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A study of elevated red cell distribution width (RDW) in early-onset neonatal sepsis

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Abstract

Background: Neonatal sepsis is a serious infection occurring within the first 28 days of life. It is a significant cause of mortality and morbidity. Red cell distribution width (RDW) is estimated within the standard CBC profile and considered a simple tool for the diagnosis of neonatal sepsis without additional cost. Our aim in this study is to investigate the potential role of red cell distribution width (RDW) in the diagnosis of early-onset neonatal sepsis (EONS). The aim of our study is to detect the role of red cell distribution width (RDW) in the diagnosis and prognosis of early-onset neonatal sepsis (EONS).

Results: This case-control study was conducted at the NICU of Beni-Suef University Hospital and revealed that RDW% was highly significantly higher among cases than among controls (16.65 ± 4.28, 11.13 ± 0.62, respectively); regarding the severity of neonatal sepsis, we divided our cases into three groups (sepsis group includes 21 neonates, severe sepsis group includes 31 neonates, and septic shock group includes 48 neonates), there were statistically significant differences between the three groups (sepsis, severe sepsis, and septic shock) regarding RDW (15.15 ± 1.65, 16.78 ± 2.01, 17.02 ± 2.02, respectively) as *P* value (0.027).

Conclusion: This study revealed that RDW is associated with the diagnosis and prognosis of early-onset neonatal sepsis, so further study is needed to prove causation as it is being simple, less expensive, available, and easily repeated as it is routinely done with CBC, so it will be a good indicator for prognosis of neonatal sepsis.

Keywords: Red cell distribution width, Neonatal sepsis, Early-onset neonatal sepsis

Background

Neonatal sepsis is a serious infection occurring within the first 28 days of life. It is a significant cause of mortality and morbidity [1].

Early-onset sepsis is a significant cause of morbidity often complicated by meningitis or pneumonia. Most newborns with early-onset infection present within 24 h, few neonates may present at 24–48 h, and rarely, neonates with early-onset sepsis may present between 48 h and 6 days of life [2].

When the standard deviation in red blood cell (RBC) size is divided by the mean corpuscular volume (MCV), red cell distribution width (RDW) is calculated. RDW is a simple tool for the diagnosis of neonatal sepsis [3].

Although the exact mechanisms that explain the association between RDW and mortality are unknown, high RDW is associated with the presence of an ongoing disease process, such as inflammation, tissue hypoperfusion oxidative stress, or renal failure [4].

Recently, RDW can act as a prognostic factor in some life-threatening diseases such as sepsis. The same observation was also demonstrated recently in an adult population of patients being admitted to the emergency wards [5].

Red cell distribution width (RDW) reflects the different sizes of red blood cells (RBC) during circulation. This is a simple index for inflammation, oxidative stress, and arterial underfilling in severe cases [6].

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RDW was observably higher in newborns with EONS. The pro-inflammatory cytokines released during sepsis have been found to inhibit erythropoietin-induced erythrocyte maturation and proliferation and downregulate erythropoietin receptor expression, which are associated with RDW increases. In sepsis, high oxidative stress releases reactive oxygen species that decreases red blood cell survival and leads to the release of large premature red blood cells into the peripheral circulation, so there is an increase in RDW [7].

The aim of our study is to detect the role of red cell distribution width (RDW) in the diagnosis and prognosis of early-onset neonatal sepsis (EONS).

Methods

This is a case-control study conducted at the neonatal intensive care unit (NICU) at Beni-Suef University Hospital. The study included 100 term neonates (57 females and 43 males) with early-onset neonatal sepsis (EONS) and 100 term healthy neonates (43 females,57 males) [as a control group], and both cases and controls aged from 1 to 3 days. Written informed consent was obtained from parents or legal guardians for all participants.

All cases were divided according to the standard formulated by the international conference of pediatric sepsis into the sepsis group (21 cases), severe sepsis group (31 cases), and septic shock group (48 cases) [8]. Follow-up of all cases was made to know the number of recovered discharged cases and deceased cases.

For all neonates, the following were performed:

1. History taking:
    (a) Including the most common symptoms of sepsis
    (b) Maternal history (diabetes mellitus, maternal fever > 38 °C, maternal antibiotics, maternal UTI, etc.), premature rupture of the membrane (PROM), and prolonged 2nd stage of labor, etc.
    (c) Postnatal history (low Apgar score at 1 and 5 min, aggressive resuscitation, respiratory distress, cyanosis, fever, jaundice, etc.)
2. Thorough clinical examination:
    (a) Gestational age assessment using new Ballard score
    (b) Birth weight measurement
    (c) Detection of clinical signs of sepsis
    (d) Detection of the score of sepsis
3. Investigations:
    (a) Complete blood picture with differential count (CBC)
    (b) Red cell distribution width (RDW)
    (c) C-reactive protein (CRP)
    (d) Blood culture and sensitivity for cases with neonatal sepsis not for controls

Sample collection

In a peripheral blood sample via venipuncture, the blood was collected using a clean technique. The volume of the blood is divided for blood culture and CBC in tubes containing EDTA and CRP in dry tubes.

Inclusion criteria

Term neonates with signs and symptoms suggestive of early-onset sepsis were taken as cases; meanwhile, age and weight-matched healthy term neonates were taken as controls. Term newborns (cases and control) were of both sexes with gestational age between 37 and 40 weeks delivered by normal vaginal delivery, aged from 1 to 3 days and weight $\geq$ 1.75 kg.

Exclusion criteria

Preterm neonates < 37weeks of gestation, weight < 1.75 kg, and age > 3 days; neonates suffering from congenital anomalies and perinatal asphyxia; and neonates with birth trauma were excluded from the study.

Statistical analysis

All data were revised, described, and analyzed by IBM-compatible PC by using the SPSS (Statistical Package for the Social Science) program version 22.0.0, Microsoft Office Excel 2007, and GraphPad Prism 6.

Analytical comparison between the groups was done by using the Student *t* test and analysis of variance (ANOVA) for comparing the parametric data when normally distributed. For comparing non-parametric data, Fisher's exact test was used instead of the chi-square test as Fisher's test calculates an exact *P* value, while chi-square only calculates an approximation.

The level of significance was calculated according to the following probability (*P*) values:

- $P > 0.05$ = non-significant (NS)
- $P < 0.05$ = significant (S)
- $P < 0.001$ = highly significant (HS)

Results

The current study showed that there were highly statistically significant differences regarding the total leukocytic count TLC and red blood cell count between cases

with early-onset sepsis and controls (*P*-value 0.000). The cases with sepsis showed leukopenia in 20% of cases while it was 0.0% in controls and leukocytosis with a shift to the left in 80% of cases while it was 0.0% in controls; meanwhile, red blood cell count was lower in cases than in controls (4.45 ± 1.07, 5.26 ± 0.63, respectively), while positive blood culture in cases with sepsis showed that 96% of cases was *Klebsiella*, 2% was other Gram-ve Bacilli, and 2% was multi-drug-resistant *Klebsiella* (MDR/*Klebsiella* (Table 1).

Comparison between cases with early-onset neonatal sepsis and controls regarding CRP, HB, RDW, and PLT showed that CRP was highly significantly increased in cases compared to controls (43.80 ± 57.68, 4.2 ± 0.86, respectively); HB level and platelets were highly significantly decreased (HS) in comparison with the controls (*P*-value 0.000) (for Hb, it was 14.36 ± 2.58, 17.88 ± 2.13, respectively). Meanwhile, for platelets, it was 223.77 ± 82.15 and 300.29 ± 67.75, respectively, while the mean of RDW was highly significantly increased than controls (16.65 ± 4.28, 11.13 ± 0.62, respectively) (*P*-value 0.000) (Table 2).

The current study revealed statistically significant differences in the mean HB level and CRP between the three groups of sepsis (sepsis group 21 cases (21%), severe sepsis group 31 cases (31%), and septic shock group 48 cases (48%)); meanwhile, CRP was higher in the septic shock group than in other groups (*P*-value 0.000) which is a highly statistically significant difference, while there were statistically significant differences between the three groups (sepsis, severe sepsis, and septic shock) regarding RDW (15.15 ± 1.65, 16.78 ± 2.01, 17.02 ± 2.02, respectively) (*P*-value 0.027);there was no statistically significant difference between the three groups regarding PLT (*P*-value > 0.05) (Table 3).

The comparison between cases with low HB level [20 cases] (20%) and cases with normal HB level [80 cases] (80%) as regards RDW showed non-statistically significant difference (*P*-value > 0.05) (Table 4).

Table 1 Comparison between controls (no. = 100) and cases with early-onset neonatal sepsis (no. = 100) regarding TLC, blood culture, and RBCs

		Control cases	Cases with early-onset neonatal sepsis	Chi-square value	*P*-value
		No. = 100	No. = 100		
*TLC	Leukopenia	0 (0.0%)	20 (20.0%)		
	Normal	100 (100.0%)	0 (0.0%)	200.0	0.000 HS
	Leukocytosis	0 (0.0%)	80 (80.0%)		
*Blood culture	*Klebsiella*	–	96 (96.0%)		
	Other Gram-ve Bacilli	––	2 (2.0%)	–	–
	MDR/*Klebsiella*		2 (2.0%)		
	No growth	–	0 (0.0%)		
Red blood cells (RBCs)	Mean ± SD	5.26 ± 0.63	4.45 ± 1.07	6.493	0.000 HS
	Range	4.1–6.5	2.8–9.01		

HS highly significant

Table 2 Comparison between control cases (no. = 100) and cases with early-onset neonatal sepsis (no. = 100) regarding CRP, HB, RDW, and PLT

Laboratory investigation		Control cases	Cases with early-onset neonatal sepsis	*T*-value	*P*-value
		No. = 100	No. = 100		
C-reactive protein (CRP)	Mean ± SD	4.2 ± 0.86	43.80 ± 57.68	6.8	0.000 HS
	Range				
Hemoglobin (HB), g/dl	Mean ± SD	17.88 ± 2.13	14.36 ± 2.58	10.49	0.000 HS
	Range	14.6–23	9.2–22.5	5	
Red cell distribution width (RDW)	Mean ± SD	11.13 ± 0.62	16.65 ± 4.28	− 12.74	0.000 HS
	Range	10–12.1	10–39	8	
Platelet (PLT)	Mean ± SD	300.29 ± 67.75	223.77 ± 82.15	7.186	0.000 HS
	Range	184–508	63–444		

HS highly significant

Statistical analysis revealed that there was a highly statistically significant difference in CRP between the discharged group from NICU (52 cases (52%)) and the deceased group in the NICU (48 cases (48%)), where the mean of CRP was higher in the deceased group than in the discharged group (*P*-value 0.00), while RDW was statistically significant (17.52 ± 2.61, 14.85 ± 2.30, respectively) (*P*-value (0.02)), but there were no statistically significant differences between the two groups regarding HB and PLT (*P*-value > 0.05) (Table 5).

Discussion

Neonatal sepsis is manifested by bacteremia and clinical manifestations due to microorganism invasion and their toxins. Neonatal sepsis diagnosis should include infection establishment with a systemic illness in which non-infectious explanations for patho-physiologic abnormality are excluded [9].

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 as red cell distribution width (RDW) which is an early cheap and available biomarker for diagnosis of neonatal sepsis [10].

In our study, the mean RDW was highly significantly higher in cases compared to controls (16.65 ± 4.28, 11.13 ± 0.62, respectively) ($P = 0.000$); this finding is in agreement with Jianping et al. [11] who reported significant statistical difference regarding RDW value between cases of sepsis and controls (19.61 ± 1.48, 16.04 ± 1.25, respectively) (*P*-value = 0.0001). Increased RDW may comprehensively reflect the pathophysiological mechanisms in the occurrence and development of sepsis as

Table 3 Comparison between the sepsis group (no. = 21), severe sepsis group (no. = 13), and septic shock group (no. = 66) regarding HB, RDW, PLT, CRP, and RBCs in cases with early-onset neonatal sepsis

Cases with early-onset neonatal sepsis		Sepsis group No. = 21	Severe sepsis group No. = 31	Septic shock group No. = 48	*T*-value	*P*-value
Hemoglobin (HB), g/dl	Mean ± SD Range	15.54 ± 2.44 13–21	14.90 ± 1.78 11.3–17.2	13.88 ± 2.64 9.2–22.5	3.804	0.026 **S**
Red cell distribution width (RDW)	Mean ± SD Range	15.15 ± 1.65 10.1–19.9	16.78 ± 2.01 13.9–16.8	17.02 ± 2.02 10–39	3.755	0.027 S
Platelet (PLT)	Mean ± SD Range	231.19 ± 67.93 147–368	200.23 ± 53.62 145–337	226.05 ± 90.52 63–444	0.640	0.530 NS
C-reactive protein (CRP)	Mean ± SD Range	7.16 ± 1.43 6–9.5	13.56 ± 1.57 10.56–15.5	61.42 ± 64.29 15.5–276.8	10.933	0.000 HS

S significant, *NS* not significant, *HS* highly significant

Table 4 Comparison between cases with low HB levels and cases with normal HB levels regarding RDW

Cases with early-onset neonatal sepsis		Cases with low HB levels (20%)	Cases with normal HB levels (80%)	*T*-value	*P*-value
Red cell distribution width (RDW)	Mean ± SD Range	16.01 ± 4.20 13–27	16.81 ± 4.32 10–39	− 0.74	0.456 NS

NS not significant

Table 5 Comparison between cases discharged from NICU (no. = 52) and deceased in NICU (no. = 48) regarding HB, RDW, PLT, CRP, and RBCs in cases with early-onset neonatal sepsis

Cases with early-onset neonatal sepsis		Cases discharged from NICU, no. = 52	Cases deceased in NICU, no. = 48	*T*-value	*P*-value
Hemoglobin (HB), g/dl	Mean ± SD Range	15.04 ± 2.72 10.1–22.5	13.63 ± 2.21 9.2–19.2	0.816	0.421 NS
Red cell distribution width (RDW)	Mean± SD Range	14.85 ± 2.30 10–17	17.52 ± 2.61 13–39	3.816	0.02 S
Platelet (PLT)	Mean ± SD Range	212.83 ± 65.10 86–368	235.63 ± 96.64 63–444	1.394	0.173 NS
C-reactive protein (CRP)	Mean ± SD Range	12.48 ± 5.08 3.4–26	77.74 ± 68.68 22.2–276.8	12.214	0.000 HS

NS not significant, *S* significant, *HS* highly significant

inflammation may cause an increase of neuro-hormone and endocrine hormone in the body including noradrenaline, angiotensin 1, and other angiotensin levels. These neurotransmitters can stimulate RBC proliferation by promoting the generation of erythropoietin (EPO) to result in an RDW increase [12]; inflammatory factors may affect the bone marrow hemopoietic system and iron metabolism to cause RDW increase [13]. RDW increase may indicate unstable cytomembrane which may cause multiple organ dysfunctions that make the patients' condition deteriorate, thus leading to poor prognosis and increased mortality. Studies found that the materials providing the nutrition to the body and cell, such as blood cholesterol, albumin, and others, are lacking while RDW increases. Therefore, increased RDW may reflect the cell membrane instability due to the lack of cholesterol and other substances in the body [14]. Severe sepsis/septic shock may be combined with multiple organ dysfunction.

Our study revealed a highly statistically significant difference regarding Hb levels between cases and controls (14.36 ± 2.58, 17.88 ± 2.13, respectively) (*P*-value = 0.000); there were 20 cases with low Hb levels (20%) and 80 cases (80%) with normal Hb levels while controls (100%) had normal Hb level; meanwhile, RDW showed a non-statistical significant increase in the group of sepsis with normal Hb level than the other groups with low Hb level (16.81 ± 4.32, 16.01 ± 4.20, respectively) (*P*-value = 0.45). This may point to the multifactorial causes of low HB % other than sepsis, and the increase of RDW in sepsis cases in spite of normal Hb level proves that the RDW can be used as an early indicator for the diagnosis of sepsis. The current study showed a highly statistically significant relation regarding leukocytic count 20% of cases had leukopenia while 80% of cases had leukocytosis with a shift to the left; meanwhile, all controls (100%) had normal leukocytic count (*P*-value = 0.000). This finding is in agreement with the large number of studies that have been performed to evaluate the use of CBC, differential count, and immature to total leukocyte ratio (I:T) for the diagnosis of neonatal sepsis [15]. Saleh et al. [15] reported that CBC has a poor predictive value, and serial normal values can be used to enhance the prediction that bacterial sepsis is not present.

In this study, 21 of the cases (22%) had sepsis, 31 cases(31%) had severe sepsis, and 48 cases (48%) had septic shock, which reflects the high prevalence of severe sepsis and spotlights the need to diagnose this problem early to minimize its complications and burden on the health system and future development of such patients.

As regards the severity of neonatal sepsis, our study revealed statistically significant differences in the mean HB level, CRP, and RDW between the three groups of sepsis (sepsis, severe sepsis, and septic shock); the mean HB level was higher in the sepsis group than in the severe group and septic shock group (15.54 ± 2.44, 14.90 ± 178, 13.88 ± 2.64, respectively) (*P*-value 0.026); meanwhile, CRP was higher in the septic shock group than in the severe sepsis group and sepsis group (61.42 ± 64.29, 13.56 ± 1.57, 7.16 ± 1.43, respectively) (*P*-value = 0.00), while there were statistically significant differences between the three groups (sepsis, severe sepsis, and septic shock) regarding RDW (15.15 ± 1.65, 16.78 ± 2.01, 17.02 ± 2.02, respectively) (*P*-value 0.027).

RDW was correlated with the severity of neonatal sepsis; this suggests that septic neonates with RDW ≥ 17% may have a higher severity of illness, and RDW may have value in differentiating between more severe and less severe cases of neonatal sepsis; this finding is in agreement with Kader et al. [16] who reported that incidence of RDW increase in neonatal sepsis and increased with increasing severity of the disease. He also stated that the mean RDW value in less severe patients was 16.04 ± 0.7, and the mean RDW value in more severe patients was 19.75 ± 1.9.

The mean RDW difference in both groups was statistically significant ($P < 0.001$) with the severity of the disease higher in severe cases than in mild ones. Saleh et al. [15] reported that RDW is statistically significantly correlated with the severity of neonatal sepsis.

The current study revealed non-statistical significant differences between 48 deceased neonates in the NICU and 52 neonates discharged from the NICU, regarding HB (13.63 ± 2.21, 15.04 ± 2.72, respectively), but RDW was statistically significant (17.52 ± 2.61, 14.85 ± 2.30, respectively) (*P*-value 0.02); meanwhile, our statistical analysis revealed that there was highly statistically significant difference in CRP between the discharged group from NICU and the deceased group in the NICU, where the mean of CRP was higher in the deceased group than in the discharged group (77.74 ± 68.68, 12.48 ± 5.08, respectively) (*P*-value 0.00). Recent studies showed that RDW% can be taken as a "marker" of death in critically ill patients and may be used to predict death risk independently in such patients [17].

Conclusions

This study revealed that RDW is associated with the diagnosis and prognosis of early-onset neonatal sepsis, so further study is needed to prove the causation as it is due to being simple, less expensive, available, and easily repeated as it is routinely done with CBC, so it will be a good indicator for prognosis of neonatal sepsis. We recommend that future studies with larger samples are needed to confirm these findings, with added emphasis on multivariable diagnostic models that incorporate biomarkers in addition to RDW.

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Authors' contributions
MH: interpretation of patients' data, design the experiment, writing and revising of the manuscript. DM: design of the experiment, interpretation of patients' data, and revision of the manuscript. AH: revision of the methodology part of the manuscript and interpretation of patients' data. NW: design of the experiment, interpretation of patients' data, and writing and revision of the manuscript. All authors have read and approved the final manuscript.

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Availability of data and materials
All data are available upon request. All materials are available upon request.

Declarations

Ethics approval and consent to participate
The study protocol was reviewed and approved by the ethical committee of the Faculty of Medicine, Beni-Suef University. Informed written consent was obtained from one of the parents of the children prior to enrollment in this study recruitment.

Consent for publication
Not applicable

Competing interests
The authors declare that they have no competing interests.
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