

***Original Research Article***

**PREDICTABILITY OF PRE-ECLAMPSIA WITH HAEMATOLOGICAL PARAMETERS; A RETROSPECTIVE CROSS-SECTIONAL STUDY IN A TEACHING HOSPITAL, GHANA**

**Running Title:** Predictability of pre-eclampsia with haematological parameters

**Abstract**

**Aim:**To assess the predictive values of neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and mean platelet volume (MPV) in pre-eclamptic patients.

**Study Design:** Retrospective cross-sectional study

**Place and Duration of Study:** Obstetrics and Gynecology unit of Tamale Teaching Hospital, Tamale, Ghana from January to December, 2021.

**Methodology:** The study recruited 161 pregnant women (79 pre-eclamptic pregnant women and 81 apparently healthy pregnant women as controls). Full blood count parameters were assessed using fully automated haematology analyzer. Neutrophil/lymphocyte ratio, and platelet/lymphocyte ratio were calculated. Data analysis was done with SPSS version 22.0 and  $P < 0.05$  was considered statistically significant.

**Results:** Pregnant women with PE had lower parity [1 (0-3) vs 2 (0-3),  $P < .001$ ] and gestational ages in [35 (31-38) vs 37 (34-39) weeks,  $P < .001$ ] than their counterparts without PE. Haemoglobin (Hb), red blood cells (RBC), haematocrit (HCT), absolute monocyte and MPV were significantly higher in the PE group compared to the controls [Hb: 10.70(9.60-11.90) vs 10.10 (8.88-11.10) g/dl,  $P = .007$ ; RBC: 4.13 (3.64-4.53) vs 3.83 (3.47-4.18)  $\times 10^{12}/L$ ,  $P = .003$ ; HCT: 32.70 (29.30-36.80) vs 30.90 (27.57-33.92) %,  $P = .01$ ; Abs. Monocyte: 0.52 (0.34-0.68)

Comment [WK1]: 160?

vs 0.37 (0.23-0.54)  $\times 10^9/L$ ,  $P=.001$ ; MPV: 7.10 (6.80-7.60) vs 6.90 (6.47-7.32)fL,  $P=.02$ ]. MPV significantly predicted PE (AUC: 0.609,  $P<.02$ ) in pregnancy than NLR and PLR.

**Conclusion:** Lower parity and gestational ages are significantly associated with pre-eclampsia. Hb, RBC, HCT, absolute monocyte count and MPV were higher in pre-eclamptic pregnant women. MPV was a better marker in predicting PE. MPV is an essential marker for predicting asymptomatic PE in pregnancy.

**Keywords:** Haematological profile, Predictability, Pre-eclampsia, NLR, PLR, MPV

### **Introduction**

Pre-eclampsia (PE) is a multi-organ condition that arises after 20 weeks' gestation and is characterized by high blood pressure (BP  $>140/90$ mmHg) and proteinuria. It is amongst the most prevalent pregnancy problems, involving 3–5% of all expectant mothers and common cause of maternal and perinatal mortality[1, 2]. PE accounts for 12% of all maternal deaths worldwide,<sup>1</sup> but its contribution to fetomaternal morbidity and mortality is worsened in developing countries, with 10% rate of complication compared to the global complication rate of 2–8%[3, 4]. The prevalence of PE differs greatly globally, with its occurrence estimated to be seven times higher in developing countries, constituting 2.8% of live births as compared to 0.4% in developed countries[5].

The state of PE in Ghana may be worse as the reported prevalence of the condition is between 6.55% to 7.03%[6]. There exists spectrum of predisposing factors that contribute to the risk of developing PE. Owiredu et al.,[7] confirmed that women who are obese, having gestational diabetes, multifetal pregnancy, a family record of PE, primigravida, and pregnancy at an advanced age of 40 and above or a young age of 18 and below are at higher risk of developing

pre-eclampsia. Also, pre-existing medical disorders such as women with persistent high blood pressure, are at a higher risk factors of developing PE in pregnancy[7].

Although the etiology and pathogenesis of PE presently remain unclear[8], pre-eclampsia may be related to a defective placental growth due to improper spiral artery remodeling and poor trophoblast invasion/differentiation. This results in a poor perfusion leading to ischaemia, triggering the production of cytokines like soluble fms-like tyrosine kinase-1 (sFlt-1) and vascular endothelial growth factor (VEGF), which cause systemic endothelial malfunction as well as the disease's systemic consequences[9, 10]. Approximately 5-7% PE related pregnancy complications usually results from a diffused endothelial cell dysfunction, and this is associated with systemic inflammatory response in the mother[11]. The systemic changes caused by PE may affect hematological parameters during pregnancy. Recent studies have proposed the use of systemic inflammatory markers such as Neutrophil to Lymphocyte Ratio (NPR), Platelet to Lymphocyte Ratio (PLR), Red Cell Distribution Width (RDW), Mean Platelet Volume (MPV) and Plateletcrit (PCT) to predict and/or diagnose various diseases including ischaemic heart disease, and systemic inflammatory diseases such as pre-eclampsia[11, 12].

Few studies have investigated the nature of the hematological parameters in patients with PE, and have reported conflicting findings[12-16]. Also, almost all of the studies done so far singularly assessed individual ratio at a point in time, and did not consider combining all the ratios from the hematological parameters to predict PE in pregnancy. Again, to the best of our knowledge, no study has ever assessed the predictive and/or diagnostic values of the above hematological markers for PE in the Northern part of Ghana.

Therefore, this study was designed to assess the predictive values of NLR, PLR and MPV for pre-eclampsia in pregnancy in Tamale.

## **Materials and Method**

### **Study Site & Study Design**

This retrospective cross-sectional study was carried out at the Pre- and Post-Natal Care Units of the Obstetrics and Gynecology Department of the Tamale Teaching Hospital (TTH) from January to December, 2021. TTH is the main referral hospital to the inhabitants of the Northern, the Upper East, the Upper West, Savannah, and North East Regions of Ghana. The essential units in the Obstetrics and Gynecology Department of the hospital include the Pre- and Post-Natal units where antenatal, delivery, and post-natal care are given to women during and after pregnancy. Tamale, being the capital of the Northern region of Ghana has a total estimated land size of 646.90180sqkm, with population of about 233,252. Geographically, Tamale Metropolis lies between latitude 9°16 and 9°34 North and longitudes 0° 36 and 0° 57 West [17].

### **Study Population and Data Collection**

A total of 161 pregnant women attending TTH were selected for the study. Pregnant women diagnosed of pre-eclampsia at gestational age of 20 weeks and above were recruited into the study as cases. Pregnant women without PE and of gestational ages equal to or above 20 weeks who visited the Pre- or Post-Natal Units of the Tamale Teaching Hospital were selected as controls. Data on the participants were collected from the hospital's records. Pregnant women with history of chronic hypertension, renal disorders, haematological disorders prior to pregnancy and other known abnormalities were excluded. Also, pregnant women who were on any medication that may influence the results of complete blood count were excluded from the

study. The study again excluded participants whose data were not complete from the hospital's register.

### **Diagnostic Criteria**

Diagnosis of Pre-eclampsia was based on American College of Obstetricians and Gynecologists (ACOG) criteria which is described as new-onset high blood pressure (systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg) and new-onset proteinuria in a formerly normotensive woman after 20 weeks of pregnancy. It also includes the presence of proteinuria which is described as a urine protein/creatinine ratio of 0.3 mg/dL or 300 mg of protein in 24 hours; however, in its absence, the urine dipstick should be utilized[18].

### **Blood Pressure Measurements(using Krotkoff 1 and 5)**

Blood pressure was measured by trained personnel using a mercury sphygmomanometer and a stethoscope. Measurements were taken from the left upper arm after participants sat >5 min in harmony with the recommendations of the American Heart Association. Duplicate measurements were taken with a 5-minute rest interval between measurements and the average value was recorded in mmHg. Hypertension was established when the systolic blood pressure (SBP) as >140 mm Hg and diastolic blood pressure (DBP) >90 mm Hg[19].

### **Laboratory Investigations**

About 5 ml of whole blood was collected from each participant and dispensed into Ethylenediaminetetraacetic acid (EDTA) tube and mixed gently. Complete blood count was performed on participant's blood using URIT 5250 5 parts Hematology analyzer, China, to estimate RBC count, Hb concentration, mean cell volume, mean cell Hb, mean cell Hb concentration and red cell distribution width at the Hematology Laboratory unit of TTH. Dipstick

proteinuria using reagent strips from Yercon Diagnostic Co.Ltd, P.R. of China, were also performed on fresh urine samples collected from the participants.

### **Data Analysis**

The data obtained was captured with Microsoft Excel and analyzed using IBM Statistical Package for the Social Sciences (SPSS) version 23. The data were presented in tables and figures. Normality test for the distribution of the data was performed using Kolmogorov-Smirnov test. The numerical data were presented as medians (25<sup>th</sup>-75<sup>th</sup> percentiles). Mann-Whitney U-Test was used to compare bivariate numerical data and correlations were performed by the Spearman rank correlation test. ROC analysis was performed to determine the sensitivity, specificity and area under the curve (AUC) of the variables. Statistical significance was set at  $p < 0.05$ .

### **Results**

#### **Demographics and Obstetric Parameters of the Study Participants Stratified by the Presence or Absence of Pre-eclampsia**

A total of 161 participants were involved in this study; comprising 79 (49%) pre-eclamptic pregnant women and 81(51%) healthy pregnant women without pre-eclampsia. There was no statistical difference between the median ages of the pre-eclamptic pregnant women and the controls [31 (26-34) vs 29 (24-33),  $P = .13$ ]. The median parity and gestational ages were significantly lower in the pre-eclamptic pregnant women compared with the apparently healthy pregnant women without PE: [Parity: 1 (0-3) vs 2 (0-3),  $P < .001$ ; Gestational age: 35 (31-38) vs 37 (34-39),  $P < .001$ ], as shown in Table 1.

**Table 1: Demographics and Obstetric Parameters of the Study Participants Stratified by the Presence or Absence of Pre-eclampsia**

Variables	Pregnant Women with	Pregnant Women without	P-value
	Pre-eclampsia (n=79)	Pre-eclampsia (n=82)	
Age (years)	31 (26-34)	29 (24-33)	.13
Parity	1 (0-3)	2 (0-3)	<.001*
Gestational age (weeks)	35 (31-38)	37 (34-39)	<.001*

*Data are presented in medians (25<sup>th</sup>-75<sup>th</sup> percentiles). Mann-Whitney U test was used to generate the data and statistical significance was set at  $P<.05$ . (\*) represent statistically significant parameters.*

**Complete Blood Count Parameters of the Study Participants Stratified by the Presence or Absence of Pre- eclampsia**

Table 2 shows the results of complete blood count parameters between the two groups. Hemoglobin (Hb), Red Blood Cell Count (RBC), Hematocrit (HCT), Absolute Monocytes and Mean Platelet Volume (MPV) were all significantly higher in pre-eclamptic women compared to pregnant women without pre-eclampsia [Hb in g/dl: 10.70 (9.60-11.90) vs 10.10 (8.88-11.10),  $P=0.007$ ; RBC: 4.13 (3.64-4.53) vs 3.83 (3.47-4.18)  $\times 10^{12}/L$ ,  $P=0.003$ ; HCT: 32.70 (29.30-36.80) vs 30.90 (27.57-33.92) %,  $P=0.01$ ; Abs. Monocyte: 0.52 (0.34-0.68) vs 0.37 (0.23-0.54)  $\times 10^9/L$ ,  $P=0.001$ ; MPV: 7.10 (6.80-7.60) vs 6.90 (6.47-7.32) fL,  $P=0.02$ ]. MCV, MCH, MCHC, TWBC,

RDW, Platelet, PCT, PDW, Absolute neutrophil, lymphocyte, eosinophil and basophil did not differ between pregnant women with PE and those without the condition (Table 2).

**Table 2: Complete Blood Count Parameters of the Study Participants Stratified by the Presence or Absence of Pre-eclampsia**

Complete Blood Count Parameters	Pregnant Women with Pre-eclampsia (n=79)	Pregnant Women without Pre-eclampsia (n=82)	P-value
Hb (g/dl)	10.70 (9.60-11.90)	10.10 (8.88-11.10)	*.007
RBC ( $\times 10^{12}/L$ )	4.13 (3.64-4.53)	3.83 (3.47-4.18)	*.003
HCT (%)	32.70 (29.30-36.80)	30.90 (27.57-33.92)	*.01
MCV (fL)	82.20 (75.50-86.80)	81.65 (76.8-85.4)	.81
MCH (pg)	27.00 (24.10-28.40)	26.05 (24.52-28.40)	.81
MCHC (g/dl)	32.80 (31.60-34.00)	32.20 (31.18-33.32)	.22
RDW-CV (%)	10.20 (9.30-11.50)	10.30 (9.27-11.30)	.95
TWBC ( $\times 10^9/L$ )	8.28 (6.70-10.38)	7.71 (5.84-10.67)	.37
Abs. Neut. ( $\times 10^9/L$ )	4.87 (3.67-6.67)	4.47 (2.97-6.49)	.48
Abs. Lymph. ( $\times 10^9/L$ )	2.39 (1.60-3.20)	2.05 (1.61-3.20)	.67
Abs. Mono. ( $\times 10^9/L$ )	0.52 (0.34-0.68)	0.37 (0.23-0.54)	*.001
Abs. Eos. ( $\times 10^9/L$ )	0.09 (0.05-0.14)	0.08 (0.04-0.11)	.28
Abs. Baso ( $\times 10^9/L$ )	0.01 (0.01-0.02)	0.01 (0.01-0.02)	.12
Platelet ( $\times 10^9/L$ )	220.00 (154.00-277.00)	202.50 (161.8-258.3)	.90
MPV (fL)	7.10 (6.80-7.60)	6.90 (6.47-7.32)	*.02

PCT (%)	0.15 (0.11-0.19)	0.14 (0.11-0.18)	.51
PDW (%)	8.60 (7.90-9.70)	8.30 (7.60-9.47)	.14

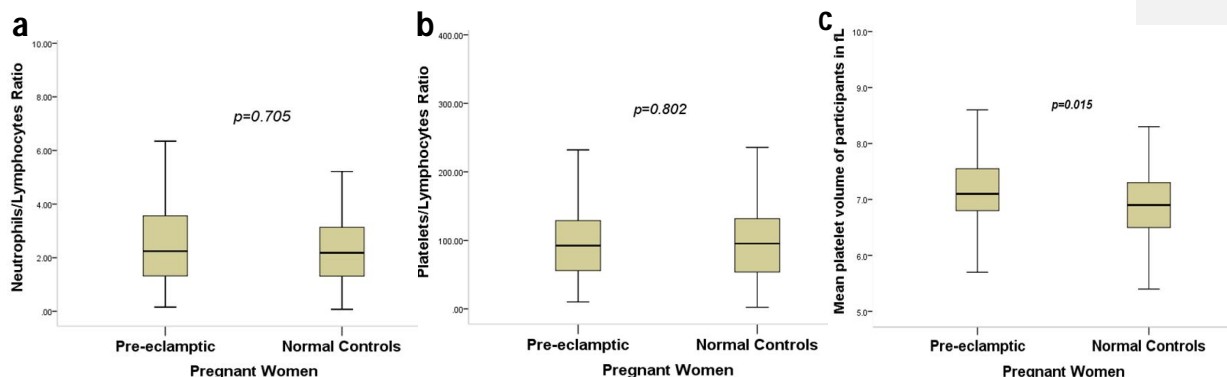
*Hb= Hemoglobin; RBC= Red Blood Cell; HCT= Hematocrit; MCV= Mean Cell Volume; MCH= Mean Cell Hemoglobin; MCHC= Mean Cell Hemoglobin Concentration; RDW-CV= Red Cell Distribution Width- Coefficient of Variation; g/dl= grams per deciliter; fL= Femtolitre; pg=Pico gram; L=Litre. Data are presented in medians (25<sup>th</sup>-75<sup>th</sup>) Percentiles, Data were compared using Mann- Whitney U test and statistical significance was set at  $P<.05$ . (\*) represent statistically significant parameters*

**Comparison of NLR, PLR and MPV between Pregnant Women with Pre-eclampsia and those without Pre-eclampsia**

Figure 1 shows the median NLA (1A), PLR (1B) and MPV (1C) of pregnant women with pre-eclampsia compared with the healthy pregnant women without pre-eclampsia. The medians were compared using Mann-Whitney U Test. The median NLR among the pre-eclamptic group was higher, 2.24 (1.29-3.35) compared with the healthy pregnant women without pre-eclampsia, 2.18 (1.31-3.13), but this was not significant statistically ( $P= .71$ ).

When the median PLR of pregnant women with PE was compared with the median PLR of the

**Figure 1: Comparison of [a] NLR, [b] PLR, and [c] MPV between Pregnant Women with Pre-eclampsia and those without Pre-eclampsia. Statistical significance was set at  $P<.05$**



pregnant women without PE, no significant difference was observed: [92.28 (54.63-130.55) vs 95.32 (53.73-136.29),  $P= .80$ ]. However, the MPV among the pregnant women with pre-eclampsia was relatively higher [7.10 (6.80-7.60)] compared with the apparently healthy pregnant women without pre-eclampsia [6.90 (6.47-7.32)] and this was statistically significant ( $P= .02$ ) as shown in Figure 1.

### **Predictive Values of NLR, PLR and MPV for Pre-eclampsia in Pregnancy**

Table 3 shows a multivariate analysis used in determining the diagnostic values of NLR, PLR and MPV in pregnant women with pre-eclampsia. With the optimum cut-offs points for NLR, PLR and MPV at 3.08, 126.80 and 10.40 respectively, the sensitivity and specificity of the markers were: NLR (Sensitivity:55.3%, Specificity: 53.5%, 95%CI: 0.4333-0.612,  $P= .62$ ), PLR: (Sensitivity:50.0%, Specificity: 51.3%, 95%CI: 0.396-0.575,  $P= .75$ ), and MPV: (Sensitivity: 44.8%, Specificity: 40%, 95%CI: 0.522-0.696,  $P= .02$ ). MPV showed as the better predictive marker for pre-eclampsia in pregnancy (AUC=0.609,  $P= .02$ ) (Table 3).

**Table 3: Predictive Values of NLR, PLR and MPV for Pre-eclampsia in Pregnancy**

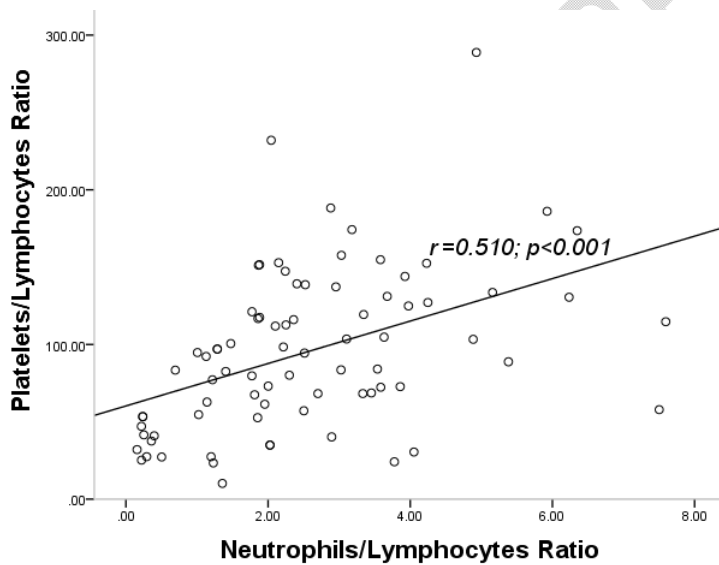
<b>Markers</b>	<b>Sensitivity</b>	<b>Specificity</b>	<b>Cut-off value</b>	<b>AUC</b>	<b>95% CI</b>	<b>P-value</b>
<b>NLR</b>	55.3	53.5	3.08	0.523	0.433-0.612	.62
<b>PLR</b>	50.0	51.3	126.8	0.486	0.396-0.575	.75
<b>MPV</b>	44.8	40.0	10.4	0.609	0.522-0.696	.02*

*NLR= Neutrophil to Lymphocyte Ratio; PLR= Platelet to Lymphocyte Ratio; MPV= Mean*

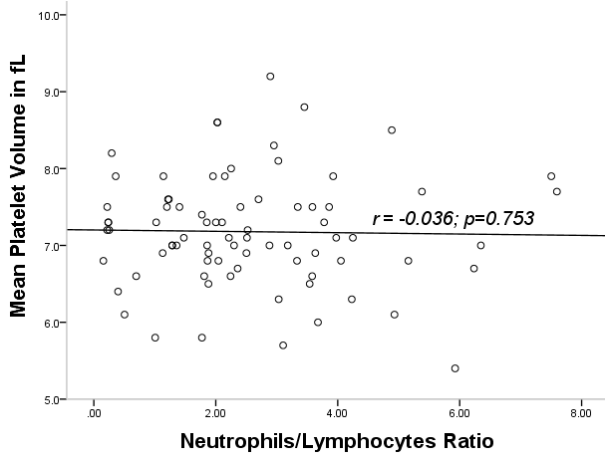
*Platelet Volume. 95% CI-95% Confidence Interval, AUC= Area Under Curve.*

### **Correlation between NLR and PLR, NLR and MPV, and PLR and MPV among the Pregnant Women with Pre-eclampsia**

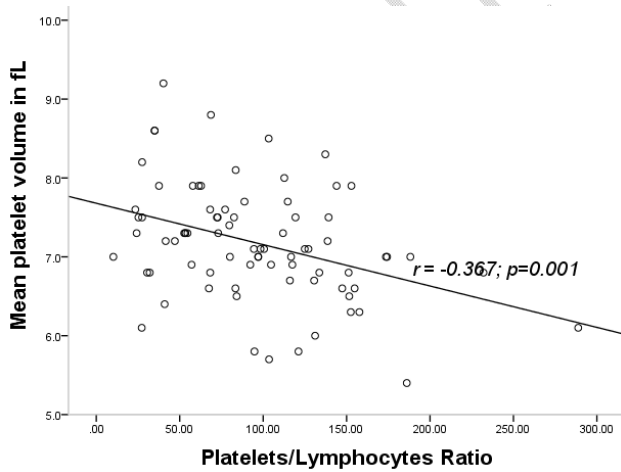
Spearman rank correlation was used to describe the correlation between NLR and PLR, NLR and MPV, and PLR and MPV in Figure 2A, 2B and 2C respectively. A moderate positive correlation between NLR and PLR was observed among the pregnant women with pre-eclampsia and this was statistically significant ( $r=0.510$ ,  $P<.001$ ) as shown in Figure 2A. As shown in Figure 2B, a very weak negative correlation existed between MPV and NLR among the pre-eclamptic pregnant women; however, this was not statistically significant ( $r= -0.036$ ,  $P= .75$ ). Also, a significant but weak negative correlation was found between PLR and MPV among the pre-eclamptic women ( $r= -0.367$ ,  $P= .001$ ) as shown in Figure 2C.



**Figure 2A: Correlation between Platelets/Lymphocytes Ratio and Neutrophil/Lymphocytes Ratio among the Pre-eclamptic Pregnant Women.**  $r=$  correlation coefficient and  $P<.05$  was considered statistically significant.



**Figure 2B: Correlation between Mean Platelet Volume and Neutrophil/Lymphocytes Ratio among the Pre-eclamptic Pregnant Women.**  $r$  = correlation coefficient, fL= Femtolitre and  $P < .05$  was considered statistically significant.



**Figure 2C: Correlation between Mean Platelet Volume and Platelets/Lymphocytes Ratio among the Pre-eclamptic Pregnant Women.**  $r$  = correlation coefficient, fL= Femtolitre and  $P < .05$  was considered statistically significant.

## Discussion

Pre-eclampsia (PE) is one of the significant contributors of feto-maternal morbidity and mortality globally, but the situation is pronounced especially in developing countries. Early diagnosis coupled with appropriate management may prevent the associated complications on both the mother and the fetus or newborn[20]. The diagnosis of PE is limited to hypertension (BP >140/90 mmHg) and proteinuria at 20 or more weeks of gestation[18]. This study aimed to assess the diagnostic values of full blood count parameters: NLR, PLR and MPV for the prediction and/or diagnosis of PE.

In this study, median parity and gestational ages were significantly lower in the pre-eclamptic pregnant women compared with the apparently healthy pregnant women without PE. The significant association between lower parity and pre-eclampsia observed in this study is in consonance with an earlier retrospective case-control study[21]. Pre-eclampsia is known to complicate nulliparous pregnancies in 25-30% of cases, and affects more primigravida women than multigravida women, therefore making the first pregnancy a significant risk factor[22]. Consequently, pre-eclampsia reduces the blood flow to the placenta, resulting in poor intrauterine growth and abnormally early birth[23]. Unfortunately, pre-eclampsia is currently treated only with birth[20]. Lower gestational age was identified to be significantly associated with pre-eclampsia in the current study, and this agrees with a retrospective study by Mannaerts et al.,[24]. Their study reported mean gestational age of  $32.94 \pm 4.02$  weeks in pre-eclamptic pregnant women compared with gestational age of  $38 \pm 3.29$  weeks in pregnant women without pre-eclampsia.

Again, advanced maternal age has been linked with the development of PE. A similar study by Owiredu et al.,[7] in Ghana indicated that the probability of getting PE rose considerably with

maternal age, from twice among women with ages 35-39 to almost thrice among women with ages between 40-44 when compared to women between the ages of 25-29. Women below 25 years were not at an increased risk of PE when compared to women between the ages of 25 and 29. However, the current study did not find any significant difference in the maternal ages of pregnant women with PE and those without PE. This finding from the present study is similar to the findings from the Çintesun et al., study[21] which did not detect any association between maternal age and pre-eclampsia. This variation may be related to the differences in geographical settings of the studies.

The pregnant women with pre-eclampsia in this study had significantly higher Hematocrit (HCT), Hemoglobin (Hb), Red blood cells (RBC) and absolute monocytes compared with their counterparts. The observed significantly increased HCT, Hb and RBC in the pregnant women with pre-eclampsia are comparable to a previous finding[25]. The Pritchard et al.,[25] study suggests that endothelial dysfunction, which is a common occurrence in PE, causes widespread leakage of fluid into the interstitial tissues, resulting in hemoconcentration. Again, regardless of the usual rise in intravascular volume during normal pregnancy, pre-eclamptic pregnant women experience serum protein loss and a rise in the permeability of capillary endothelium leading to a drop in the intravascular volume and increased tissue oedema[26]. Elevated HCT and Hb are thus seen as better indicators of PE, and a decrease in recurring hematocrit levels could improve clinical outcome[27]. The Walker [27] study appreciates the unique roles of the liver, lung and brain, especially in fluid distribution. Therefore, a malfunction in essential organs including the heart, liver, kidneys, etc which occur in PE, contribute to hemoconcentration leading to decreased plasma volume and increased RBC, HCT and Hb. However, contrary to our study, a

retrospective study in 2016 found significantly lower Hb in PE compared to pregnant women without PE[28].

Also, the current study revealed a significantly higher MPV in the pregnant women with PE compared to the control group of healthy pregnant women. Järemo et al.,[29] also demonstrated a higher MPV ( $9.8 \pm 0.7$  fL) in women with PE than in pregnant women without PE ( $8.8 \pm 1.2$  fL). Another study reported MPV increase in PE when comparing severe PE and normotensive pregnant women ( $9.6 \pm 1.1$  vs  $9.1 \pm 0.9$  fL)[30]. Similarly, a recent retrospective study reported significantly higher MPV ( $8.64$  fL  $\pm 1.17$ ) in the PE group compared to the control group with a mean MPV ( $8.06 \pm 0.87$  fL,  $p=0.006$ )[24]. Findings from a longitudinal study by Dundar et al.,[31] demonstrated that during normal pregnancy, MPV levels rise, but this rise is more prominent in women with pre-eclampsia. Again, Yücel and Ustun reported a significantly higher MPV value in the severe PE group,  $9.92$  fL ( $6.84$ - $16.61$  fL) compared to control group of  $8.60$  fL ( $5.18$ - $14.32$ )[11]. Thrombocyte activation and aggregation results in increased consumption of platelets and this is a common occurrence in PE[32]. This depletion of platelets in the peripheral blood triggers the bone marrow's compensatory mechanisms to compensate for the loss by synthesizing several new platelets. As the rise in platelet aggregation is counterbalanced by an increase in platelet synthesis, platelets of varying sizes are released into the circulation as compensatory mechanism to prevent bleeding and this causes the MPV to appear increased, especially in pregnancy[33]. Gladwin and Martin's study[34], showed that low oxygen levels in circulation stimulates both the synthesis and breakdown of platelets, resulting in an increase in MPV levels. MPV is indirectly proportional to platelet count in physiological conditions, which is associated with maintaining haemostasis and maintaining continuous platelet mass[35]. On the contrary, findings from the current study disagree with some previous studies. In the study by

Çintesun et al.,[21] MPV value was shown to be significantly higher in the control group compared to both mild and severe PE, nevertheless, no significant variation was discovered in mild and severe PE groups. Again, the aforementioned study presented no significant difference in platelet count and MPV values between PE group and control group. Other studies reported lower platelets and higher MPV in the PE group than in the control group[24-30]. The inconsistencies in the findings could be attributed to: pre-analytical factors such as; the expertise of the phlebotomist, phlebotomy method (with or without stasis), the correct filling of the tube with blood, the proper mixing of sample and the anticoagulant utilized for blood collection; centrifugation of the blood put into citrate anticoagulant could result in platelet activation, causing the presence of more active large platelets; difference in MPV value is reduced in platelet rich plasma as measured against whole blood.

This study did not find any significant difference in NLR values between PE group and the control group. This finding is in agreement with previous studies[11, 16, 21]. In contrast to findings from this study, a previous study comprising 107 pregnant women found NLR values to have been significantly increased in pre-eclamptic women than in their control group[36]. Similarly, a retrospective study involving pregnant women reported a significantly higher NLR values in the PE group than in the control group without PE[24]. Also, the present study did not observe any significant difference in the PLR values between the preeclamptic women and the control group, and this finding is consistent with previous studies[37, 38]. Surprisingly, the Kirbas et al.,[38] study stratified the PE subjects into severe and mild groups, where a significantly higher PLR was recorded among the former group. The discrepancies in their findings were attributed to the period and state of the pregnant women; as the evaluation was done in early months of pregnancy.

Furthermore, MPV was observed to be a better predictor of pre-eclampsia compared to NLR and PLR in this study. This finding is similar to a study by Dundar et al.,[31] where a sensitivity and specificity of 78% and 86%, respectively, for detecting pre-eclampsia using MPV at 24-28 weeks gestation were recorded. Another study by Yücel and Ustun also recorded similar finding in 2017[11]. The variation in the sensitivity and specificity may be related to the differences in cut-off values employed as well as the sample sizes used. The current study used MPV cut-off point of 10.4fL whilst the Dundar et al.,[31] and Yücel and Ustun[11] used cut-off points of 10.5fL and 8.04fL, respectively. The present study did not identify NLR and PLR as better inflammatory markers for predicting pre-eclampsia in pregnancy.

Again, the current study found a moderate negative correlation between MPV and PLR, and this is consistent with a previous study[24]. The Mannaerts et al.,[24] study realized changes in MPV, PLR, and platelet values between 20<sup>th</sup> and 30<sup>th</sup> weeks of gestation in pregnant women with PE; where they observed linear increment in MPV values with decreasing PLR. However, a significant moderate positive correlation was seen between NLR and PLR in this study. PE may exert excessive maternal vascular inflammatory response, and neutrophils play exceptional role in acute inflammation[39]. This study did not find any correlation between NLR and MPV in preeclampsia. The study was limited by our inability to assess other inflammatory markers.

### **Conclusion**

Lower parity and gestational ages are significantly associated with pre-eclampsia. Pregnant women with pre-eclampsia had significantly higher Hb, RBC, HCT, absolute monocytes and MPV. Also, MPV was observed to be a better predictive and/or diagnostic marker for pre-eclampsia. Again, a significant moderate positive correlation between NLR and PLR, and a weak negative correlation between PLR and MPV were observed among the pregnant women with

pre-eclampsia. The study provides useful basic information for clinical practice in detecting asymptomatic women at increased risk for pre-eclampsia. It is recommended that periodic assessment of haematological parameters, including MPV be done for pregnant women, and those with high levels be monitored closely for signs of pre-eclampsia.

### Consent

Due to the retrospective nature of the study, informed consent could not be obtained from the participants.

### Ethical Considerations

Ethical clearance for the study was obtained from the Department of Research and Development at Tamale Teaching Hospital (TTH/R&D/SR/164). Permission was also sought from the management of TTH.

### References

1. Roberts J and Cooper DW. Pathogenesis and genetics of pre-eclampsia. *The Lancet*. 2001; 357, 53-56.
2. Witlin A and Sibai B. Magnesium sulfate therapy in preeclampsia and eclampsia. *Obstet. Gynecol.* 1998; 92, 883–889.
3. Vata PK, Chauhan NM, Nallathambi A, et al. Assessment of prevalence of preeclampsia from Dilla region of Ethiopia. *BMC Res. Notes*. 2015; 8, 1–6.
4. Nakimuli A, Chazara O, Byamugisha J, et al. Pregnancy, parturition and preeclampsia in women of African ancestry. *Am. J. Obstet. Gynecol.* 2014; 210, 510–520.
5. WHO. *The World health report: 2005: make every mother and child count*. (World Health Organization, 2005).

Comment [WK2]: Doi numbers can be added to all references.

6. Obed SA and Patience A. Birth weight and ponderal index in pre-eclampsia: a comparative study. *Ghana Med. J.* 2006; 40, 8.
7. Owiredu W, Ahenkorah L, Turpin CA, et al. Putative risk factors of pregnancy-induced hypertension among Ghanaian pregnant women. *J. Med. Biomed. Sci.* 2012; 1, 62–76 (2012).
8. Hung TH., Skepper JN, Charnock-Jones DS, et al. Hypoxia-reoxygenation: a potent inducer of apoptotic changes in the human placenta and possible etiological factor in preeclampsia. *Circ. Res.* 2002; 90, 1274–1281.
9. McKeeman GC, Ardill JES, Caldwell CM, et al. Soluble vascular endothelial growth factor receptor-1 (sFlt-1) is increased throughout gestation in patients who have preeclampsia develop. *Am. J. Obstet. Gynecol.* 2004; 191, 1240–1246.
10. Widmer M, Villar J, Benigni A, et al. Mapping the theories of preeclampsia and the role of angiogenic factors: a systematic review. *Obstet. Gynecol.* 2007; 109, 168–180.
11. Yücel B and Ustun B. Neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, mean platelet volume, red cell distribution width and plateletcrit in preeclampsia. *Pregnancy Hypertens. An Int. J. Women's Cardiovasc. Heal.* 2017; 7, 29–32.
12. Vilchez G, Lagos M, Kumar K, et al. Is mean platelet volume a better biomarker in preeclampsia? *J. Obstet. Gynaecol. Res.* 2017; 43, 982–990.
13. Abor PA. Managing healthcare waste in Ghana: a comparative study of public and private hospitals. *Int. J. Health Care Qual. Assur.* 2013.
14. Han L, Liu X, Li H. Blood coagulation parameters and platelet indices: changes in normal and preeclamptic pregnancies and predictive values for preeclampsia. *PLoS One.* 2014; 9, e114488.

15. Kashanian M, Hajjarian M, Khatami E, et al. Evaluation of the value of the first and third trimester maternal mean platelet volume (MPV) for prediction of pre-eclampsia. *Pregnancy Hypertens. An Int. J. Women's Cardiovasc. Heal.* 2013; 3, 222–226.
16. Kurt RK, Aras Z, Silfeler D, et al. Relationship of red cell distribution width with the presence and severity of preeclampsia. *Clin. Appl. Thromb.* 2015; 21, 128–131.
17. Ghana Statistical Service. Tamale metropolis. *District Analytical Report: Tamale Metropolis.* 2014, Ghana.
18. American College of Obstetricians and Gynecologists. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' task force on hypertension in pregnancy. *Obstet. Gynecol.* 2013; 122, 1122–1131.
19. Nkansah C, Addai-Mensah O, Mensah K, et al. Plasminogen Activator Inhibitor-1 in poorly controlled vs well controlled Type-2 Diabetes Mellitus patients: A case-control study in a district hospital in Ghana. *PLoS ONE.* 2021; 16, e0250090.
20. Snyder S. Major changes in diagnosis and management of preeclampsia. *J. Midwifery Womens. Health.* 2014; 59, 596–605.
21. Çintesun E, Çintesun FNI, Ezveci H, et al. Systemic inflammatory response markers in preeclampsia. *J. Lab. Physicians.* 2018; 10, 316–319.
22. Serhal P and Craft I. Immune basis for pre-eclampsia evidence from oocyte recipients. *Lancet (London, England).* 1987; 2, 744.
23. Duley L. The global impact of pre-eclampsia and eclampsia. *Seminars in perinatology. Elsevier.* 2009; 33, 130–137.
24. Mannaerts D, Heyvaert S, De Cordt C, et al. Are neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and/or mean platelet volume (MPV) clinically useful as

- predictive parameters for preeclampsia? *J. Matern. Neonatal Med.* 2019; 32, 1412–1419.
25. Pritchard JA, Cunningham FG and Pritchard SA. The Parkland Memorial Hospital protocol for treatment of eclampsia: evaluation of 245 cases. *Am. J. Obstet. Gynecol.* 1984; 148, 951–963.
  26. Chappell L and Bewley S. Pre-eclamptic toxæmia: the role of uterine artery Doppler. *BJOG An Int. J. Obstet. Gynaecol.* 1998; 105, 379–382.
  27. Walker JJ. Pre-eclampsia. *Lancet.* 2000; 356, 1260–1265.
  28. Gezer C, Ekin A, Ertas IE, et al. High first-trimester neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios are indicators for early diagnosis of preeclampsia. *Ginekol. Pol.* 2016; 87, 431–435.
  29. Järemo P, Lindahl T, Lennmarken C, et al. The use of platelet density and volume measurements to estimate the severity of pre-eclampsia. *Eur. J. Clin. Invest.* 2000; 30, 1113–1118.
  30. Freitas LG, Alpoim PN, Komatsuzaki F, et al. Preeclampsia: are platelet count and indices useful for its prognostic? *Hematology* 2013; 18, 360–364.
  31. Dunder O, Yoruk P, Tutuncu L, et al. Longitudinal study of platelet size changes in gestation and predictive power of elevated MPV in development of pre-eclampsia. *Prenat. Diagnosis Publ. Affil. With Int. Soc. Prenat. Diagnosis* 2008; 28, 1052–1056.
  32. Piazzè J, Gioia S, Maranghi L, et al. Mean platelet and red blood cell volume measurements to estimate the severity of hypertension in pregnancy. *J. Perinat. Med.* 2006; 34 246–247. DOI 10.1515/JPM.2006.044. (2006).
  33. Stubbs TM, Lazarchick J, Van Dorsten JP, et al. Evidence of accelerated platelet production and consumption in nonthrombocytopenic preeclampsia. *Am. J. Obstet.*

*Gynecol.* 1986; 155, 263–265.

34. Gladwin AM and Martin JF. The control of megakaryocyte ploidy and platelet production: biology and pathology. *Int. J. Cell Cloning.* 1990; 8, 291–298.
35. Thompson CB and Jakubowski JA. The pathophysiology and clinical relevance of platelet heterogeneity. *Blood.* 1988; 72, 1-8.
36. Serin S, Avcı F, Ercan O, et al. Is neutrophil/lymphocyte ratio a useful marker to predict the severity of pre-eclampsia? *Pregnancy Hypertens. An Int. J. Women's Cardiovasc. Heal.* 2016; 6, 22–25.
37. Yavuzcan A, Caglar M, Ustun Y, et al. Mean platelet volume, neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in severe preeclampsia. *Ginekol. Pol.* 2014; 85 (3). DOI: 10.17772/gp/1713.
38. Kirbas A, Ersoy AO, Daglar K, et al. Prediction of preeclampsia by first trimester combined test and simple complete blood count parameters. *J. Clin. diagnostic Res.* 2015;9, QC20.
39. Ramma W, Buhimschi IA, Zhao G, et al. The elevation in circulating anti-angiogenic factors is independent of markers of neutrophil activation in preeclampsia. *Angiogenesis.* 2012; 15, 333–340.