

Role of Red Cell Distribution Width in Late-onset Preeclampsia: A Single-Center Experience

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ABSTRACT

Background: Red cell distribution width (RDW) is an inflammatory biomarker and a component of complete blood count that gains increased attention. Pre-eclampsia (PE) is a unique pregnancy syndrome for which inflammation was proposed for pathogenesis.

Objectives: We aimed to examine RDW's role in PE and explore confounders that limit its implication in practice.

Materials and methods: A case-control study recruited 120 participants matched in body mass index (BMI) and gestational age into 3 subgroups; late-onset severe PE cases (30/120), late-onset non-severe PE cases (30/120), and healthy controls (60/120). Participants' demographics (age, BMI, systolic and diastolic blood pressure (SBP, and DBP), hematological and biochemical parameters were evaluated.

Results: RDW was significantly higher in PE cases (P-value < 0.01); In addition, RDW was positively correlated to SBP, DBP, and protein urea, $r = 0.5$, $r = 0.46$, and $r = 0.47$; P-value < 0.0001, respectively. Liver enzymes, hemoglobin, and white blood cell count were all significantly linked to RDW ($r = 0.27$, P-value = 0.015), ($r = 0.32$, P-value = 0.005), ($r = -0.27$, P-value = 0.02) and ($r = 0.39$; P-value = 0.0004) respectively. Applying ROC Curve analysis showed that RDW cut-off value of > 14.4% discriminated PE cases from healthy controls (P-value < 0.001). At a cut-off value > 15.6% RDW distinguished severe from non-severe PE cases (P-value < 0.001).

Conclusion: RDW was significantly correlated to PE predictors and severity markers independent of gestational age and BMI. The ROC curve showed that RDW distinguished PE from healthy controls in addition to non-severe from severe PE cases with high sensitivity and specificity. Being an inexpensive, reliable test with good predictive and prognostic value warrants further studies for RDW's role in PE screening and follow-up.

Keywords: Red cell distribution width; Late-onset pre-eclampsia; Body mass index; Diagnostic performance; Severity.

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INTRODUCTION

To date, pre-eclampsia (PE) continues to fascinate scientists. Despite much research, no definitive cause for PE was identified [1]. The current understanding of PE is limited, and the curable treatment is to terminate the pregnancy. PE negatively affects pregnancy; moreover, women who survive have a shorter life

expectancy due to an increased risk of cardiovascular illness, stroke, and diabetes. In contrast, babies born to mothers with PE have greater risks of preterm birth, cognitive impairment, cardiovascular and metabolic disorders, and even death [1, 2]. For that reason, a timely diagnosis of pre-eclampsia is crucial for both the mother's and child's health in order to reduce PE morbidity and mortality [2].

There is a pressing need for reliable early diagnostic markers. These markers may lead to discovering preventative and therapeutic interventions [2, 3]. Some hypothesized that abnormal placentation was the fundamental cause, which leads to hyper-reactivation of inflammatory cells and immunologic

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reactions, resulting in signs of the systemic inflammatory response [3, 4]. In the end, these inflammatory markers lead to endothelial dysfunction and changes in the values of complete blood parameters, such as red cell distribution width (RDW), mean platelet volume (MPV), platelet count, platelet distribution width (PDW), and total and differential white blood cells counts (WBC) [5].

The RDW measures red blood cell size variations. It is present in the majority of full blood counts. RDW was used to diagnose certain types of anemia, including but not limited to iron-deficiency anemia, thalassemia, and sickle cell anemia [6, 7]. Moreover, RDW is a predictive and prognostic biomarker for cardiovascular events, metabolic syndrome, and patients on chemo and radiation therapy [8–10].

Recently, it was used as an inflammatory marker to monitor patients with chronic conditions such as cancer or HIV/AIDS and even COVID-19 cases. Elevated RDW values were associated with adverse COVID-19 outcomes. However, the underlying causes of increased RDW are not well understood [11].

In pursuing an earlier and more accurate prediction model, complete blood count (CBC) parameters were widely researched to forecast the onset or severity of PE, but the results have been conflicting [12, 13]. One of the drawbacks of RDW assessment is its insensitivity in patients with mild episodes of anemia. Age is another factor that affects the RDW, leading to false positives or negative tests and making it less reliable in practice [14]. This study primarily aims to evaluate RDW's potential role in women with PE. The secondary objective was to explore RDW reliability regarding frequent confounders that limit its usage in clinical practice.

MATERIALS AND METHODS

Study style

The current study was conducted at the Department of Obstetrics and Gynecology, Al Yarmouk Teaching Hospital, Baghdad/Iraq, for a total study time of one year from the beginning of February 2021 till the beginning of January 2022. Out of 157 attendees to our department, 120 pregnant women satisfied our inclusion criteria. The ethical committee of Mustansiriyah University/ Department of Obstetrics and Gynecology had approved the protocol of the study (IRB 192 dated Jan 2021); All participants gave informed consent to be enrolled in the study.

Sample size calculation

The sample size was calculated based on the following formulae [15].

$$r+1(P^*)(1-P^*)(Z\beta + Z\alpha/2)^2/r(P_1-P_2)^2$$

r = is the ratio of control to cases, in our study, equal to two. P^* = represents average proportion exposed = proportion of exposed study cases + proportion of control exposed divided by two. P_1-P_2 = different in proportion expected based on previous studies. P_1 = proportion in cases, P_2 = proportion in control. $Z\beta$ is the standard normal variant, and it is 0.84 for 80% study power. $Z\alpha/2$ is the standard normal variant, and it is 1.96 at 0.05 P-value.

Therefore, the study sample size equals 70, and we recruited 120 participants.

Inclusion criteria

An enrollment was made to pregnant with new diagnoses of late-onset PE (at gestational age >34 weeks calculated on confirmed dates and/or reliable ultrasound dating) who have not started medication. Their ages ranged from 18–35 years, with a BMI of < 30 kg/m².

Study participants were further assigned to (60/120) healthy controls and (60/120) PE cases defined based on the International Society Studying Hypertension in Pregnancy (ISSHP) [16]; they were further subdivided into two groups:

1. Severe PE group (30/120): defined as new onset hypertension in the previously normotensive female after twenty weeks of gestation where BP equal or more than 160/110 mmHg, associated by one or more of the following: albuminuria 2 g /day, oliguria lower than 500 ml /24 hour, abnormal liver function tests, pulmonary edema or cyanosis, epigastric or right-upper abdomen pain, cerebral or visual disturbances, restriction of fetal growth, and thrombocytopenia.
2. Non-severe PE group (30/120): where the SBP is equal to or more than 140 mmHg and/or DBP is equal to or more than 90 mmHg in 2 readings taken at least four hours apart with proteinuria > 500 mg/day in the absence of features of severity.

Control group (60/120): healthy pregnant women were selected as the control group after matching their age and duration of gestation. All were described in the Study flowchart (Figure 1).

Mean arterial pressure (MAP): was calculated according to the formula $MAP = DP + 1/3 (SP-DP)$ [16].

Exclusion criteria

1. Uncertain gestational age, twins' pregnancy, congenitally malformed or dead baby.
2. A medical history of diabetes, hypertensive disease of pregnancy, preexisting or gestational hypertension, thyroid, or an inflammatory disease.
3. A drug history of aspirin or corticosteroid intake.
4. Cases with Hb < 10 mg/dl or blood dyscrasias.
5. Cases with incomplete or missing data.
6. Smoking.
7. Decline to participate.

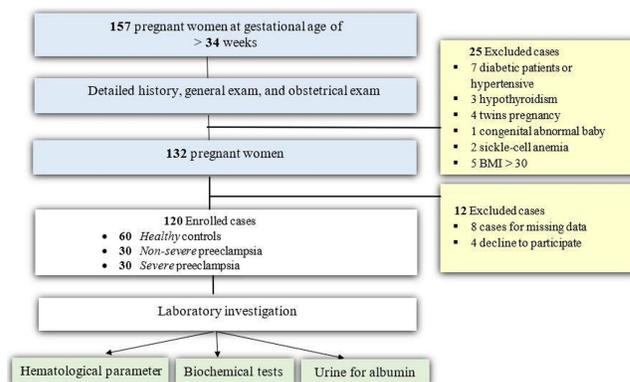


Figure 1. Study flowchart.

Study flow

Recruited cases were evaluated by history, general and obstetrical examination; including systolic and diastolic blood pressure; height, and weight for calculation of BMI. The lab investigations were done after one night fast, which included CBC [hemoglobin; white blood cell count, red distribution width, platelet count, mean platelet volume, platelet distribution width], a serological biomarker [including aspartate aminotransferase, alanine aminotransferase, blood urea, serum creatinine], and urine sample for albumin in urine.

Statistical analysis

The data normality was checked by the Kolmogorov Smirnov test. The clinical and laboratory information was interpreted and analyzed using Statistical Package for the Social Sciences (SPSS) IBM version 24. The data were presented as means and standard deviations. T-test and one-way ANOVA were applied to assess the significance of variables' differences. A series of linear regression equations tested the correlation between RDW versus all the study parameters taken as dependent variables.

Analysis of Co-variance (ANCOVA) was used to examine the effect of MAP, BMI, urine for albumin, and the severity of PE on the RDW with respective P-values. The ROC curve was constructed to estimate the RDW cut-off values associated with the highest specificity and sensitivity for screening PE severity between cases and healthy controls and between non-severe and severe PE cases. P-value < 0.05 implied a significant difference.

RESULTS

The maternal age, gestational age, and BMI were in significant among the three subgroups (P-value was > 0.05). The SBP, DBP, and MAP were significantly higher among severe PE cases (P-value = 0.02, 0.01, and 0.001) respectively. Likewise, AST, ALT, urea, creatinine, and albumin in urine were meaningfully higher in severe PE subgroups (P-value was < 0.05). The sociodemographic criteria are described in Table 1.

The hematological indices in the three subgroups, hemoglobin, RDW, and WBC, were statistically significant among the three subgroups (P-value = 0.02, < 0.01, and < 0.01), respectively. In contrast, the platelet counts show a trend decrease in the severe PE cases with a P-value of 0.05 as shown in Table 2.

Table 3 tested the correlation between RDW against clinical, biochemical, and hematological parameters defining PE severity. The SBP and DBP scored the highest correlation with a correlation coefficient (r) of 0.51 and 0.46; P-value < 0.0001, respectively. Albumin in urine was moderately correlated to RDW with $r = 0.47$ (P-value < 0.0001). The BMI, blood urea, and platelets count had insignificant correlation ($r = -0.02$, P-value = 0.88) and ($r = -0.17$, P-value = 0.15) and ($r = 0.07$; P-value = 0.54), respectively. Liver enzymes, hemoglobin, and WBC were all significantly linked to RDW ($r = 0.27$, P-value = 0.015), ($r = 0.32$, P-value = 0.005), ($r = -0.27$, P-value = 0.02) and ($r = 0.39$; P-value = 0.0004), respectively. Analysis of co-variance examined the effect of study parameters on RDW value; the severity of PE, MAP, and albumin in urine were all influential to RDW as P-value < 0.05; while BMI had no effect on RDW, as shown in Table 4.

Finally, the ROC defines the RDW cut-off value that discriminates PE cases from healthy controls, RDW at > 14.4% with 100 specificity and 69.9% sensitivity, and P-value <

0.001. Additionally, the RDW value that discriminated non-severe vs. severe PE was defined at a cut-off value > 15.6% with a respective 96.7% specificity, 66.7% sensitivity, and P-value < 0.001, shown in Table 5.

DISCUSSION

Analysis showed statistically higher levels of RDW in the PE cases, which was correlated to all the parameters defining PE severity. The correlation of RDW was highest for the SBP, DBP, urine for albumin, LFT, and RFT. The BMI and platelets were not significantly correlated to RDW.

In agreement with our results, Yilmaz et al. [17] and Reddy et al. [18] studies found that RDW values were significantly high in PE cases vs. healthy controls. Moreover, RDW values were higher in severe vs. non-severe PE women; they recommended RDW as a diagnostic and prognostic biomarker in PE at a cut-off value of 15.9%. Reddy et al. confirmed that RDW discriminated non-severe from severe PE cases at 71% and 65% sensitivity and specificity, respectively [17, 18].

Senyu study assessed RDW as a predictor for PE at gestational ages ranging from 20 to 28 weeks and found significant differences. Cases with higher RDW had a 2.68 odds ratio for developing PE 95% confidence interval (1.47–6.095). RDW at a value of 14%, accurately predicted pregnant hypertensive disease with a maximum sensitivity of 72.6% and a specificity of 77.93% [19]. However, their study design was for prediction rather than diagnostic performance for PE as in the current study.

Overall, these studies suggest [17–19] that RDW is a valid predictor of PE and should be incorporated into normal prenatal care to assist in identifying women at risk prior to the onset of PE clinical manifestations.

Tanindi et al. study examined RDW in three groups: hypertensive, pre-hypertensive, and healthy controls. The RDW was correlated to SBP and DBP ($r = 0.8$, $r = 0.7$) P-value < 0.01, respectively. RDW had the highest increase in the hypertensive group vs. the pre-hypertensive group; the least RDW was reported in the normal population [20].

However, Abdullahi et al. [12] confirmed no association between RDW and PE development nor severity in a study involving severe vs. non-severe PE cases; RDW had an OR of 0.9; 95% CI (0.7–1.1), and P-value = 0.9.

Cintesun et al. studied various systemic inflammatory biomarkers in three sub-groups: severe, non-severe PE cases, and healthy controls. RDW and other inflammatory biomarkers were not shown to be statistically significant. Only MPV was identified as a valid biomarker in the prediction of PE [21].

The relation of RDW in PE cases could be explained based on the oxidative and inflammation theory that underlies PE where premature destruction of the RBC occurs. Thus, anisocytosis and RDW are increased. Another reason could be erythropoietin during an inflammatory reaction; an erythrocyte stimulating agent whose levels are inhibited or modified in inflammation consequently shortens RDW life span [7].

The inconsistency in earlier works may be attributed to sampling bias; RDW is affected by anemia, so we excluded anemic cases; another limitation is the age, which was positively linked to inflammatory cytokines in older cases and negatively linked with erythropoietin levels in older women [19]. Finally, different gestational ages, different maternal demographics criteria, and inflammatory responses among pregnant women can all affect blood indices [22].

Table 1. Clinical and biochemical variables of the study participants *.

| Variable | Controls (N = 60) | Non-Severe PE (N = 30) | Severe PE (N = 30) | P-value |
|--------------------------|-------------------|------------------------|--------------------|----------------------|
| Age (years) | 24.3 ± 4.8 | 27.4 ± 4.7 | 26.4 ± 6.8 | 0.53 |
| Gestational age (weeks) | 37.12 ± 3.2 | 36.1 ± 2.7 | 35.6 ± 1.9 | 0.27 |
| Systolic BP (mmHg) | 114.38 ± 8.78 | 146.25 ± 4.95 | 165.56 ± 11.23 | 0.02 [†] |
| Diastolic BP (mmHg) | 71.29 ± 8.46 | 92.22 ± 6.77 | 107.4 ± 7.64 | 0.01 [†] |
| Mean arterial BP | 90.51 ± 7.04 | 110.06 ± 10.32 | 126.66 ± 7.39 | < 0.001 [†] |
| BMI (Kg/m ²) | 27.32 ± 4.2 | 26.25 ± 6.3 | 28.1 ± 4.0 | 0.24 |
| AST (IU/L) | 22.39 ± 52 | 24.85 ± 7.9 | 28.50 ± 6.2 | 0.04 [†] |
| ALT (IU/L) | 18.8 ± 7.2 | 20.69 ± 6.6 | 22.3 ± 6.4 | 0.01 [†] |
| Urea (mg/dl) | 20.47 ± 2.5 | 23.64 ± 5.6 | 26.37 ± 6.7 | < 0.01 [†] |
| Creatinine (mg/dl) | 0.58 ± 0.12 | 0.81 ± 0.23 | 0.89 ± 0.21 | < 0.01 [†] |
| Albumin in urine | 211.26 ± 72.73 | 240.60 ± 113.10 | 464.81 ± 162.36 | < 0.001 [†] |

* All values are presented as Mean ± SD; BP: blood pressure, BMI: body mass index, AST: aspartate aminotransferase, ALT Alanine aminotransferase † Significant at P-value <0.05.

Table 2. Hematological variables of the participants*.

| Variable | Controls (N = 60) | Non-Severe PE (N = 30) | Severe PE (N = 30) | P-value |
|---|-------------------|------------------------|--------------------|---------------------|
| Hemoglobin (gm/dl) | 12.53 ± 0.9 | 11.29 ± 1.5 | 11.56 ± 1.6 | 0.02 [†] |
| Red cell Distribution Width(%) | 13.06 ± 0.8 | 14.4 ± 0.9 | 16.53 ± 2.1 | < 0.01 [†] |
| White blood cell count /mm ³ | 10.03 ± 2.23 | 10.4 ± 3.56 | 13.6 ± 4.24 | < 0.01 [†] |
| Platelet count (10 ³ /UL) | 214.17 ± 39.8 | 196.77 ± 45.8 | 176.63 ± 57.9 | 0.05 |

* All values are presented as Mean ± SDBP: blood pressure, BMI: body mass index, AST: aspartate aminotransferase, ALT Alanine aminotransferase † Significant at P-value < 0.05.

Table 3. Linear regression testing the correlation between red cell distribution width versus all the study parameters taken as dependent variables with respective 95% CI and P-value *.

| Red cell distribution width vs. Parameters | Correlation coefficient | 95%CI | P-value |
|--|-------------------------|-----------------|-----------------------|
| Systolic BP (mmHg) | 0.51 | 0.33 to 0.66 | < 0.0001 [†] |
| Diastolic BP (mmHg) | 0.46 | 0.26 to 0.62 | < 0.0001 [†] |
| BMI Kg/m ² | -0.02 | -0.24 to 0.20 | 0.88 |
| AST (IU/L) | 0.27 | 0.06 to 0.47 | 0.015 |
| ALT (IU/L) | 0.32 | 0.10 to 0.50 | 0.005 [†] |
| Blood Urea (mg/dl) | -0.17 | -0.37 to 0.06 | 0.148 |
| Creatinine (mg/dl) | 0.24 | 0.01 to 0.44 | 0.038 [†] |
| Albumin in urine | 0.47 | 0.28 to 0.63 | < 0.0001 [†] |
| Hemoglobin (mg/dl) | -0.27 | -0.46 to -0.048 | 0.02 [†] |
| White blood cell count(X10) | 0.39 | 0.18 to 0.56 | 0.0004 [†] |
| Platelets count(10 ³ /UL) | 0.07 | -0.16 to 0.29 | 0.544 |

* BP: blood pressure, BMI: body mass index, AST: aspartate aminotransferase, ALT Alanine aminotransferase † Significant at P-value <0.05.

Table 4. Analysis of co-variance (ANCOVA) was used to examine the effect of study parameters on red cell distribution width with respective P-values *.

| Red cell distribution width vs. Parameters | F-ratio | P-value |
|--|---------|---------------------|
| The severity of Pre-eclampsia | 4.95 | 0.01 |
| Mean arterial BP | 57.56 | 0.001 [†] |
| Albumin in urine | 375.49 | <0.001 [†] |
| BMI | 0.36 | 0.55 |
| Gestational age | 0.595 | 0.443 |

* BP: blood pressure, BMI: body mass index, † Significant at P-value < 0.05.

Various blood indices were tested in practice; what is unique about RDW is that it was significantly correlated to important parameters in PE prediction and its severity. ANCOVA confirmed that mean arterial BP, urine for albumin, and PE severity had the strongest correlation to RDW. Earlier work discussed the relationship between RDW and numerous unfavorable pregnancy outcomes, including placental invasion problems, gestational diabetes, and recurrent abortion [23].

Interestingly, Beksac et al. proposed that patients with proven inflammatory biomarkers (like RDW) might benefit from prophylactic doses of low molecular weight heparin to avoid complications, such as abruption and eclampsia, owing to the immunomodulatory and anti-inflammatory action of heparin. This implies a new role of RDW in preventing PE complications, adding to its prediction and prognostic

Table 5. The red cell distribution width cut-off value that defined PE cases from controls and that defines severe from non-severe PE cases at maximum sensitivity, specificity, and P-value *.

| Parameter | Criterion | Sensitivity | Specificity | AUC | P- value |
|--|-----------|-------------|-------------|-------|----------|
| RDW in healthy controls vs. PE cases | > 14.4% | 69.2% | 100% | 0.878 | < 0.001 |
| RDW in non-severe PE vs. severe PE cases | > 15.6% | 66.7% | 96.7% | 0.81 | < 0.001 |

* RDW: red cell distribution width; PE: preeclampsia.

value [24].

One of the strengths of this study is that; it confirmed the reliability of RDW independent of gestational age. The diagnostic performance of RDW independent of BMI is another point of strength. Many biomarkers were examined in practice with BMI as a cofounder to their performance in practice; for example, serum adiponectin shows a negative correlation to weight among normal weight PE cases. Conversely, it showed a positive correlation to weight among overweight PE women [25].

RDW had a good discriminating power by the ROC curve for women destined to have PE with good sensitivity and specificity, possibly due to tight inclusion criteria that positively improved the results.

RDW is an inexpensive test and can be easily interpreted in primary care centers, even in a low-resource setting. It has predictive and prognostic value added to its promising role in preventing PE complications, allowing timely intervention, and guiding obstetricians in therapeutic decisions. That made RDW a recommendable biomarker for predicting PE onset and severity and choosing preventive therapeutic strategies. We must acknowledge the study's limitations; being a single center is one. We were hoping to have a larger sample size; however, COVID-19 lockdown greatly impacted recruitment numbers [26, 27].

CONCLUSION

The current study found that elevated RDW is strongly associated with higher SBP and DBP independently of gestational age and BMI among women with late-onset PE. Further research is recommended with a larger sample size to appreciate the kinetics of RDW in PE and shed light on a potential application in practice.

ETHICAL DECLARATIONS

Acknowledgements

None.

Ethics Approval and Consent to Participate

The ethical committee had approved the protocol of the study of the Department of Obstetrics and Gynecology, College of Medicine (IRB 192 dated Jan 2021). All participants gave informed consent to be enrolled in the study.

Consent for Publication

Not applicable (no individual personal data included).

Availability of Data and Material

The datasets generated during and/or analysed during the current study are available from the corresponding author upon reasonable request.

Competing Interests

The authors declare that there is no conflict of interest.

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Authors' Contributions

Nori W and Hamed BH were responsible for the conception and conducting formal analysis. Helmi ZR and Salman AF were responsible for data collection and literature review. Nori W wrote and drafted the manuscript. All authors read and approved the final version of the manuscript.

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