0001).

Table 5: Differences between study groups as regards MPV and UA levels.

Variable	Case (n=50)	Control (n=50)	P-value#
MPV (fl)	11.2 (6.7-16.7)	9.7 (7.5-11.4)	<0.0001*
UA (mg/dl)	2.6 (1.4-5.4)	3.85 (1.4-11.7)	<0.0001*

*#Mann Whitney-U test, *Significant.*

Table 6 shows no statistically meaningful difference in MPV instances between men and women (p =0.316). Furthermore, there was no meaningful difference in UA between male and female subjects (p =0.163).

Table 6: Relationship of MPV and UA with gender among cases.

Variable	Male	Female	P-value#
MPV (fl)	11.2 (6.7-16)	11.2 (9-16.7)	0.316
UA (mg/dl)	3 (1.4-5.4)	2.45 (1.57-5.4)	0.163

#Mann Whitney-U test,

Male cases had a lower prevalence of positive blood cultures than female ones (p =0.044. As shown in **Table 7**, there is no substantial difference between male and female patients with positive CRP (p =1.000).

Table 7: Relationship between Gender and Blood culture and CRP in cases.

Variable		Male	Female	P-value#
Blood Culture	Positive	6 (20.7%)	10 (47.6%)	0.044*
	Negative	23 (79.3%)	11 (52.4%)	
CRP	Positive	28 (96.6%)	21 (100%)	1
	Negative	1 (3.4%)	0 (0%)	

*# Chi-squared test, *Significant.*

Table 8 demonstrates that, with a p-value of 0.174, there was no statistically meaningful difference in PROM and MPV among individuals. Moreover, p-value = 0.232 showed that PROM and UA did not

differ   statistically   meaningfully   across   instances.

Table 8: Relationship between PROM, MPV, and UA among cases.

PROM	Yes	No	P-value#
MPV (fl)	11.9 (6.7-14.3)	10.7 (7.7-16.7)	0.174
UA (mg/dl)	3.1 (2.3-4.56)	2.6 (1.4-5.4)	0.232

 # Mann Whitney-U test.

When contrasted to individuals with undamaged membranes, the occurrence of positive blood cultures was considerably greater in instances with PROM before delivery (63.6 % vs. 23.1 %), p =0.024. As seen in Table 9, there was no substantial difference in CRP between patients with and without PROM (p = 1.000). Also, there was no significant difference in the mood of delivery between MPV and UA (**Table 10**).

Table 9: Relationship between PROM, Blood culture and CRP in cases.

PROM		Yes	No	P-value#
Blood Culture	Positive	7 (63.6%)	9 (23.1%)	0.024*
	Negative	4 (36.4%)	30 (76.9%)	
CRP	Positive	11 (100%)	38 (97.4%)	1
	Negative	0 (0%)	1 (2.6%)	

*# Chi-squared test, *Significant.*

Table 10: Association between Mode of Delivery and Levels of MPV and UA among cases.

Variable	Vaginal	CS	P-value#
MPV (fl)	10.6 (8.4-16)	11.2 (6.7-16.7)	0.953
UA (mg/dl)	3 (1.4-5.4)	2.6 (1.44-5.4)	0.991

 # Mann Whitney-U test.

Table 11 implies no meaningful variation between vaginal birth or CS in cases as regards the blood culture (p = 1.000). Regarding CRP, there was no meaningful variation between vaginal birth and CS in any case ($p = 0.220$), as well.

Table 11: Relationship between Mode of Delivery, Blood culture, and CRP in cases.

Variable		Vaginal	CS	*P-value#*
Blood Culture	Positive	3 (27.3%)	13 (33.3%)	1
	Negative	8 (27.7%)	26 (66.7%)	
CRP	Positive	10 (90.9%)	39 (100%)	0.22
	Negative	1 (9.1%)	0 (0%)	

 # Chi-squared test.

According to **Table 12**, there was no meaningful variance between both positive and negative blood cultures in cases regarding MPV ($p = 0.232$) and UA ($p = 0.925$). Positive CRP cases did not differ from negative CRP meaningfully in terms of median MPV ($p = 0.840$). Although, in terms of UA, positive CRP cases differed meaningfully from negative CRP ($p = 0.040$). UA was lower in positive CRP cases than in negative CRP cases.

Table 12: Relationship between MPV and UA with Blood culture and CRP among cases.

Variable		MPV (fl)	*P-value#*	UA (mg/dl)	*P-value#*
Blood culture	Positive	11.45 (6.7-14.3)	0.232	2.7 (1.57-4.56)	0.925
	Negative	10.56 (7.7-16.7)		2.6 (1.4-5.4)	
CRP	Positive	11.2 (6.7-16.7)	0.84	1.4 (1.4-1.4)	0.04*
	Negative	11.4 (6.9-16.9)		2.6 (1.44-5.4)	

*# Mann Whitney-U test, *Significant.*

There was no considerable link between MPV and age or weight among the cases ($p = 0.152$ and 0.434, respectively). As indicated in **Table 14**, there was no notable link between UA and age or weight ($p = 0.177$ and 0.448, respectively). There was no notable link between (MPV and UA altogether) and many other laboratory measures like (TLC, PLT, and RBS) ($p > 0.05$). There was no meaningful correlation between (MPV and UA) and many other laboratory measures, such as (TLC, PLT, and RBS), ($p > 0.05$).

Table 13: Correlation of MPV and UA with demographic and lab measures among cases.

Variable	Age (days)	Weight (kg)	TLC/1000	PLT/1000	RBS (mg/dl)
MPV (fl)	0.206	0.113	0.098	-0.068	0.072
P-value	0.152	0.434	0.449	0.637	0.621
UA (mg/dl)	-0.194	-0.11	0.055	0.079	-0.029
P-value	0.177	0.448	0.702	0.586	0.841

4. Discussion

Sepsis is a severe disease primarily affecting neonates and young infants that causes one-third of four million neonatal fatalities, the yearly global newborn fatalities [13]. Bacterial meningitis and sepsis persist as major reasons for newborn deaths, particularly in low-birth-weight infants [13].

It is imperative to detect and treat septic infections in infants as soon as possible to avoid severe consequences. Sepsis in newborns can be hard to diagnose, especially in preterm neonates, because of its unclear clinical signs and lack of suitable diagnostic techniques [14].

The average size of platelets is measured by mean platelet volume (MPV). Sepsis has been linked to higher MPV levels [4]. MPV is linked with a variety of parameters, especially platelet age, and is useful for evaluating anomalies in platelet performance or quantity. It has also been connected to a variety of medical and non-medical disorders [15].

The quantity of uric acid (UA) in bodily fluids has a substantial impact on its antioxidant activity, as it can eliminate free radicals and limit oxidation. In human blood, UA can account for up to 60% of the free radicals [7].

Free radicals used to be linked to the development of septicemia; serum uric acid (SUA) levels were much lower in newborns with septicemia [8].

The purpose of the study was to determine how well MPV and SUA evaluations worked as markers for the diagnosis of septicemia in newborns. Two groups of 100 newborns, each of which had 50 newborns, participated in the study. In this study, newborns in the case group have been diagnosed with sepsis, while those in the control group have been healthy.

In the current study, we found that a lower birth weight was meaningfully associated with an increased frequency of sepsis. This was also observed in several other studies: Turhan et al. (2015), De Benedetti et al. (2007), Gomella et al. (2004), and Gerdes (2004). Birth weight is much lower when compared to term infants, neonates have an insufficient immune response, low complement system concentrations, and weak mucosal defences, elevating the neonatal infection incidence by 26 times [16–19].

Preterm membrane rupture was shown to be much more prevalent in our case group when it came to increased risk for neonatal sepsis. This agrees with the findings of Turhan et al. (2015) and Leal et al. (2012) [20, 21].

In the current study, poor circulation, hypotension, feeding intolerance, temperature fluctuation, lethargy, breathing distress, and GIT discomfort were the most frequent clinical complaints in newborns with sepsis.

In this study, there was a meaningful decline in platelet count and a meaningful rise in WBC count, I/T ratio, and MPV in some cases. These results correlated with those of Annam et al. (2015) and Narasimha et al. (2011) [22, 23].

In the current study, CRP was meaningfully higher in cases than in controls. This comes in agreement with the results of the study by Ganesan et al. (2016), Hisamuddin et al. (2015), and Park et al. (2014). As it's one of the acute phase reactants that are synthesised in the liver in response to trauma or invasion of microorganisms, Hofer et al. (2012) [24–27].

Regarding the types of bacterial isolates from blood cultures in this investigation, 16 cases (32%) showed positive culture results, whereas 34 cases showed negative results (68%). Comparable findings were reported in the study of Hisamuddin et al. (2015), who found that culture-proven sepsis occurred in 30% of cases with sepsis [25].

We reported Klebsiella pneumoniae as the most abundant organism in the blood cultures of the positive cases, followed by methicillin-resistant Staphylococcus aureus and Acinetobacter Baumannii. This is congruent with the findings of Celik et al. (2015), who discovered that K. pneumoniae was the most common bacteria in positive blood cultures [28].

We uncovered that MPV was greater in cases than in controls. MPV is a measure of platelet size. MPV is engendered by full blood count analyzers as a portion of the typical complete blood count test cycle; however, it is frequently neglected by practitioners [20].

MPV is a widely used substitute indicator for assessing platelet role. Large platelets have more granules, faster collagen aggregate, higher thromboxane A2 levels, and more glycoprotein Ib and

IIb/IIIa receptors compared to small platelets. The study reveals the presence of tenderness in numerous conditions, like unstable angina, ulcerative colitis, preeclampsia, myocardial infarction, Crohn's disease, and acute pancreatitis [20].

Compared to the control group, the patients' SUA showed significant decrease. Numerous medical conditions, including as cancer, neurological diseases, aging, and coronary heart disease, have been related to oxidative stress. In body fluids, UA has a major antioxidant role, neutralizing almost half of the free radicals in blood. It was anticipated that UA's antioxidant properties would increase longevity and maybe lower the incidence of cancer [29].

Batra et al. (2000) found that UA levels were significantly lower in sepsis patients in their research of 30 newborns with sepsis and 20 neonates without sepsis [30]. According to Kapoor et al. (2006), sepsis newborns showed reduced uric acid levels in their study, comparing 44 instances of sepsis to 84 healthy neonates [8]. According to Aydn et al. (2014), infants with sepsis had lower UA levels than babies in good health [31].

In contrast to our findings, Hooman et al. (2010) found that increased UA levels were an additional threat factor in sepsis. This difference might be attributed to a variation in demographic data, as they concentrated on sepsis in the pediatric ICU [32].

Conclusion

From this study, we concluded that mean platelet volume increases meaningfully in neonatal sepsis and serum uric acid decreases meaningfully in neonatal sepsis. Based on the results of our study, we recommend that mean platelet volume is a novel marker for the diagnosis of neonatal sepsis and should be further evaluated and investigated. Also, uric acid in neonatal sepsis needs further investigation to assess its role and implications in the sepsis cascade. CRP, MPV, and UA should be assessed in the early diagnosis of neonatal sepsis.

Ethical consideration and patient consent: The study was approved by the Faculty of Medicine, Fayoum University Research Ethical Committee (Approval No 43; 12/11/2017).

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