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The capacity of RDW and platelet indices in defining pre-eclampsia severity: a cases-control study

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ABSTRACT

Objective. Pre-eclampsia (PE) is a peculiar pregnancy complication with adverse foeto-maternal outcomes. Red blood cell distribution width (RDW) and platelet indices are complete blood count parameters; tested as a marker for cardiovascular diseases. The inflammatory theory was proposed for PE aetiology; therefore, we aimed to investigate the role of RDW and platelet parameters in determining pre-eclampsia severity.
Patients and Methods. At Al-Yarmouk Hospital, we conducted a case-control study. 120 pregnant women satisfied inclusion criteria, divided into two groups. According to American guidelines, PE cases (60/120) and healthy controls (60/120). PE cases were subdivided into severe PE (34/60) and non-severe PE (26/60) cases. A blood sample was aspirated for complete blood count, including RDW, mean platelet volume (MPV), and platelet distribution width (PDW).
Results. RDW and MPV were meaningfully higher in PE cases than controls, with a P-value of 0.003 and 0.004, respectively. A significant difference was found in the RDW and PDW in subgroups analysis of severe *vs* non-severe PE cases, with P-values of 0.001 and 0.037, respectively. Only RDW was significantly correlated with systolic BP: r = 0.47; diastolic BP: r = 0.399. At a cut-off value of > 15.6%, RDW showed 56.7% sensitivity and 95.8% specificity, p < 0.001, distinguishing severe from non-severe PE pregnancies.
Conclusions. RDW discriminated PE severity with good accuracy and preceded platelets indices, implying its validity as a marker of severe PE. RDW is a simple, inexpensive test available in antenatal care services. Accurate diagnosis permits early focused treatment, vigorous monitoring, and timely interventions for improving pregnancy outcomes.

INTRODUCTION

Pre-eclampsia is a serious pregnancy-specific syndrome. It almost always causes adverse effects for the pregnant and her unborn neonate [1]. PE is defined by the development of hypertension beyond 20 weeks of gestation in pregnant who previously did not have hypertension with or without albuminuria or hypertension that causes end organ failure [2].

Preeclampsia has two stages. The first stage starts when a defect in trophoblast implantation causes hypoxia and less blood flow to the uterine arteries, which leads to early-onset PE (less than 34 weeks). When PE becomes symptomatic, the second stage begins in response to oxidative stress and placental factors released into maternal blood; the latter will trigger inflammatory cells and immunologic reactions to produce a systemic inflammatory state. This is evident by alterations in the values of blood parameters and many inflammatory indicators [2, 3]. Ultimately, these indicators cause endothelial dysfunction and damage, which is the whole mark of PE [4].

Although diagnostic criteria for both PE sub-types are the same, early onset PE carries a higher risk of adverse outcomes for both the mother and unborn foetus. In contrast, late-onset PE has a less severe course. This disparity in pathogenesis underlies the heterogeneity of PE syndrome [5]. Despite significant fieldwork, no definite cause has been found. Pre-eclampsia was hypothesized to be multifactorial in aetiology; genetic, immunological, and inflammation are all proposed risk factor. Many blood indices were examined and proved to be valuable in predicting and evaluating PE severity [6].

Red cell distribution width (RDW) is a measurement of red blood cell size diversity and is included in most complete blood counts. RDW has been used to determine the cause of anaemia, such as iron deficiency anaemia and sickle cell anaemia [7, 8]. Some suggest it as a predictor and prognostic biomarker for high cardiovascular events [9]. Inflammation, oxidative stress, and metabolic syndrome have all been linked to increased RDW. However, the reasons for the increased RDW are unknown [10].

Platelets, on the other hand, play a substantial pathophysiological role in PE. Their count appears to diminish in pregnancies complicated by severe pre-eclampsia, yet there are conflicting reports regarding the mean platelet volume (MPV) and platelet distribution width (PDW) [4, 11].

Some reports discuss that platelet indices change with the severity of PE as well as gestational age, while others deny such association [12].

A wide diversity of mechanisms that underlie PE pathophysiology has urged us to examine the usefulness of combined blood biomarkers in PE to enhance their performance. In addition, many inconsistencies are reported in the published literature regarding the value of blood indices [13].

This study examined the value of RDW and platelet parameters as possible diagnostic markers of PE severity among patients with late-onset PE, and since pre-eclampsia severity is the most detrimental to maternal and foetal outcomes, we aimed to reduce the PE health burden and improve its prognosis.

PATIENTS AND METHODS

A case-control study was conducted in the Obstetrics Department at Al Yarmouk Hospital in Baghdad for one year, from January 2021 to January 2022. Informed consent was taken from all participants in the study that the ethical committee approved of Mustansiriyah University/College of Medicine (IRB /146 on the 23rd Nov 2020).

A total of 120 women satisfied our inclusion criteria grouped into PE cases (60/120) comprised of pregnant diagnosed with pre-eclampsia and (60/120) healthy women as a control group. Both groups were matched regarding age, gestational age, and body mass index (BMI). PE cases were further subdivided into severe PE (34/60) and non-severe PE (26/60) cases.

Inclusion criteria

1. Pregnant in their 34-36 weeks, gestational age was confirmed by early pregnancy dating ultrasound and/or reliable last menstrual periods dates.
2. Maternal age range included was 20-40 years for both groups, with BMI < 30 Kg/m^2.
3. Singleton pregnancy.

Exclusion criteria

1. Multiple pregnancies, congenital foetal anomaly.
2. Pregnant with anaemia, blood dyscrasia, and medical diseases, including infectious, endocrine, inflammatory, and chronic diseases.
3. Pregnant with uncertain dates, smokers, and those with BMI exceeding thirty were excluded.

4. Pregnant who were already on anti-hypertensive drugs or taking drugs like aspirin and steroids.
5. Pregnant with incomplete or missing data.

The study flow chart (**Figure 1**) highlighted the recruitment, inclusion, and exclusion criteria.

Study parameters and workflow

Pre-eclampsia was defined based on the American College guidelines and involved cases admitted to the hospital and fulfilled the diagnostic criteria of pre-eclampsia, blood pressure equal to or over 140/90 mm/Hg on two occasions six hours apart with proteinuria 300 mg/dl or more per day. Features of severe PE include blood pressure ≥ 160/110 mmHg, accompanied by one or more of proteinuria ≥ 500 mg per day, oliguria less than 500 ml per 24 h, impaired hepatic function, pulmonary oedema or cyanosis, epigastric or right-upper abdominal pain, cerebral or visual disturbance, and foetal growth restriction, and thrombocytopenia [1, 14].

The control group included 60 women who were normotensive pregnant ladies randomly selected based on hospital records; we chose even serial numbers from those who attended the hospital for routine antenatal visits.

Besides a detailed clinical history, all participants had a general and obstetrical physical examination. The blood pressure was measured using a mercurial sphygmomanometer for the women resting in the sitting or lateral lying position over the cubital fossa and repeated to confirm the diagnosis if seen as abnormal.

Participants were subjected to laboratory analysis, including general urine examination for protein urea and complete blood count, including red blood cells, haematocrit, haemoglobin, RDW, MPV, and PDW, biochemical markers, including renal and liver function tests. The above data were collected and analysed.

The sample size calculation

Based on the prevalence rate of PE, which is 5-10% [2], corresponding with a 95% confidence level and

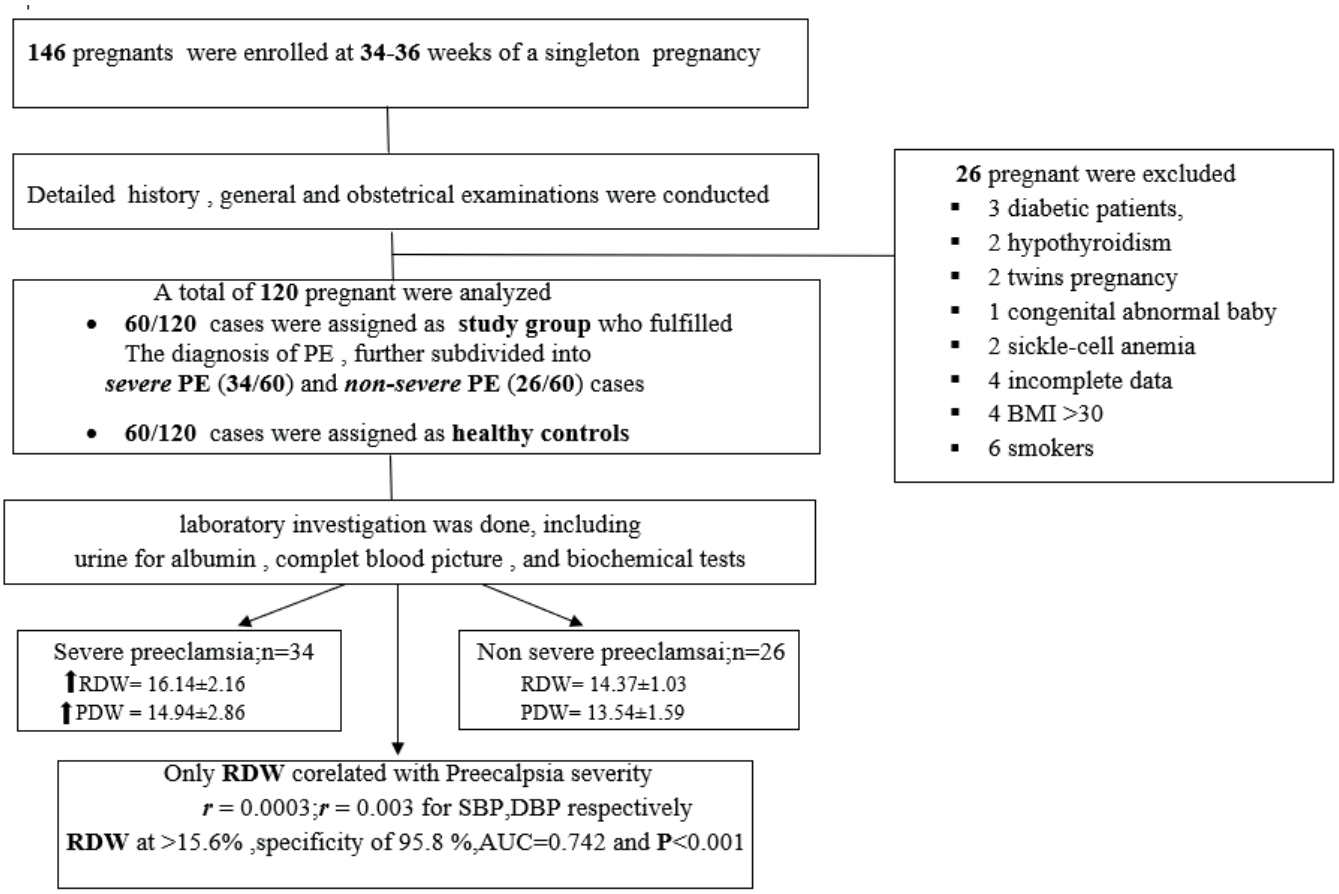

Figure 1. *Study flow chart with main results highlighted.*

5% deviation from the population, it was estimated to be 60 patients as a case group [15] with reasonable controls.

Statistical analysis

Data have been expressed as means ± standard deviation, and a student t-test was used to analyse the difference between the two groups. One-way ANOVA tested the difference in haematological parameters pre-eclampsia sub-groups, between severe *vs* non-severe PE cases. Pearson correlation assessed the strength of association between RDW, PDW, and MPV as an independent variable against systolic and diastolic blood pressure in PE sub-groups to estimate their relation to the degree of PE severity.
The ROC (receiver operator characteristic) Curve determined the cut-off value for red cell distribution width that distinguished severe from non-severe PE cases with its respective sensitivity, specificity, and AUC. P-value was significant when less than 0.05.

RESULTS

The analysis included 120 pregnant grouped into two groups PE cases and healthy controls. The maternal age (26.43 ± 7.10 *vs* 29.03 ± 4.97) years and BMI (28.4 ± 2.13 *vs* 27.7 ± 3.99) Kg/m^2 was statistically insignificant among the two, with P-value of 0.106 and 0.57, respectively.
The clinical and biochemical parameters of the studied groups are clarified in **Table 1**; the systolic, diastolic blood pressure, blood urea, aspartate aminotransferase, and protein urea were significantly higher in PE cases *versus* healthy controls. In contrast, maternal age, gestational age, serum creatinine, total bilirubin, and alanine aminotransferase showed non-significant differences between the two groups.
The haematological variables of the studied groups showed a significantly raised RDW in PE cases *versus* control (15.21 ± 2.08% *versus* 13.86 ± 1.07%), P-value of 0.003. Likewise, mean platelet volume MPV was higher in PE cases than control group (10.71 ± 1.17 *versus* 9.87 ± 0.96) fL, P-value = 0.004. Other haematological variables were statistically insignificant, namely RBC, Haematocrit HCT, haemoglobin, platelet counts, and platelet distribution width PDW. These results are clarified in **Table 2.**
Table 3 highlighted subgroups analysis of PE cases based on PE severity; it was shown that out of 60 PE cases, 26/60 were diagnosed with non-severe PE, and 34/60 were diagnosed with severe PE. A significant difference was found in the RBC, RDW, and PDW with P-values of 0.000, 0.001, and 0.037, respectively, while MPV failed to have a statistical value with p > 2.255.
In **Table 4**, Pearson correlation was constructed to highlight the strength of association of blood

Table 1. *The clinical and biochemical parameters for pre-eclampsia cases and healthy controls.*

Parameter	Gestation weeks	Systolic BP (mmHg)	Diastolic BP (mmHg)	ALT (U/L)	AST (U/L)	Blood Urea (mg/dl)	S.Creatinine (mg/dl)	T.bilirubin (mg/dl)	Albumin in urine (mg/dl)
Study group (n = 60)	34.13 ± 2.6	163 ± 7.85	105 ± 9.59	19.20 ± 8.30	23.03 ± 5.25	23.15 ± 8.98	0.64 ± 0.16	0.37 ± 0.28	372.31 ± 16
Control group (n = 60)	35.31 ± 1.9	115 ± 5.9	80 ± 6.17	16.07 ± 5.44	18.88 ± 7.21	18.19 ± 7.48	0.59 ± 0.11	0.34 ± 0.16	189.26 ± 72.7
Significance	0.56	**< 0.01***	**< 0.01***	0.091	**0.014***	**0.024***	0.19	0.63	**0.002***

*Significant at 0.05; BP: Blood pressure; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase. S.Creatinine: serum creatinine; T.bilirubin: total bilirubin.

Table 2. *The study's hematological parameters for pre-eclampsia cases and healthy controls.*

Parameter	RBC (10^6/UL)	HCT (%)	HB (g/dl)	RDW (%)	Platelets (103/UL)	MPV (fL)	PDW (fL)
Study group (n = 60)	4.41 ± 0.48	35.66 ± 3.92	11.79 ± 1.42	15.21 ± 2.08	223.90 ± 93.63	10.71 ± 1.17	14.68 ± 3.02
Control group (n = 60)	4.22 ± 0.48	35.15 ± 2.67	12.01 ± 1.13	13.86 ± 1.07	248.40 ± 52.55	9.87 ± 0.96	13.05 ± 2.12
Significance	0.059	0.56	0.51	**0.003***	0.216	**0.004***	0.19

*Significant at 0.05; all data are presented as means ± standard deviations (M ± SD); RBC: Red blood cells; HCT: Hematocrit; HB: Hemoglobin; RDW: Red cell distribution width; MPV: Mean platelet volume; PDW: Platelet distribution width.

Table 3. *ANOVA sub-groups analysis for the study's hematological parameters for severe (n = 34/60) and non-severe (n = 26/60) pre-eclampsia cases.*

Parameter	RBC (106/UL)	HCT (%)	HB (g/dl)	RDW (%)	Platelets (103/UL)	MPV (fL)	PDW (fL)
Severe PE cases (n = 34)	4.41 ± 0.48	35.66 ± 3.92	11.79 ± 1.42	15.21 ± 2.08	223.90 ± 93.63	10.71 ± 1.17	14.68 ± 3.02
Non-sever PE cases (n = 26)	4.22 ± 0.48	35.15 ± 2.67	12.01 ± 1.13	13.86 ± 1.07	248.40 ± 52.55	9.87 ± 0.96	13.05 ± 2.12
Significance	0.059	0.56	0.51	**0.003***	0.216	**0.004***	0.19

*Significant at 0.05; all data are presented as means ± standard deviations (M ± SD); RBC: Red blood cells; HCT: Hematocrit; HB: Hemoglobin; RDW: Red cell distribution width; MPV: Mean platelet volume; PDW: Platelet distribution width.

Table 4. *Pearson correlation coefficient showing the correlation between RDW, MPV and PDW as an independent variable with systolic and diastolic blood pressure taken as dependent variables among non-severe (26/60) and severe (34/60) PE cases.*

Maternal RDW	Correlation Coefficient (r)	Significance
Systolic BP (mmHg)	0.47	**0.0003***
Diastolic BP (mmHg)	0.399	**0.003***
Maternal MPV	**Correlation Coefficient (r)**	**P-value**
Systolic BP (mmHg)	0.099	0.52
Diastolic BP (mmHg)	0.007	0.962
Maternal PDW	**Correlation Coefficient (r)**	**P -value**
Systolic BP (mmHg)	0.168	0.23
Diastolic BP (mmHg)	0.185	0.181

BP: blood pressure; RDW: Red cell distribution width; MPV: Mean platelet volume; PDW: Platelet distribution width; *Significant at 0.05.

parameters to the severity of late-onset PE; only RDW was correlated with systolic BP: r = 0.47, p = 0.0003, and diastolic BP: r = 0.399, p = 0.003, both PDW and MPV were statistically insignificant.

Figure 2 clarifies the diagnostic value of RDW in determining the degree of severity of PE among affected women. The RDW cut-offs value (> 15.6%) showed 56.7% sensitivity, 95.8% specificity, respectively, in distinguishing non-severe from severe PE cases with a reliable AUC of 0.742.

DISCUSSION

The RDW and MPV were significantly higher in PE cases than in healthy controls. PDW and RDW were significantly higher in subgroups analysis of PE cases, and only RDW was correlated to PE severity. The RDW cut-off value linked with PE severity was > 15.6, associated with good sensitivity and specificity. The AUC was 0.7, implying a strong predicting marker.

Pre-eclampsia represents one of the critical causes of perinatal morbidities and mortalities, with the termination of gestation as the definitive treatment. Thus, an accurate and feasible severity-assessment strategy will reduce the disease burden, which can be accomplished by early preventive strategies, close anti-natal surveillance, and prophylactic interventions. Currently, the combination of anamnestic, anthropometric, biophysical, and maternal biochemical variables is the most recommended screening method [16].

Yücel *et al.'s* study investigated the value of MPV in identifying the severity of pre-eclampsia, and in concordance with our results, MPV levels were considerably higher in individuals with PE than in controls [17].

MPV was heavily examined in PE cases; some linked them to PE onset while others associated them with PE severity [18, 19]. Another study looked into MPV's role in severe PE as a predictor for growth-retarded infants. Both MPV and PDW were strongly correlated with Doppler indices. However, PDW and not MPV predicted growth restriction with an odds ratio of 16, (95%CI 161.8-143.12), P-value = 0.01 [4].

Some researchers discussed that PDW is a more sensitive marker for PE severity than MPV [20].

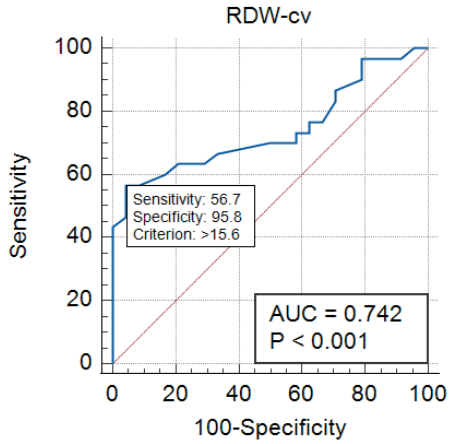

Figure 2. *The ROC curve estimated the RDW cutoff value that distinguishes severe vs non-severe PE cases with the highest sensitivity and specificity.*

Table 5. *Highlighting the summary of findings and conclusion of the study.*

Parameter	Groups	t-test	P-value	Pearson Correlation for SBP andDBP	P-value	ROC
Red distribution width	Severe PE	15.21 ± 2.08	**0.003***	0.47	**0.0003***	At > 15.6% RDW had 95% specificity for severe PE
	Non severe PE	13.86 ± 1.07		0.399	**0.003***	
Platelets distribution width	Severe PE	14.68 ± 3.02	0.19	0.168	0.23	-
	Non severe PE	13.05 ± 2.12		0.185	0.181	
Mean platelet volume	Severe PE	10.71 ± 1.17	**0.004***	0.099	0.52	-
	Non severe PE	9.87 ± 0.96		0.007	0.962	
Conclusion	Only the RDW constantly stayed significant in t- test and correlation analysis. In addition to its good accuracy in ROC in distinguishing the severity of PE with p < 0.001and reliable AUC (0.742)					

PE: preeclampsia; SBP: systolic blood pressure; DBP: diastolic blood pressure; * Indicate statistically significant.

The platelets undergo consumption once pre-eclampsia begins, and their number decline in response: the bone marrow will produce newer platelets to replace them. However, newer platelets tend to be bigger, which is why platelet indices are altered in PE patients [4, 20, 21].

In good agreement with our results, Kurt *et al*. confirmed that RDW distinguished pre-eclampsia severity among subgroups with and without PE; their study linked inflammatory parameters (total WBC, RDW, and C-reactive protein) in two research subgroups with and without PE [22].

Conversely, Yücel *et al*. and Gogoi *et al*. discussed significantly higher RDW in severe PE patients; they recommended it as a predictor marker for PE onset and did not link RDW to severity owing to the disparity in the number of severe and non-severe cases, which may have hander their results in Yücel *et al*. and small sized sample in Gogoi *et al*. study [17, 18].

Interestingly, Abdullahi's study had contradicting outcomes: RDW values were not linked with the onset nor severity of pre-eclampsia [23].

The link between RDW and the risk of having hypertension was explored by Seo *et al*. outside the pregnancy context. They recruited 124,260 healthy participants (both genders) in a retrospective cohort model and tracked them for eleven years. Incorporating RDW in the prediction equation improved the 95 percent confidence interval, p < 0.001. Furthermore, RDW had a strong and independent correlation with the development of hypertension [24].

The particular mechanism underlying a high RDW level in PE is not yet entirely known. However, it may be a reflection of increased inflammation [22]. Inflammatory cytokines may disrupt iron metabolism, hence shortening the lifespan of red blood cells and raising RDW values [25]. The increased RDW with other inflammatory indicators, such as C-reactive protein, is in good agreement with our hypothesis [26].

Oxidative stress, on the other hand, may have a role in anisocytosis and elevated RDW [27]. Both inflammatory process and oxidative stress are characteristics of pre-eclampsia, which may explain the higher levels of RDW in severe pre-eclampsia [1, 2, 4].

Riise *et al*. have discussed the risk ratio for maternal cardiovascular diseases (CVD) after premature PE to be raised five-fold; conversely, the risk is ten folds higher should PE occur before 34 weeks [28]. The real challenge in obstetric medicine is to find a biomarker, or even better, a panel of biomarkers, for an early diagnosis of pre-eclampsia onset and severity aiming to mitigate adverse foeto-maternal outcomes, not to mention reducing the prospective maternal risk of CVD [29, 30].

Platelets indices (MPV and PDW) are already validated markers of PE, and the RDW has outstood them both, showing a significantly higher value in PE women; RDW constantly stayed significant in sub-groups and correlation analysis. In addition to its good accuracy in distinguishing the severity of PE with good sensitivity and specificity, which makes RDW is a reliable marker for assessing the severity of late-onset PE.

Study limitation late-onset PE is suggested to be dependent on maternal risk factors [3, 31]; the current study did not take into account the foetus's gender (male sex increases late onset PE risk) or maternal ethnicity; our community is a mixture of more than one ethnicity which was not addressed in sampling. Another limitation is being a sin-

gle-centre study which may decrease the sample population's diversity and range. Since our hospital is a tertiary referral centre, it receives hundreds of cases alongside referral cases, so we think that patient diversity was accomplished. Lastly, the study design is another limitation: being observational rather than interventional in addition to being un-useful in studying rare diseases [32].

Study strengths

None of the earlier studies scored such reasonable specificity with RDW or other blood parameters in the evaluation of PE severity; in fact, many inconsistencies exist in the literature. A possible explanation is that these studies recruited participants of different gestational ages and inclusion criteria. In addition, they did not consider factors that influence RDW estimation, including anaemia's state, serum ferritin, and iron, which could explain the disparity in results [33-35].
The current study has endorsed strict inclusion criteria and careful sampling since it's a single-centre study.

CONCLUSIONS

The study concludes that RDW is correlated with PE severity with good specificity and sensitivity. It preceded both MPV and PDW with an area under the curve of 0.7, indicating its reliability. RDW is a simple, inexpensive test readily available in antenatal care services which permits early diagnosis, focused treatment, vigorous monitoring, and possible preventive measures for improving pregnancies outcome.

COMPLIANCE WITH ETHICAL STANDARDS

Authors contribution

W.N.: Study design, conceptualization, writing – original draft, writing – review & editing. Z.A.H.: Literature review. A.F.S.: Data collection, literature review. B.H.H.: writing – original draft, statistical analysis.

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None.

Study registration

N/A.

Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

The ethical committee of Mustansiriyah University/College of Medicine approved the study (IRB/146 on the 23rd of November 2020). The study followed the Helsinki declaration, and all study methods were done under the Helsinki tent and comparable medical standards.

Informed consent

All pregnant women in the current study gave informed consent prior to enrolment.

Data sharing

Data are available under reasonable request to the corresponding author.

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