

Prognostic Validity of Red Cell Distribution Width in Neonatal Sepsis

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Abstract

Background

Neonatal sepsis is one of the most critical illness in neonates that is responsible for a great proportion of morbidity and mortality in neonates so early diagnosis and identification of high risk cases is a challenging aim of our study. The purpose of this study was to investigate the prognostic value of red cell distribution width (RDW), in neonatal sepsis at the time of admission to neonatal intensive care unit (NICU).

Materials and Methods

This prospective case control study included 3 groups divided into Group 1: Neonates with sepsis (78 neonates), Group 2: Neonates with severe sepsis (42 neonates) Group 3: Neonates as a control group (60 neonates) were gender, gestational and postnatal ages matched. Red cell distribution width was determined for all included neonates. The score for neonatal acute physiology (SNAP II) was determined within 12 hours of admission to the NICU.

Results

One hundred and two sepsis newborns (85%), including 66 (64.7%) cases from sepsis group and 36 (35.3%) cases from severe sepsis group, the mortalities were 15.4% (n= 12), and 71.4% (n= 30) for group 1 and 2, respectively. The incidence of RDW increase in survivors group (45.7%) was significantly lower than in the non- survivors group (92.9%, n=39). The score for neonatal acute physiology (SNAP II) was positively correlated with RDW increase in newborns ($r= 0.735$ and $p<0.05$), and the mortality was positively correlated with RDW increase ($r= 0.598$ and $P<0.05$).

Conclusion

In our study RDW is a helpful prognostic marker for early diagnosis of neonatal sepsis and identification of high risk cases.

Key Words: Mortality, Neonatal sepsis, Red cell distribution width.

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1- INTRODUCTION

Neonatal sepsis still represents one of the most common causes of morbidity and mortality in both term and preterm infants (1). The incidence of sepsis in the neonate is greater than at any other period of life. Neonatal sepsis remains a major cause of death in developing countries; while some reports from developed countries demonstrated that the incidence of neonatal sepsis varies from 1 to 5 cases per 1000 live births, some other population-based studies from developing countries have reported clinical sepsis rates ranging from 49-170 per 1000 live births (2).

In the 1990s, Richardson et al. developed a system of assessment for the most important physiological variables affecting mortality in the first hours following admission. Each variable was assigned points based on the values found, and the result was the Score for Neonatal Acute Physiology (SNAP) (3), followed by a simplified version of the score, using only 5 variables to be measured within 12 hours of admission (SNAP II), and its perinatal extension (SNAPPE II). These scoring systems have been validated in studies with large numbers of patients and have been shown to be good predictors of mortality in newborns in neonatal intensive care units (NICU). Use of scoring systems has also allowed comparison of mortality rates from NICUs of different perinatal hospitals adjusted by severity of the disease at admission (4). Numerous studies have found red cell distribution width (RDW) and platelet morphology to vary significantly in pathological conditions associated with inflammation and infection (5). Several studies have reported that RDW shows the predictive value of all-cause mortality in critically ill or intensive care unit (ICU) patients (6). In this study, we aimed to investigate the prognostic value of RDW in neonatal sepsis at the time of admission to neonatal intensive care unit (NICU). As,

this marker is already available, as it is a part of any routine complete blood count. We compared it to the clinical outcome and SNAP II score.

2- MATERIALS AND METHODS

2-1. Method

This prospective study was carried in neonatal intensive care unit (NICU), Minia University Children Hospital, El-Minia city, Egypt. During the period from May 2015 - December 2015 divided into three groups: Group 1: Neonates with sepsis (78 neonates) were diagnosed based on the standard formulated by the International Joint Conference of Pediatric Sepsis (7), Group 2: Neonates with severe sepsis (42 neonates) according to the severity of the disease, the standard formulated by the International Joint Conference of Pediatric Sepsis, Group 3: Neonates as a control group with no clinical signs or laboratory evidence of sepsis delivered in the hospital (60 neonates). We excluded from our study, premature neonates and neonates with congenital heart diseases, congenital anomalies, hypoxic-ischemic encephalopathy, hyaline membrane disease and prior antibiotic exposure.

All enrolled neonates in group I had their illness severity assessed using score for neonatal acute physiology (SNAP II). This score consists of 6 physiological parameters, namely lowest mean arterial pressure (MAP), worst ratio of partial pressure of oxygen (PaO₂) to a fraction of inspired oxygen (FiO₂), lowest temperature, lowest serum pH, the occurrence of multiple seizures, and urine output (<1mL/kg/hr). The data collection window was the first 12 hours from the onset of severe septicemia, during which period the above parameters were prospectively recorded. Higher scores indicate more severe illness. The severity of the illness was arbitrarily graded according to the SNAP-II score as follows: Mild: 1-20, moderate: 21-40, and severe:

>40 (8). Neonates who satisfied the eligibility criteria were enrolled after explaining the nature of the study to the parents and obtaining a written informed consent. The study had the approval of the Institute Ethics Committee. All subjects were followed up until discharge from NICU or death. The key outcome measure was the difference in SNAP II between survivors and non-survivors.

2-2. Samples collection

Three ml of venous blood was withdrawn by well-trained nursing staff during first 12 hours after admission before starting antibiotic therapy under completely aseptic conditions from all participating neonates for hematological and biochemical laboratory tests. Complete blood count (CBC) samples were collected in anti-coagulants EDTA tubes and CBC was performed immediately and serum was separated following sample clotting in plain tubes by centrifugation and analyzed immediately for serum C-reactive protein.

2-3. Laboratory methods

Complete blood counts (CBC) of all patients were evaluated by automated cell counter, Sysmex KX-21N (TAO Medical Incorporation, Japan) (2). Total WBCs count, red cell distribution width (RDW), was noted. CRP was measured by NycoCard Reader II (Axis-Shield PoC AS, Oslo, Norway) CRP levels < 6 mg/dl were considered normal.

2-4. Statistical analysis

Data entry and analysis were all done with I.B.M. compatible computer. The collected data were statistically analyzed using statistical package for social sciences (SPSS) program for windows version 22.0. Quantitative results were presented as the mean \pm standard deviation (SD); while qualitative data were presented by frequency distribution as percent (%). Student sample t-test was used to compare between two means and Chi-square test

was used to compare proportions. Analysis was done for not normally distributed quantitative variables using the Kruskal Wallis test to determine the difference between more than two groups. Correlations were performed by using Pearson correlation coefficient (r). Receiver operating characteristic (ROC) curve analysis was performed to determine: the optimal cut-off values, the predictive ability of different studied markers and scores and their sensitivities and specificities for the outcome. The probability of less than 0.05 was used as a cutoff point for all significant tests.

2-5. Ethical approval

The study was designed to respect the expected ethical aspects. It was performed according to the Declaration of Helsinki 1975, as revised in 2008 and approved by the Institutional Review Board and Medical Ethics Committee of Minia University, Egypt.

3- RESULTS

In this study, no difference was noted in the perinatal data between the neonates diagnosed with neonatal sepsis, severe sepsis and the control group regarding gender, gestational age, postnatal age or weight ($P > 0.05$). Comparison between sepsis and severe sepsis groups as regard RDW is shown in **Table.1**. There were statically significant differences between the 2 groups as regard RDW which was higher in severe sepsis group than the sepsis group ($p = 0.001$). As regards the outcome in sepsis and severe sepsis groups **in Table.2**. In sepsis group, among 78 neonates, 84.6% of them were survived (66/78), and 15.4% of them were dead (12/78). On the other hand, the outcome of severe sepsis group, among 42 neonates, 28.6% of them were survived (12/42) and 71.4% of them were dead (30/42). There were statistical significant differences between two groups as regard mortality,

which was higher in severe sepsis group than sepsis group ($p = 0.001$). Comparison between sepsis and severe sepsis groups as regard SNAP II is shown in **Table.3**. There were high statically significant differences between the 2 groups regarding SNAP II which was higher in severe sepsis group than sepsis group ($p = 0.0001$). Comparison between survivors and non survivors groups as regard RDW is shown in **Table.4** The incidence of RDW increase in survivors group (45.7%) was significantly lower than in the non-survivors group (92.9%, $n=39$).

Correlations between SNAP II and CRP and RDW are shown in **Table.5**. There were a moderate positive correlation between SNAP II and CRP ($r= 0.697$ and $p=0.0001$) and moderate positive correlation between SNAP II and RDW($r= 0.735$ and $p= 0.0001$), and these

correlations were statistically highly significant. The relation between RDW and mortality is shown in **Table.6**. Among the septic neonates; the median of RDW is higher in dead septic neonates (19.5%) than that of living septic neonates (16%). There was high statistically significant difference between RDW and mortality ($p = 0.001$), this relation was the cornerstone in our study.

Also, Roc Curve analysis of RDW in the diagnosis of neonatal sepsis is shown in **Tables 7 and 8**, at a cutoff point of RDW 14.3%; the sensitivity was 85% and the specificity 100%. Increasing the cutoff point to 18%, the sensitivity decreased to 64.3% and the specificity decreased to 84.6%. So, neonates developed sepsis when RDW became more than 14.3% and other neonates developed severe sepsis when RDW became more than 18%.

Table-1: The comparison between sepsis and severe sepsis groups as regard RDW

RDW (%)	Sepsis (n=78)	Severe sepsis (n= 42)	P- value
Mean \pm SD	16.6 \pm 2.13	18.5 \pm 2.9	0.001
Minimum	11.8	12.5	
Maximum	21	23	
Median	17	19	

RDW: Red cell distribution width; SD: Standard deviation.

Table-2: The comparison between sepsis and severe sepsis groups as regard outcome.

Outcome	Sepsis (n= 78)	Severe sepsis (n= 42)	P – value
Survived, Number (%)	66 (84.6%)	12 (28.6%)	0.001
Dead, Number (%)	12 (15.4%)	30 (71.4%)	

Table-3: The comparison between sepsis and severe sepsis groups as regard SNAP II

Score	Sepsis (n= 78) Mean \pm SD	Severe sepsis (n = 42) Mean \pm SD	P – value
SNAP II	7 - 66 25. 08 \pm 15.4	28 - 96 64.4 \pm 22.09	0.0001

SNAP II: Score for neonatal acute physiology II; SD: Standard deviation.

Table-4: Comparison between survival and death groups as regard RDW increase

Variables	Increased RDW	Normal RDW	Increase rate (%)
Survival group (n=78)	63	15	45.7
Death group (n=42)	39	3	92.9
Total	102	18	56.7
P-value			0.002

Table-5: The correlations between SNAP II and CRP and RDW.

Pearson Correlation		CRP	RDW
SNAP II	r	0.697	0.735
	P-value	0.0001	0.0001

SNAP II: Score for neonatal acute physiology II; RDW: red cell distribution width; SD: Standard deviation; CRP: C-reactive protein.

Table-6: The relation between RDW and mortality

Outcome	RDW				
	Number	Mean \pm SD	Minimum	Maximum	Median
Dead Neonates	42	19.95 \pm 2.06	17	23	19.5
Living Neonates	78	15.53 \pm 2.244	11.7	20	16

RDW: Red cell distribution width; SD: Standard deviation.

Table-7: The ROC Curve analysis for diagnosis of neonatal sepsis by RDW at cutoff point >14.3

Variable	AUC	Cut-off	P-value	Sensitivity (%)	Specificity (%)
RDW	0.924	>14.3	<0.001	85	100

RDW: Red cell distribution width; AUC: Area under the curve.

Table-7: ROC Curve analysis for diagnosis of neonatal severe sepsis by RDW at cutoff point >18

Variable	AUC	Cut-off	P-value	Sensitivity (%)	Specificity (%)
RDW	0.739	>18	<0.001	64.3	84.6

RDW: Red cell distribution width; AUC: Area under the curve.

4- DISCUSSION

Neonatal sepsis with its high mortality rate, still remains a diagnostic and

treatment challenge for the neonatal health care providers, an early diagnosis of neonatal septicemia helps the clinician in

instituting antibiotic therapy at the earliest time, thereby reducing the mortality rates in the neonates, an early identification of an infected neonate also helps in avoiding the unnecessary treatment of a non-infected neonate. The blood culture not only takes time, but it is also complicated, with a low yield (9). Mortality rate increases in the developing countries because of the lack of early diagnosis and identification of high risk cases (10). Neonatal sepsis increases the length of hospital stay and cost of treatment especially in developing countries with insufficient neonatal intensive care facilities and personnel leading to problems for families, community and health system. However, accurate diagnosis is made by blood culture which is a time-consuming method.

For this cause, neonatologists tested a number of other biochemical markers for accurate diagnosis of sepsis in the shortest time (11) so in our study we test red cell distribution width as an early cheap and available biomarker for diagnosis of neonatal sepsis. In the current study, the mean RDW level in severe sepsis group was significantly higher than sepsis group. There was statistically significant difference between two groups (p -value = 0.03), similar result was observed by Jianping et al. (2015) (12), who found that the mean RDW level in severe sepsis was significantly higher than sepsis group (p = 0.000). This can be explained by inflammation may cause an increase of neurohormone and endocrine hormone in the body including noradrenaline, angiotensin I and other angiotensin levels and renal ischemia. These neurotransmitters can stimulate red blood cell proliferation through increasing the secretion of erythropoietin (EPO) leading to increase in RDW and inflammatory factors which may affect marrow hemopoietic function and iron metabolism in the body to cause RDW increase (13).

In the current study, among neonates of the sepsis group, 84.6% of them were survived and 15.4% of them were dead; while among neonates of the severe sepsis group, 28.6% of them are survived and 71.4% of them are dead. There was statistically significant difference between two septic groups (p = 0.001) so from our results we noticed that neonatal sepsis is complicated with a high mortality which become higher with severe sepsis this finding is similar to study done by Babaei et al. (14) who found that the neonatal sepsis is the second cause of mortality of neonates. This can be explained by severe sepsis is always associated with organ dysfunction and massive hypoperfusion rather than sepsis which eventually leads to death (15). The high rate of mortality in our study may be attributed to late admission of septic neonates in serious and life threatening condition, lack of equipments such as some inotropes and high frequency ventilators. In the current study, the mean of score for neonatal acute physiology II (SNAP II) in severe sepsis group was higher than sepsis group (p = 0.0001).

This result was in agreement with Venkataseshan et al.'s study (2009) (16), who studied score for neonatal acute physiology II and found that this score can predict mortality and persistent organ dysfunction in neonates with severe septicemia. This increase in SNAP II in severe sepsis group than sepsis is explained by the fact that the higher the score, the more persistent organ dysfunction and the more serious the condition (17). In the present study, our findings reported that there was significant moderate positive correlation between CRP and SNAP II (r = 0.697, p = 0.0001). So, C-reactive protein (CRP) combined with SNAP II can be taken as marker for outcome in septic newborns. In the current study, our findings reported that there was significant moderate positive correlation between RDW and SNAP II (r = 0.735, p =

0.0001). So, the use of RDW combined with SNAP II can predict prognosis in septic newborns. This result was similar to that reported by Chiesa et al. (2011) (18), who studied "C- reactive protein and procalcitonin: reference intervals for preterm and term newborns during the early neonatal period" and found that the higher the CRP and neonatal critical illness score (NCIS) values, the more serious the disease and the worse the prognosis were. In the current study, RDW was evaluated as a prognostic factor determining the outcome of neonatal sepsis. Our findings found that, among the septic dead neonates, the median of RDW (19.5%), which was higher than that of living septic neonates (16%), there was highly statistically significant difference between RDW and mortality with ($p = 0.001$). So measurement of RDW helps us in prediction of outcome and mortality rate of septic neonates, this agrees with Jianping et al.' study (2015) (12), who found that RDW in newborns of death group (92.9%) was significantly higher than that of survivors group (49.32%). We found that cutoff point of 14.3% for RDW with 85% sensitivity and 100% specificity. So, RDW with a cutoff point of 14.3% was very efficient to diagnose sepsis. We also found that cutoff point of 18% for RDW with 64.3% sensitivity and 84.6% specificity. So, RDW with a cutoff point of 18% was very efficient for early diagnosis of severe sepsis.

4-1. Limitations of the study

Long-term follow-up of the discharged neonates to study the morbidity predictability of red cell distribution width. It is one hospital based study and we need studies in the future to include more hospitals.

5- CONCLUSION

According to our results, we used RDW as a reliable marker for diagnosing and guiding antibiotic therapy in neonatal

sepsis because of several advantages; rise in infection and better correlation with outcome.

6- AUTHORS' CONTRIBUTIONS

ANM participated in the study design, data collection, analysis and manuscript writing. STA participated in manuscript writing. AMA participate in data collection, analysis. All authors read and approved the final manuscript.

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8- CONFLICT OF INTEREST: None.

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