The Egyptian Journal of Hospital Medicine (October 2021) Vol. 85 (2), Page 4338-4343

# Evaluation of Neonatal Sepsis Based on Measurement of Red Cell Distribution Width

**Aya Sami Essayed[*1], Mohamed Mamdouh Gaafar[1], Manal Mohammed Elamin[2], Sherief Mohamed El Gebaly[1]**

Departments of [1]Pediatrics and [2]Clinical Pathology, Faculty of Medicine, Zagazig University, Egypt

***Corresponding Author:** Aya Sami Essayed, **E-Mail:** ayasami8992@gmail.com

## ABSTRACT

**Background**: Infant morbidity as well as mortality are frequently caused by neonatal sepsis. Neonatal sepsis can be predicted using the red cell distribution width (RDW), according to several researches.

**Objective**: To determine if RDW can be employed as a marker for the evaluation of newborn sepsis and the assessment of its severity.

**Patients and Methods**: 40 newborns, 20 of whom were infected and the other 20 of whom were non infected, participated in this case-control research. Patients and controls were collected from neonatal intensive care unit (NICU), Zagazig University Hospitals. Full history was taken from all participants parent, with clinical and laboratory examination were done; complete blood picture, and creatinine, blood culture, and serum level of C-reactive protein (CRP).

**Results:** We revealed significant link between RDW and all of total leukocyte count (TLC), immature to total neutrophil ratio (I/T ratio), absolute neutrophil count (ANC), CRP, procalcitonin, severity of sepsis, and mortality. RDW and platelet count, on the other hand, have a strong negative association. With a sensitivity of 83.3 percent, specificity of 50 percent, a positive predictive value (PPV) of 71.4 percent, and a negative predictive value (NPV) of 66.7 percent, accuracy of 70 percent ($p>0.05$), the best RDW cutoff for diagnosing newborn sepsis severity was ≥17.9.

**Conclusion**: Predictors of illness severity and death in newborn sepsis may be accurately predicted using baseline RDW measurements, which is critical for treatment of neonates who are at great risk of sepsis.

**Keywords**: Neonatal Sepsis, Red Cell Distribution Width.

## INTRODUCTION

As a result of a malfunction in the body's response to infection, sepsis is a life-threatening illness **(1).** Sepsis is one of the most prevalent causes of newborn death and illness **(2).** Neonatal sepsis is more common than at any time in a person's life. In underdeveloped nations, Severe neonatal sepsis is the main cause of death among newborns; As many as five newborn sepsis infections per thousand live births are common in wealthier nations, however, other population-based research from poor nations have shown rates of 49-170 per 1,000 live births in these countries **(3).**

Predominantly mild, nonspecific symptoms and indications of newborn sepsis are often followed by septic shock, a condition known as dispersed intravascular coagulation (DIC), and death. In this regard, determining which neonates are most likely to have a negative clinical outcome is of critical importance, and more intensive treatment should be given to those who need it the most **(4).**

Traditional methods for detecting sepsis include blood cultures. Blood cultures, on the other hand, take a long time to perform; typically, to detect the organism in the blood, it takes between two and five days. A decrease in blood culture sensitivity occurs when antibiotic therapy is initiated or when a slow-growing or fastidious organism is being cultured **(5).**

A complete blood count (CBC) is utilized in conjunction to a blood culture to determine sepsis. Even with current severity levels and indicators derived from the whole blood count, predicting the outcomes of infant sepsis is still a challenge. There are a number of traditional screening tests that may be useful in determining the severity of sepsis; however these tests are not able to reliably predict the severity of sepsis **(6).**

Prognostic indicators for newborn sepsis have been examined using a variety of substances, procalcitonin, soluble E-selectin, C-reactive protein (CRP), CD64, IL-6, IL-8 and are all examples of these biomarkers **(7).**

The variance in red blood cell volume within a blood sample is described by the red cell distribution width (RDW). All normal complete blood cell counts include RDW as an indicator of anisocytosis of the red blood cells **(8).** Pathological diseases linked with infection as well as inflammation have been observed to alter the width of the red blood cell dispersion considerably in recent researches **(9).** Many studies have found that RDW can accurately predict all-cause death in ICU as well as critically ill patients **(10).** In inflammatory or viral settings, the RDW may rise due to a lack of red blood cell formation or an increase in the breakdown of red blood cells **(11).** The traditional screening index for iron deficiency anemia is the width of the red cell distribution. It's been shown to play a role in the prediction of poor outcomes in sepsis and other clinical circumstances, involving critically ill children in general, infective endocarditis, heart failure, coronary artery disease, malignancy, acute pancreatitis as well as peritoneal dialysis **(12).**





Received: 20/8/2021
Accepted: 2/10/2021

It was the goal of this work to determine if RDW may be used as a marker for the evaluation of newborn sepsis and its severity in contrast to other recognized indicators or not.

## PATIENTS AND METHODS

The newborns hospitalized to the neonatal intensive care unit at Zagazig University Hospitals between September 2019, and September, 2020 served as the subjects for this case-control study.

**Ethical considerations:**

**As long as all parents of participants signed informed consent forms and submitted them to Zagazig University's Research Ethics Committee, the study was allowed (ZU-IRB#6250). We followed the World Medical Association's ethical code for human experimentation, the Helsinki Declaration.**

**Inclusion criteria:** Aged from 1-28 days, full-term, preterm, low birth weight, extremely low birth weight, and sepsis-related symptoms like fever, breathing issues, diarrhea, and decreased suckling are all possible outcomes.

**Exclusion criteria:** Age: > 28 days, neonates with congenital abnormalities or cases of perinatal asphyxia, as well as those who had experienced birth trauma.

**Children were divided into two groups: Group A:** included 20 patients with sepsis, and **Group B:** (control): included 20 apparently healthy neonates

This is what all of the participants in this research had to go through:

**History:** The patient's age, sex, gender, maternal risk factors, gestational age, prenatal, natal history were all recorded in a thorough medical history.

**Clinical examination:**

Weight of a newborn suckling and Moro reflexes were performed on the newborns as well as vital parameters such as heart rate and respiration rate, spotting the early indications of sepsis:

Restlessness, sleepiness, pallor, and mottled skin characterises the infant's condition.

A fluctuation in temperature, either hyperthermia or hypothermia problem with the respiratory system (signs of respiratory distress, apnea). Circulatory dysfunction (poor peripheral circulation, hypotension, prolonged capillary refill). A problem with the digestive system (hepatomegaly, feeding intolerance, abdominal distension, as well as jaundice). Disruption of the brain (lethargy, hypotonia, irritability). Petechiae or bleeding from puncture wounds are signs of hemorrhagic diathesis. Sclerema: this is a common symptom in the later stages of any major illness, especially in preterm infants. It was characterized as sepsis plus cardiovascular or respiratory organ dysfunction, or two or more organ dysfunctions, as well as sepsis.

**Laboratory evaluation:**

Blood samples were taken at the time of sepsis suspicion. Skin was rubbed with antiseptic and 4 cm of blood was taken: 1 cm of blood was collected in a test tube containing 20 mcg of EDETA for CBC, 2 cm of blood was collected in a plain test tube for CRP and serum creatinine, 1 cm of blood injected into culture bottle.

**Complete Blood Count:**

Analysed by sysmex 21-kx cell counter for hemoglobin level, red blood cell count, RDW, hematocrit value, platelet count and white blood cell (WBC) count (Total and differential). Results of CBC were interpreted using Hematological scoring system by **Rodwell *et al.*** [13].

It was only documented that RDW was obtained on the same day as blood cultures were done. In our laboratory, the normal range for RDW is 11.5 to 14.5 percent, and this was used to divide newborns into two groups: those with low RDW and those with high RDW.

**Quantitative C- reactive protein (CRP):**

1 cm of blood was taken, blood was collected in a plain test tube, left to clot, then centrifuged for 10 minutes at 1500 rpm, Turbox plus was used to separate and analyze serum. Above 6 mg/l, results were deemed positive.

**Blood culture.**

**Estimation of serum creatinine:**

1 cm of blood was taken, blood was collected in a plain test tube, left to clot, then centrifuged for 10 minutes at 1500 rpm, serum was separated and analyzed using Biosystem 15A.

***Statistical analysis***

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Quantitative data were presented as median and range and were compared by the Mann-Whitney test (Z). Qualitative data were presented as number and proportions and were compared using the Chi-square test ($X^2$). RDW levels and predicted parameters were correlated using the Spearman Correlation coefficient (r). The diagnostic and prognostic utility of RDW in newborn sepsis were evaluated using Receiver Operating Characteristics (ROC) analysis. P value 0.05 was considered statistically significant. It was judged highly significant when the P value was 0.001.

## RESULTS

A statistically insignificant difference in age or gender was found between the two groups of neonates investigated. Seventy percent of patients had LOS while 60% had severe sepsis **(Table 1).**

**Table (1): Results from comparisons of the study groups in terms of demographic variables, sepsis type and severity**

| Parameter | Groups | | Test | |
|---|---|---|---|---|
| | Case group | Control group | $\chi^2$/Z | p |
| | N=20 (%) | N=20 (%) | | |
| **Gender:**<br>Female<br>Male | <br>7 (35)<br>13 (65) | <br>10 (50)<br>10 (50) | 0.921 | 0.337 |
| **Age (days):** Median (Range) | 5 (6 hours – 17 days) | 3.5 (18 hours – 7 days) | -0.939 | 0.347 |

| | N=20 | % |
|---|---|---|
| **Type of sepsis:**<br>Early-onset neonatal sepsis (EOS)<br>Late-onset sepsis (LOS) | <br>6<br>14 | <br>30<br>70 |
| **Severity of sepsis:**<br>Mild<br>Severe | <br>8<br>12 | <br>40<br>60 |

Z: Mann Whitney test, $\chi^{2:}$ Chi square test

Thirty five percent of patients had sepsis due to E. coli and the same percent had K. pneumonia **(Figure 1).**

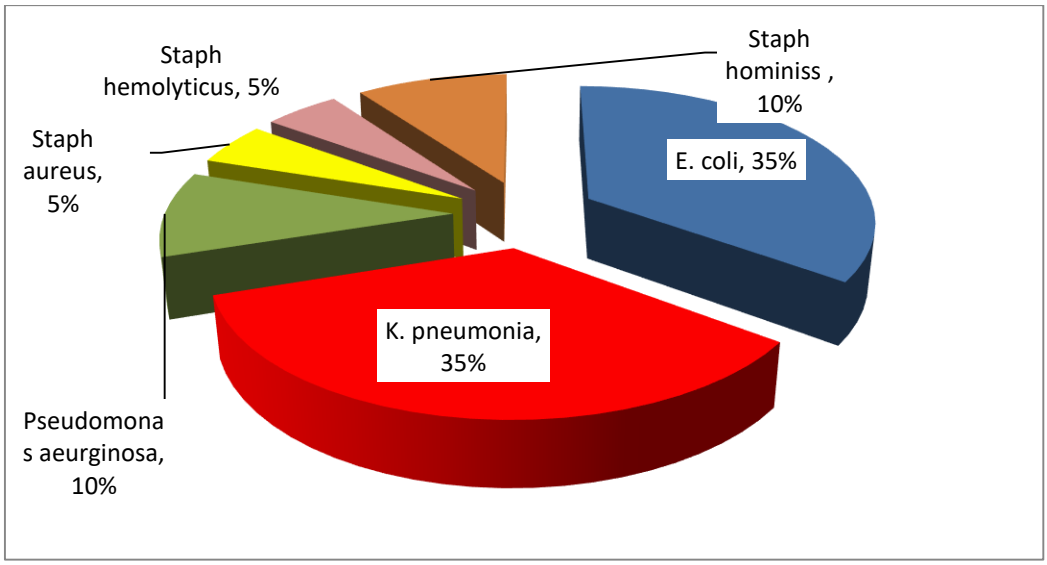


**Figure (1): Diagram illustrating the distribution of patients (cases) based on blood culture findings**

RDW and all of TLC, I/T ratio, ANC, CRP, and procalcitonin had a statistically significant positive connection. On the other hand, RDW and platelet count had a strong negative association. The connection between RDW and hemoglobin in the case group was insignificant **(Table 2).**

**Table (2): Correlation between RDW and laboratory parameters among case group**

| Parameters | RDW | |
|---|---|---|
| | r | p |
| TLC | 0.347 | 0.028* |
| I/T ratio | 0.672 | <0.001** |
| ANC | 0.44 | 0.005* |
| Hemoglobin | -0.254 | 0.113 |
| Platelet count | -0.676 | <0.001** |
| CRP | 0.83 | <0.001** |
| Procalcitonin | 0.807 | <0.001** |

*: Statistically significant, **: Statistically highly significant, r: Spearman rank correlation coefficient

A link between RDW and gestational age was statistically insignificant among the case group **(Table 3).**

**Table (3): Correlation between RDW and age of patients within case group**

| Parameters | RDW | |
|---|---|---|
| | r | p |
| Age | -0.007 | 0.968 |
| Gestational age | -0.126 | 0.44 |

**r: Spearman rank correlation coefficient**

RDW and kind of sepsis had no statistically significant relationship. A statistically significant correlation existed between RDW and the severity of sepsis among the patients in the case group. The more RDW a patient had, the more severe their illness was **(Table 4)**.

**Table (4): Relation between RDW and both type and severity of sepsis among case group**

| Sepsis | RDW | | Test | |
|---|---|---|---|---|
| | Median | Range | Z | p |
| **Type:** | | | | |
| LOS | 18.4 | 15 – 23.1 | -0.784 | 0.443 |
| EOS | 18.85 | 17.3 – 25.1 | | |
| **Severity:** | | | | |
| Mild | 17.9 | 15 – 19 | -1.968 | 0.049* |
| Severe | 19.15 | 15.7 – 25.1 | | |

***: Statistically significant, Z: Mann Whitney test**

Among patients in the case group, RDW was statistically linked to mortality. A higher RDW was linked to a decreased life expectancy **(Table 5).**

**Table (5): Relation between RDW and mortality among case group**

| Mortality | RDW | | Test | |
|---|---|---|---|---|
| | Median | Range | Z | p |
| No | 17.8 | 15 – 19.3 | | |
| Yes | 19 | 17.2 – 25.1 | -1.967 | 0.048* |

***: Statistically significant, Z: Mann Whitney test**

The performance of RDW in diagnosis of neonatal sepsis and its severity is shown in **table 6.**

**Table (6): Performance of RDW in diagnosis of neonatal sepsis, and severity of neonatal sepsis among the studied patients respectively**

| Cutoff | AUC | Sensitivity | Specificity | PPV | NPV | Accuracy | p |
|---|---|---|---|---|---|---|---|
| ≥15.65 | 0.964 | 95 | 70 | 76 | 93.3 | 82.5 | <0.001** |
| **Cutoff** | **AUC** | **Sensitivity** | **Specificity** | **PPV** | **NPV** | **Accuracy** | **p** |
| ≥17.9 | 0.766 | 83.3% | 50% | 71.4% | 66.7% | 70% | 0.049* |

***: Statistically significant, **: Statistically highly significant,**

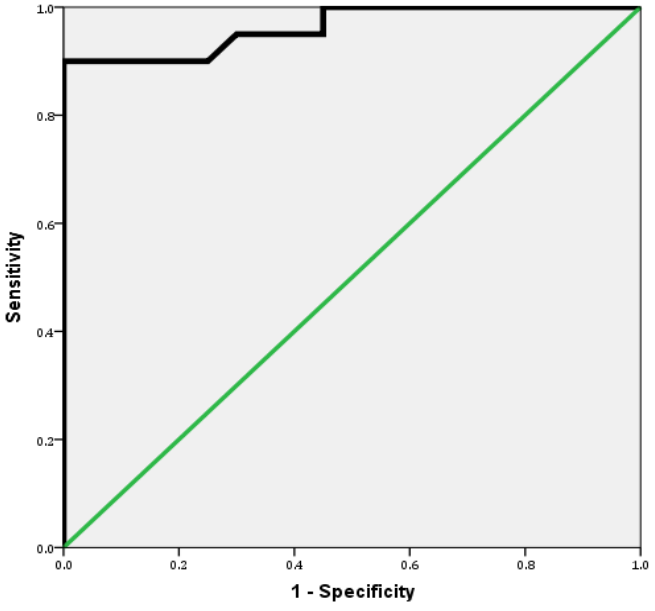


**Figure (2): ROC curve showing performance of RDW in diagnosis of neonatal sepsis among the studied patients**

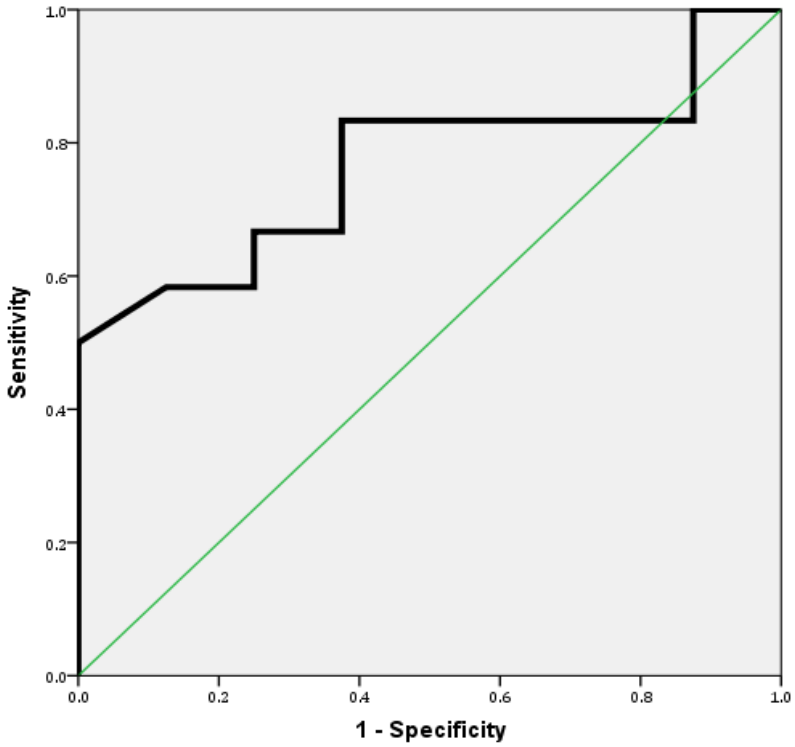


**Figure (3): ROC curve showing performance of RDW in diagnosis of severity of neonatal sepsis among the studied patients.**

## DISCUSSION

When it comes to very low birth weight (VLBW) newborns (1500 g), diagnosis of neonatal sepsis is difficult and challenging for neonatal health care workers, making it a prevalent health care burden [(3)].

Detecting sepsis early and excluding noninfectious causes has been a long-standing goal for clinicians. It is common to express RDW-coefficient of variation (RDW-CV) in terms of red blood volume heterogeneity (RDW-CV). RDW can be used in the clinic to determine if the RBC volume is evenly distributed. Volume heterogeneity increases with an increase in RDW and an increase in RBC size variability [(10)].

Concerning the incidence of early (≤ 3 day) and late (>3 day) onset sepsis, seventy percent of patients had LOS, and this comes similar incidence was noticed in an Egyptian study conducted by **Medhat *et al.*** [(14)].

In our study, we found no significant difference in sex and postnatal age between both groups. According to **Gad *et al.*** [(15)], there was no significant difference in sex between the two groups. But **Aderem and Underhill** [(16)] reported that male newborns are four times more likely than females to get sepsis. Thymus function or immunoglobulin synthesis gene situated on X-chromosome may be responsible for this.

Concerning the isolated organisms from cultures, thirty five percent of patients had sepsis due to E. coli and the same percent had K. pneumonia. P. aeurginosa, staph aureus, staph hemolyticus and staph hominis prevailed in 10%, 5%, 5% and 10% of patients respectively. The findings of **Dzwonek *et al.*** [(17)] are in agreement with our results. However, a study by **Garcia *et al.*** [(18)] found that 80.4 percent of the bacteria were Gram positive and 10.5 percent were Gram negative.

RDW had a statistically significant positive connection with all of TLC, I/T ratio, ANC, CRP, and procalcitonin in our study. On the other hand, RDW and platelet count had a strong negative association by **Ellahony *et al.*** [(19)], who found the same thing.

**Abdullah *et al.*** [(20)] found no statistically significant connection between RDW and gestational age or admission time in the case group, which is in agreement with the results of this study.

RDW had a substantial correlation with the severity of newborn sepsis. RDW may be useful in distinguishing between more severe and less severe cases of newborn sepsis since it is higher in severely cases than in mild cases. The findings of this study are consistent with those of **Kader *et al.*** [(21)] and **Saleh *et al.*** [(22)] who found that RDW increases in newborn sepsis and increases with increasing illness severity.

Compared to neonatal sepsis survivors, RDW was shown to be considerably higher in non-survivors, and death was significantly higher in infants with greater RDW. In conjunction with **Ellahony *et al.*** [(19)], this shows that RDW may be useful in predicting the outcome of sepsis.

Severe sepsis is characterized by a rise in RDW, which is a result of a dysregulation of erythropoiesis caused by the inflammatory cytokines [(23)]. Sepsis may also impact erythroid tissue and the circulating RBCs; this may decrease their lifespan and result in the release

of new red blood cells from the bone marrow, which may contribute to elevated RDW values [24].

A better understanding of how increased RDW affects mortality is beginning to emerge. Until now, it has never been shown that RDW is associated with decreased RBC deformability, which may in turn impede blood flow via the microcirculation, causing organ dysfunction in sepsis, according to new studies [25]. These abnormally shaped RBCs also elicit an immunological response from phagocytic cells to remove them. According to these findings. RDW and mortality are linked in more ways than one, contrary to what some researchers initially assumed [26].

The microcirculatory alterations during sepsis are not solely due to RDW. Sepsis-related alterations in nitrate, sialic acid reactive oxygen species, intracellular calcium, and 2, 3-diphosphoglycerate have been linked to decreased RBC deformability and increased RBC aggregation [27].

## CONCLUSION

In neonatal sepsis, our findings show that baseline RDW measurements can help predict mortality as well as disease severity that is critical for the care of these at-risk newborns. There are still many unanswered questions about the relevance of this easy-to-use marker in predicting the outcome of newborn sepsis.

**Financial support and sponsorship:** Nil.
**Conflict of interest:** Nil.

## REFERENCES

1. **Singer M, Deutschman C, Seymour C *et al.* (2016):** The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA., 315(8):801-10.
2. **Sharma M, Yadav A, Yadav S *et al.* (2008):** Microbial profile of septicemia in children. Indian Journal for the Practising Doctor, 5:9-10.
3. **West B, Tabansi P (2014):** Prevalence of neonatal septicaemia in the University of Port Harcourt Teaching Hospital, Nigeria. Nigerian Journal of Paediatrics, 41(1):33-7.
4. **Kari A, Ann L, Shirley F *et al.* (2014):** Early-onset neonatal sepsis. Clinical Microbiology Reviews, 27(1): 21-47.
5. **Loonen A, de Jager C, Tosserams J *et al.* (2014):** Biomarkers and molecular analysis to improve blood stream infection diagnostics in an emergency care unit. PLoS One, 9: 87315-18.
6. **Jajoo M, Kapoor K, Garg L *et al.* (2015):** To study the incidence and risk factors of early onset neonatal sepsis in an out born neonatal intensive care unit of India. Journal of Clinical Neonatology, 4(2):91-95.
7. **El Shimi M, Abou Shady N, Hamed G *et al.* (2017):** Significance of neutrophilic CD64 as an early marker for detection of neonatal sepsis and prediction of disease outcome. The Journal of Maternal-Fetal & Neonatal Medicine, 30(14):1709-14.
8. **Buttarello M, Plebani M (2008):** Automated blood cell counts: state of the art. American Journal of Clinical Pathology, 130(1): 104-16.
9. **Kim J, Kim K, Lee J *et al.* (2012):** Red blood cell distribution width as an independent predictor of all-cause mortality in out of hospital cardiac arrest. Resuscitation, 83(10): 1248-52.
10. **Zhang Z, Xu X, Ni H *et al.* (2013):** Red cell distribution width is associated with hospital mortality in unselected critically ill patients. Journal of Thoracic Disease, 5(6):730-34.
11. **Sipahi T, Köksal T, Tavil B *et al.* (2004):** The effects of acute infection on hematological parameters. Pediatric Hematology and Oncology, 21(6):511-8.
12. **Jo Y, Kim K, Lee J *et al.* (2013):** Red cell distribution width is a prognostic factor in severe sepsis and septic shock. The American Journal of Emergency Medicine, 31(3):545-8.
13. **Rodwell R, Leslie A, Tudehope D (1988):** Early diagnosis of neonatal sepsis using a hematologic scoring system. The Journal of Pediatrics, 112(5):761-767.
14. **Medhat H, Khashana A, El kalioby M (2017):** Incidence of neonatal infection in South Sinai, Egypt. International Journal of Infection, 4(1): 1-4.
15. **Gad G, Ismail R, El-Masry S *et al.* (2014):** Serum apelin in early-onset neonatal sepsis: is it diagnostic?. Journal of Neonatal-Perinatal Medicine, 7(3):207-212.
16. **Aderem A, Underhill D (1999):** Mechanisms of phagocytosis in macrophages. Annual Review of Immunology, 17(1):593-623.
17. **Dzwonek A, Neth O, Thiébaut R *et al.* (2008):** The role of mannose-binding lectin in susceptibility to infection in preterm neonates. Pediatric Research, 63(6):680-685.
18. **Garcia-Prats J, Cooper T, Schneider V *et al.* (2000):** Rapid detection of microorganisms in blood cultures of newborn infants utilizing an automated blood culture system. Pediatrics, 105(3 Pt 1):523-7.
19. **Ellahony D, El-Mekkawy M, Farag M (2020):** A study of red cell distribution width in neonatal sepsis. Pediatric Emergency Care, 36(8):378-83.
20. **Abdullah S, Moustafa A, Mohsen Anwar A (2018):** Prognostic validity of red cell distribution width in neonatal sepsis. International Journal of Pediatrics, 6(11):8579-86.
21. **Kader A, Islam M, Ferdoushi S *et al.* (2015):** Evaluation of red cell width in critically ill patients admitted in intensive care unit. Dinajpur Med Col J., 1: 67-73.
22. **Saleh M, Kasem Y, Amin H (2017):** Evaluation of neonatal sepsis and assessment of its severity by Red Cell Distribution Width indicator. Egy J Community Med., 35(3):21-30.
23. **Weiss M, Burchfield D (2004):** Adjunct therapies to bacterial sepsis in the neonate. Newborn and Infant Nursing Reviews, 4(1):46-50.
24. **Ghaffari S (2008):** Oxidative stress in the regulation of normal and neoplastic hematopoiesis. Antioxidants & Redox Signaling, 10(11):1923-40.
25. **Patel K, Mohanty J, Kanapuru B (2013):** Association of the red cell distribution width with red blood cell deformability. In: Welch W, Palm F, Bruley D, Harrison D, eds. Oxygen Transport to Tissue XXXIV. Advances in Experimental Medicine and Biology. New York (NY): Springer, Pp. 211–216.
26. **Liese A, Siddiqi M, Siegel J *et al.* (2001):** Augmented TNF-α and IL-10 production by primed human monocytes following interaction with oxidatively modified autologous erythrocytes. Journal of Leukocyte Biology, 70(2):289-96.
27. **Piagnerelli M, Boudjeltia K, Vanhaeverbeek M *et al.* (2009):** Red blood cell rheology in sepsis. In Applied Physiology in Intensive Care Medicine. Springer, Berlin, Heidelberg. Pp. 273-282.