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Serum and Urine C - Reactive Protein, Mean Platelet Volume and Neutrophil/ Lymphocyte Ratio as Diagnostic Values in Neonatal Sepsis

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Abstract

Background: Recently, many research studies with equivocal results, have found Neonatal Sepsis (NS) biomarkers and focused on single regions. Therefore, the aim of this study was to evaluate serum and urine C - Reactive Protein (CRP), Mean Platelet Volume (MPV) and Neutrophil/ Lymphocyte Ratio (NLR) as diagnostic values in NS.

Methods: This descriptive-analytical research analyzed Shahid Beheshti Hospital's probable NS patients. All individuals got a complete blood count, white blood differential, CRP, blood culture, and urine culture. Data was analyzed by SPSS v24.

Results: The data indicated that NS infants had substantially higher mean serum levels of MPV (10.63 ± 1.03 vs. 8.63 ± 0.96, P<0.001), NLR (2.08 ± 1.24 vs. 1.01 ± 0.5, P<0.001), and CRP (12.97 ± 5.09 vs 5.83 ± 2.6 and 9.61 ± 3.25 vs 4.9 ± 3.4, P<0.001).The optimum cut-off points for serum and urine CRP, NLR, and MVP were 10, 6.7, 1.2, and 9.5. The highest Area under the Curve (AUC) was detected in MPV (0.909), and the other AUC for serum and urine CRP and NLR were 0.872, 0.831, and 0.804, respectively. Serum CRP had the lowest sensitivity (73.3%) among urine, NLR, and MPV. Serum CRP had the best specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV), identified as 96.7 %, 88%, and 90%, respectively.

Conclusion: Sepsis increases MPV, serum and urine CRP, and NLR in neonates. MPV and serum CRP may detect NS early.

Key Words: C - reactive protein, Mean platelet volume, Neutrophil/ lymphocyte ratio, Neonatal sepsis.

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1- INTRODUCTION

Neonatal sepsis (NS) is a life-threatening inflammatory response syndrome brought on by an infection in a newborn (1), which causes neonatal morbidity and mortality (2). According to the reports of the World Health Organization (WHO), around 4 million newborns die from NS-related causes in the first 28 days of life every year (3). NS is defined as an infection in infants less than 28 days of life and consists of systemic signs of infection, circulatory shock, and different organ failure. NS is characterized by the presence of systemic indications of infection, circulatory shock, and multiple organ failure in newborns less than 28 days of age. Neurosyphilis may be classified as either Early-Onset (EONS) or Late-Onset (LONS); First-day-of-life (EONS) infections and sepsis (4–6) second-day-of-life (LONS) infections and sepsis (24 hours-plus); and third-day-of-life (SOD) infections and sepsis (28 days or 1 month) (7–9). Many asymptomatic newborns go through a sepsis workup if risk factors are present and/or clinically warranted because of the nonspecific presentation for NS and the high risk of morbidity and death without treatment. Only around 3–8% of all infants with a suspected case of sepsis develop positive cultures (10).

NS is characterized by vague symptoms and indications that are often misattributed to other conditions (11). Some diagnostic tests such as blood or urine cultures are time consuming; and the culturally verified rate of NS is around 2 per 1000 deliveries (12). Therefore, looking for rapid and sensitive tests that would help in NS diagnosis is necessary (13).

During sepsis, platelets release several inflammatory cytokines and mediators (14, 15), leading to ischemia, disseminated intravascular coagulation, hypoxia, and finally the development of multiple organ dysfunction syndrome (16, 17). The Mean Platelet Volume (MPV) has been considered a marker for reactivity, size, and function of platelets (18). Therefore, higher MPV increases platelet adhesion, aggregation, and thrombus development before it is supposed to, which raises the likelihood of serious problems and mortality (19). The specific association between NS and MPV is unknown, despite the fact that it has been acknowledged by various research studies in recent years (20).

The sepsis screen includes a Complete Blood Count (CBC), which is routinely performed and easily accessible. Neutrophil-Lymphocyte Ratios (NLRs) are being examined and employed in many clinical circumstances in both pediatric and adult research (21, 22). NLRs are cheap and are already a part of a CBC, so no further testing is necessary (23). Studies on NLR in neonatal bacterial infections were few at best (24).

Studies have reported that C - reactive protein (CRP) along with some other tests (Total Leukocyte Count (TLC), Absolute Neutrophil Count (ANC), and thrombocytopenia) are very sensitive in detecting negative cases of NS. (24) Thus, understanding the best diagnostic methods for NS, with high sensitivity and specificity, especially in the first hours, is one of the main steps for performing successful diagnostic proceedings. To the best of our knowledge, there isn't enough prospective study about the different diagnostic methods in detecting NS; moreover, there is not a study working on urine CRP in NS cases. In light of this, we set out to determine whether or not urine CRP, MVP, and NLR can have any diagnostic use in NS.

2- MATERIALS AND METHODS

2-1. Design and population

This case-control study was conducted in the Pediatric Department of Kashan Shahid Beheshti Hospital, center

of Iran, from January 2020 to July 2021. The urine CRP, MVP and NLR in infants with NS were compared with those of a healthy group (infants without NS).

2-2. Inclusion and exclusion criteria

Criteria for inclusion included infants referred to the Pediatric Department for NS whose parents signed a consent form to participate in the study and aged lower 28 days. Fetal inflammatory response syndrome criteria were met with infection symptoms to diagnose NS. The existence of at least two of the following characteristics were indicative of fetal inflammatory response syndrome, tachypnea (respiratory rate/ > 60 bpm) with either grunting/retraction or desaturation, abnormal leukocyte count (< 4000 or > 34 000/mm3), capillary refill time (CRT) > 3 seconds, serum CRP > 10 mg/dL, positive 16S rRNA genes PCR, and body temperature abnormalities (> 37.9 oC or < 36 oC). (25). Exclusion criteria consisted of infants with gestational age of <37 weeks, major congenital anomalies, asphyxia, congenital infection, congenital heart disease, major neurological disorder, symptomatic open ductus arteriosus, infants with terminal state, necrotizing enterocolitis, transient neonatal tachypnea, intraventricular hemorrhage, respiratory distress syndrome, hypoxic - ischemic encephalopathy, metabolic diseases, meconium aspiration, and dissatisfaction to continue participation in the study. Patients whose records were incomplete were also disqualified.

2-3. Procedure

Fig. 1 illustrates a flowchart of the research process. Ninety-five newborns met the inclusion and exclusion criteria based on clinical and paraclinical results (50 in NS group and 45 in control group). Eligible cases were enrolled, after obtaining informed consent. After obtaining informed consent from the parents and explaining the conditions of the study, before starting antibiotics, a blood sample was collected in a tube containing Ethylenediaminetetraacetic acid (EDTA), and a urine sample was collected by bag urine. The control group was also selected from infants suffering from jaundice hospitalized in Shahid Beheshti hospital in the same period of time by simple random sampling and considering the similarity of demographic criteria; and after obtaining informed consent, blood and urine samples were collected. The samples were stored at 2-8 degrees and were transported to the laboratory within a week. CBC was performed by automated hematology analyzer (model I 1800 XT, Japan) and included Differential WBC for assessing WBC using light scattering properties. In the White Blood Cell (WBC) differential, we were able to identify and quantify the absolute number of neutrophils and lymphocytes. By manually dividing the Absolute Lymphocyte Count (ALC) by the Absolute Neutrophil Count (ANC), we were able to calculate the NLR. Blood CRP was measured by immunoturbidimetric method and by Parts Azmoun's CRP Sensitive High quantitative diagnostic kit, from plasma after centrifugation of the blood sample. Urine CRP was measured by ELISA method (Sandich Immunosorbent Linked Enzyme Assay) and measured in nanograms per cc by urine CRP ELISA kit, Shanghai, Elabscience, H0043-EL-E, China.

2-4. Data analysis

Only the patients who provided all of the requested data were included in the analysis and subsequent report. The data was analyzed statistically using SPSS version 22. (SPSS Inc., Chicago, IL, USA). For comparing qualitative factors between groups, we used the Chi-square test. The quantitative study parameters were tested for normal distribution using the Kolmogorov-Smirnov test. Student t-test was used for normally distributed data,

whereas the Mann-Whitney U-test was utilized for non-normally distributed variables. For significance, a two-tailed p-value of less than 0.05 was used.

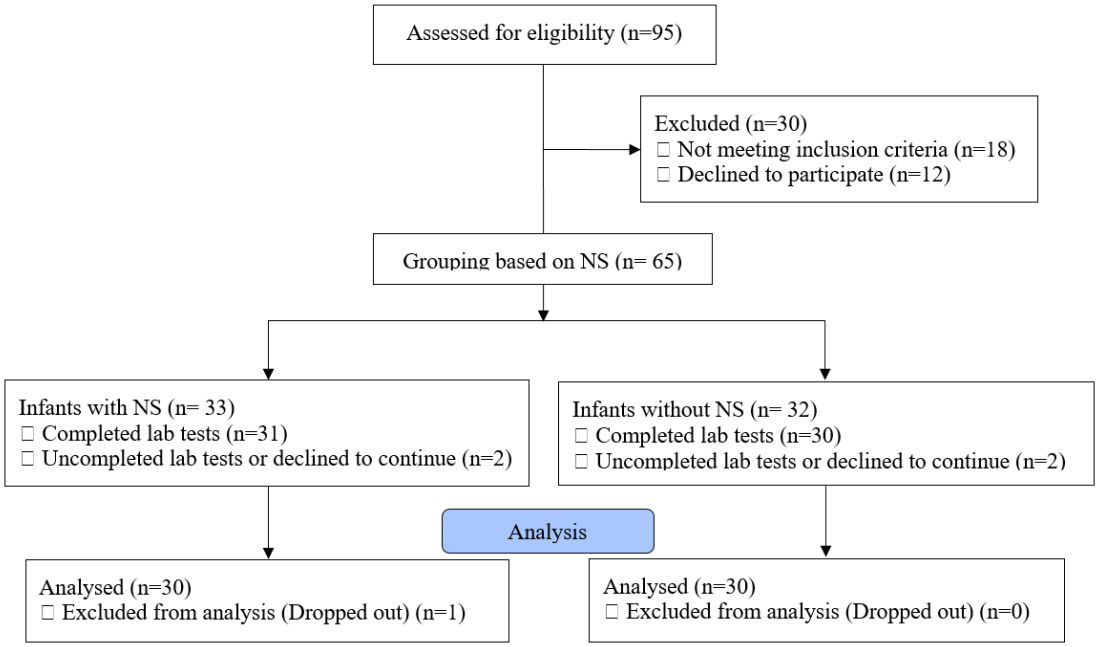

Fig 1: Study flowchart

3- RESULTS

In this study, 30 infants with NS and 30 cases in the control group were included. Infants from both groups had similar demographics in terms of gender, gestational age, birth weight and mothers' age (p>0.05). However, we found that the rate of Caesarean Section (CS) was significantly higher in the NS group as compared to the control group (64.5 % vs. 35.3 %) (P=0.039) (**Table 1**).

Furthermore, the results demonstrated that the mean serum levels of MPV (10.63 ± 1.03 vs. 8.63 ± 0.96, P<0.001), NLR (2.08 ± 1.24 vs. 1.01 ± 0.5, P<0.001), serum and urine levels of CRP (12.97 ± 5.09 vs. 5.83 ± 2.6, P<0.001 and 9.61 ± 3.25 vs. 4.9 ± 3.4, P<0.001) in the group of NS infants were notably higher than those in the group serving as a control (**Table 1**).

Table-1: Sample Characteristics and biomarkers in both NS/control infants

Variable	NS (n=30)	Control (n=30)	p-value
Gender (male)	15 (50)	15 (50)	1
Age (day)	4.53 ± 7.64	4.83 ± 3.86	0.849
Gestational age (week)	37.07 ± 0.95	38 ± 0.98	0.235
Birth weight (gram)	2803.33 ± 392.59	2950 ± 343.4	0.129
Delivery (CS)	20 (64.5)	11 (35.3)	0.039
Mothers' age (year)	30.37 ± 5.71	32.23 ± 5.28	0.194
Serum levels of CRP (mg/L)	12.97 ± 5.09	5.83 ± 2.6	<0.001
Urine levels of CRP (mg/L)	9.61 ± 3.25	4.9 ± 3.4	<0.001
NLR	2.08 ± 1.24	1.01 ± 0.5	<0.001
MPV (year)	10.63 ± 1.03	8.63 ± 0.96	<0.001

Moreover, we found that the best cut-off points for serum and urine CRP, NLR and MVP were 10, 6.7, 1.2 and 9.5, respectively. The highest Area under the Curve (AUC) was detected in MPV (0.909), and the other AUC for serum and urine CRP and NLR were 0.872, 0.831 and 0.804, respectively. Sensitivity for urine CRP, NLR and MPV were similar but the sensitivity for serum CRP was the lowest (73.3 %). Moreover, specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) of serum CRP had the highest values as compared to parameters (96.7 %, 88 %, and 90 %, respectively). Finally, we found that MPV and serum CRP have the best diagnostic values and NLR has the lowest diagnostic value for detecting NS. (**Table 2** and **Fig. 2**).

Table-2: Diagnostic values of serum and urine CRP, NLR and MVP in detecting NS

Variable	Cut-off point	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+	LR-	AUC±SE	CI %95
Serum CRP	10	73.3	96.7	88	90	7.33	0.28	0.872 ± 0.048	(0.944-0.761)
Urine CRP	6.7	83	70	73	78	2.7	0.29	0.831 ± 0.051	(0.915-0.712)
NLR	1.2	83	63	80	76	2.18	0.32	0.804 ± 0.058	(0.896-0.682)
MPV	9.5	83.3	80	83	83	4.17	0.21	0.909 ± 0.33	(0.968- 0.807)

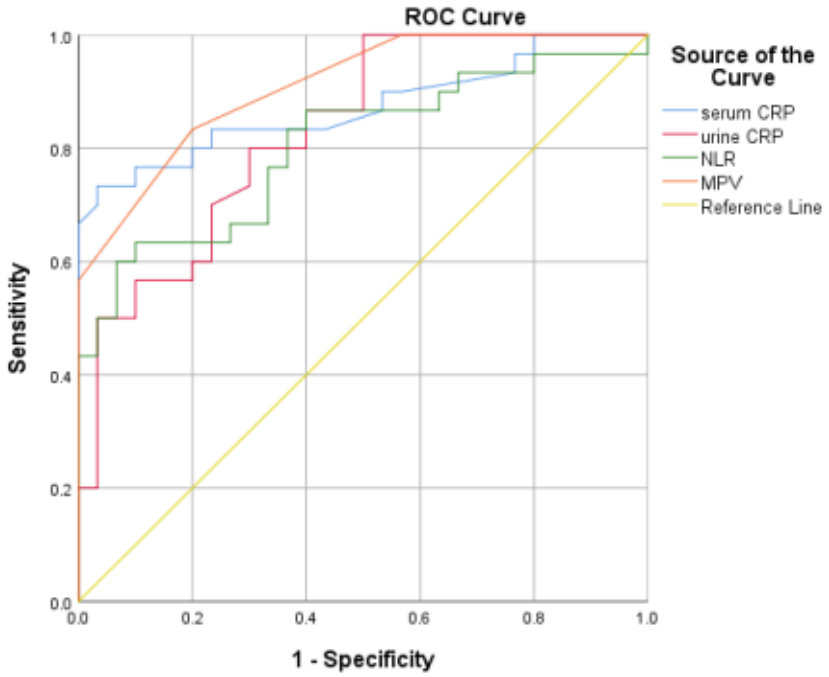

Fig. 2: ROC curve of serum and urine CRP, NLR and MVP in detecting NS

4- DISCUSSION

Various biomarkers are being used for the diagnosis of NS, which include WBC count, CRP, lipopolysaccharide-binding protein, serum amyloid A and procalcitonin (26). Most recently, Researchers are beginning to draw connections between NS and MPV. Studies performed by Shalaby (27) and Shaaban (28) showed a significant increase

in serum levels of MPV in cases with NS. Evidence from these trials and ours indicated that a regular blood test for MPV might be useful in making the diagnosis of NS. Platelet activation has a significant function in physiopathology, namely in thrombosis, inflammation, anti-infection, and immune responses (29). MPV is associated with the maturity of platelets and it is the platelet index that indicates the mean size of platelets in the peripheral blood (30). MPV is significantly decreased in patients with high-grade inflammatory diseases such as systemic lupus erythematosus, inflammatory bowel disease, and low-grade inflammatory diseases, for example psoriasis and ankylosing spondylitis (31). A systematic review performed on 11 studies on MPV and NS manifested that MPV was significantly increased in patients with NS compared to healthy subjects (SMD=1.49, 95% CI=0.84–2.14, P<.0001) (32). In patients with septic shock or severe sepsis, a greater Mean Platelet Volume (MPV) during the first 72 hours after admission is an independent risk factor for poor clinical outcomes, according to one study (33). Studies have also reported that thrombocytopenia is a good predictor of sepsis especially in infants, and the platelet count is inversely related to MPV (32).

In this study, the validity of serum and urine CRP in the diagnosis of NS was studied on 60 neonates and we found that serum levels of CRP had acceptable diagnostic value in comparison to urine levels. A previous study indicated that CRP had the sensitivity, specificity, PPV, and NPV of 58.33%, 56.52%, 67.74%, and 48.27%, respectively (34). However, we found higher diagnostic values and all the parameters were higher than 70 %. Benitz et al. (35) have reported that the sensitivity of the test is only 40%, if performed at admission and the sensitivity is increased up to 90%, if performed 24 hours after admission. The same results were reported by Mather et al. (36) who showed that the sensitivity rises from 22% to 61% along with the time increase after admission. Wagle et al. (37) reported that the sensitivity/specificity of CRP on the first day of admission were found to be 62% and 87.7% increasing up to 70.2 and 97% on the second day.

Chan et al., (38) gave a cutoff CRP serum level of 7 mg/L. The sensitivity, specificity, NPV and PPV were 56%, 72%, 71% and 57% respectively. In our study serum CRP level was found to have a high diagnostic value in cut-off point 10 mg/dl. Jave et al. (39) noted that long-term CRP monitoring may be utilized to determine therapy efficacy following the first NS diagnosis. Cherdze et al, (40) concluded in their study that quantitative CRP is a rapid, sensitive diagnostic marker for identification of NS in infants; however, we did not find any previous study using urine CRP for the diagnosis of NS. Yet our study, as the first one in this field, found that urine CRP had acceptable diagnostic values for detecting NS.

Moreover, we found that NLR was significantly higher in NS group, while NLR had the lowest diagnostic value as compared to other biomarkers. Higher serum levels of NLR were found in proven NS or infants with positive blood cultures; and higher mean NLR was detected in positive blood cultures compared to negative blood cultures (3.69±3.0 vs. 1.56±1.83, $p < 0.001$) (41). Significantly higher NLR in NS neonates compared to healthy controls was also reported in several studies. Can et al., (42) reported that term NS group had a significantly higher NLR than healthy term infants (2.88±0.16 vs. 0.21±0.12, $p = 0.02$), and Omran et al, (43) reported the same results (2.9±1.7 vs 1.6±0.4, respectively, $p < 0.001$). The high NLR value in the NS group is due to an imbalance between the levels of neutrophil and lymphocyte counts. In response to bacterial infections,

the innate immune system's first line of defense is to increase serum levels of neutrophils by stimulating the emergency granulopoiesis process. Lowered neutrophil apoptosis, decreased monocytopoiesis and lymphopoiesis, and elevated lymphocyte apoptosis all contributing to elevated neutrophil numbers and decreased lymphocyte numbers, respectively (14,44-46). The NLR cut-off in this study was lower than that in previous studies. The NLR 1.81 cut-off value in infants with NS in Dr. Moewardi Hospital, Surakarta, was found to have 86.1% sensitivity, 85.1% specificity, and 68.9% PPV, and 94.1% NPV (47). Moreover, Omran et al., (43) reported that NLR 2.7 cut-off value has 80% sensitivity and 57.1% specificity with AUC of 0.791±0.057. Furthermore, Ruslie et al., (48) reported the NLR 9.4 cut-off value with a sensitivity of 61.5% and a specificity of 66.7% in 94 neonates with NS.

5- CONCLUSIONS

Newborns with sepsis had considerably greater MPV, serum CRP, and urine NLR than the healthy controls, as shown by this research. Nevertheless, MPV and serum CRP may be useful in early detection of NS in clinical practice. Clinical factors, coupled with MPV and serum CRP values, should be addressed in screening a neonate for sepsis, due to the substantial morbidity and mortality associated with NS. Our results will be strengthened by further research on the correlation between MPV and dynamic variations in CRP and NLR in serum and urine.

6- ETHICAL CONSIDERATIONS

The research was approved by the Ethics Committee of Kashan University of Medical Sciences (IR.KAUMS.MEDNT.REC.1399.234); and all parents provided written informed permission.

7- ACKNOWLEDGMENTS

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