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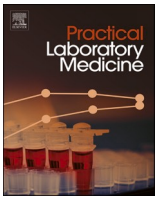

Hematological predictors of preeclampsia among pregnant women attending ante-natal clinic at Arba Minch General Hospital, South Ethiopia: A comparative cross-sectional study

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ABSTRACT

Background: Preeclampsia is a kind of pregnancy-related hypertension that affects 5.47 % of pregnancies in Ethiopia and 18.25 % of pregnant women who visit Arba Minch public health facilities for antenatal care. This study sought to identify hematological preeclampsia markers in pregnant women who received prenatal care at Arba Minch General Hospital.

Methodology: An institution-based comparative cross-sectional study was done from July 22 to October 30, 2021 at Arba Minch General Hospital. A total of 136 pregnant women were included in the study (46 with preeclampsia and 90 without preeclampsia). Epidata version 4.4. was used to enter data, and SPSS version 25.0 and Stata version17 were used for analysis. An independent sample *t*-test was used to examine the hematological parameter differences between study groups. Potential hematological markers were determined using receiver operating characteristic (ROC) analysis of the area under the curve (AUC). Statistical significance was defined if P value less than 0.05.

Results: A total of 136 pregnant women were studied. The complete blood count analysis showed that there were means differences in Red Cell Distribution (RDW) ($p < 0.036$), neutrophil-to-lymphocyte ratio (NLR) ($p < 0.016$) and relative lymphocyte count (Lymp%) ($p < 0.047$). The ROC analysis of the AUC for RDW, NLR and Lymp% resulted in 0.607, 0.609, 0.600 respectively.

Conclusion: RDW, NLR and Lymphocyte count could be potential candidate tools for the diagnosis and screening of preeclampsia. However, the robustness of the markers should be tested with prospective studies assessing changes present in each trimester.

1. Introduction

While motherhood is a wonderful and rewarding experience for many women, it is often fraught with sorrow, disease, and death. Approximately 15 % of pregnant women are likely to experience life-threatening complications during pregnancy, birth, or the

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postpartum period. These problems and sufferings are exacerbated by hypertensive disorders of pregnancy (HDP) [1,2].

A pregnant woman is considered hypertensive if her blood pressure is greater than or equal to 140/90 mmHg on two consecutive measurements at least 4 h apart [3]. HDP is a general term for increased blood pressure during pregnancy. It includes pregnancy induced hypertension (PIH) (hypertension without proteinuria), preeclampsia (hypertension with proteinuria) and eclampsia (pre-eclampsia with convulsions), gestational hypertension and chronic hypertension [1].

HDP is a global public health issue. It affects around 10 % of all pregnant women worldwide. Preeclampsia (PE) is a hypertension condition that has a significant influence on maternal and newborn health. It is a prominent cause of maternal and neonatal death and morbidity across the world. Pre-eclampsia is associated with placental anomalies that started early in pregnancy, followed by extensive inflammation and growing endothelial damage, yet the pathogenesis of the condition is still poorly understood [4].

PE and eclampsia were linked to greater rates of maternal death, perinatal mortality, and morbidity, as well as premature and small-for-gestational-age births, according to global research. When compared to women who do not have HDP, women with HDP are five times more likely to experience perinatal mortality. Every year, 76,000 mothers and 500,000 newborns die as a result of this condition across the world. PE is thought to be responsible for 40–60 % of maternal mortality in developing nations. Furthermore, compared to women in high-resource nations, women in low-resource countries are at a larger risk of getting PE [1,3].

It is well known that several maternal risk factors, including advanced maternal age, null-parity, prior history of PE, short and long inter-pregnancy intervals, use of assisted reproductive technologies, family history of PE, obesity, Afro-Caribbean and South Asian racial origin, co-morbid medical conditions, such as hyperglycemia in pregnancy, pre-existing chronic hypertension, renal disease and autoimmune diseases [3].

The prevalence of preeclampsia in developing countries ranges from 1.8 % to 16.7 % [5]. In Ethiopia pooled prevalence of pre-eclampsia/eclampsia accounts for 5.47 % (95 % CI = (3.71, 7.22) while it is about 18.25 % among pregnant women who attend antenatal care in Arba Minch public health facilities, which is higher than the global estimate and national prevalence [1].

The International Society for Study of Hypertension in Pregnancy (ISSHP) recommends that pregnant women with de novo hypertension should be investigated with laboratory tests measuring hemoglobin, platelet count, serum creatinine, liver enzymes, and serum uric acid to determine the presence of maternal organ dysfunction and the diagnosis of preeclampsia [6]. Whereas in Ethiopia, the prediction and diagnosis of PE mainly relays on the assessment of some risk factors and few diagnostic methods (blood pressure and proteinuria). Despite its high prevalence, the risk factors that have been identified lack accuracy in predicting its onset. And also, preventative therapies only moderately reduce a woman's risk of preeclampsia [7].

Therefore, being able to predict the risk of preeclampsia early in pregnancy with an effective, simple, and economic laboratory method is important to prevent complications and improve outcomes. Thus, the aim of this study was to identify hematological predictors of preeclampsia among pregnant women.

2. Methods and materials

2.1. Study setting

This comparative cross-sectional study was conducted in Arba Minch General Hospital (AMGH) which is a public hospital located in Arba Minch town, South Ethiopia. It has 200 in-patient bed capacity. It serves the population in the Gamo Zone and around. The Hospital accommodates more than 4000 pregnant women visits per year and more than 261 1st visits per month at the antenatal clinic (ANC). The study was conducted from July 22nd, 2021 to October 30th, 2021 at the antenatal clinic.

2.2. Study population and sample size

A formula of hypothesis testing for two population means was used to determine the initial sample size [8].

$$N = \frac{(r+1)\left(Z_{\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 \delta^2\Big)}{rd^2}$$

where N = total sample size, r = sample allocation ratio (n2/n1; where n1 is for cases group and n2 for the comparator (control) group), α = margin of error, 1-β = power, δ and d are the pooled standard deviation and difference of means of two groups respectively.

For the purpose of determining the appropriate sample size, the Platelet Large Cell Ratio (P-LCR) and standard deviations for PE (30.8 ± 6.6) and normotensive pregnancy (29.1 ± 6.8) from a study conducted in Mekelle, Ethiopia [9] was used. Using 0.05 of β (1-β = 0.95), 5 % of margin of error (α = 0.05), 95 % confidence level, and the aforementioned means and standard deviations, the sample size becomes 122. By adding a 10 % attrition rate, the final sample size resulted in 136. A 1:2 allocation ratio was utilized considering availability of cases (PE group). Therefore, 46 pregnant women with preeclampsia and 90 normotensive pregnant women were included using consecutive sampling techniques and systematic random sampling techniques respectively. The K value for 90 participants indicated that every ninth pregnant woman was chosen using the successive three months (July, August, and September) of the previous year's 784 ANC visits as the data source.

2.3. Eligibility criteria

2.3.1. Inclusion criteria

Pregnant women of 11th week or more who attend AMGH during the study period will be included.

2.3.2. Exclusion criteria

Pregnant women with intra-uterine fetal death, poor past obstetric history (such as recurrent miscarriage, pre-term labor, intra-uterine growth restriction), gestational or insulin-dependent diabetes, heart, renal or hepatic dysfunction, inflammation, active infection, smoking and hematological diseases were excluded from the study.

2.4. Variables

2.4.1. Dependent variables

- o Preeclampsia

2.4.2. Independent variables

- o Age
- o Gestational age
- o Gravidity
- o Parity
- o Maternal blood pressure
- o Hematological parameters

2.5. Operational definitions

Pregnant women with Preeclampsia- A pregnant woman with blood pressure $\geq$140/90 mm Hg from two consecutive measurements 4 h apart, and proteinuria $\geq$300 mg/dL as early in the 20th gestational week of pregnancy accompanied with and/or edema, other major symptoms such as head ache, blurred vision, right upper quadrant pain and confirmed by an attending Gynecologist.

2.6. Data collection and laboratory methods

2.6.1. Clinical data

The clinical data of pregnant women, including maternal age, gestational weeks, gravidity, parity, and blood pressure, were gathered using a semi-structured questionnaire by trained Midwife Nurses. Blood pressure was measured using a Mercury Sphygmomanometer by certified Midwife Nurses. The first reading was taken after the pregnant women have rested for 15 min, and the second reading was taken after 4 h.

2.6.2. Sample collection and analysis

Blood sample was collected from the study participants with anticoagulant coated 4 ml EDTA-K_3 vacutainer tube with trained Laboratory technologist. Each was tagged with participants' codes and matched with questionnaires. Complete blood count was analyzed with Sysmex KX21 automated Hematology analyzer (Sysmex, Cobe, Japan). Single random urine sample was collected with a dry leak proof container and tested for dipstick proteinuria analysis. All laboratory tests were performed as per the Standard operation procedure and manufacturer's instructions.

2.6.3. Data quality management

The quality of collected data was assured following the standard operation procedure. Every day, investigators checked the validity of the data collected from each questionnaire. Calibrated Mercury Sphygmomanometer blood pressure measurement device was used. Known control standards were used to check the quality of the hematology auto-analyzer. Each laboratory analysis was conducted as per the manufacturer's direction for the use of diagnostic instruments.

2.6.4. Data processing and analysis

Coded data was entered into Epidata version 4.4.1 and analyzed using statistical software from SPSS version 25.0 and Stata 17. Stata 17 was utilized for the ROC analysis, whereas SPSS version 25 was used for the majority of the statistical analysis. The descriptive statistics as mean with standard deviation (SD), median and interquartile ranges of all the parameters were calculated for cases and controls. Normality of data was checked with Kolmogorov-Smirnov test and the mean differences were tested with independent-sample *t*-test. The value of $p < 0.05$ was considered significant. Receiver operating characteristic (ROC) curve analysis of area under the curve (AUC) was used to determine the best hematological parameter which can be used for diagnosis and screening. $P < 0.05$ was considered statistically significant.

2.7. Ethical consideration

Ethical approval was obtained from the Institutional Review Board (IRB) of Arba Minch University (with reference number IRB/1062/21). A permission letter was obtained from Arba Minch General Hospital Administrative. Informed consent was obtained from the participants before clinical data and blood sample collection. To ensure confidentiality, participants' data were linked to a unique code number. Any abnormal test results of participants were communicated to their attending health care providers.

3. Results

3.1. Maternal and clinical characteristics of study participants

A total of 136 pregnant women (90 normotensive and 46 preeclamptic) were recruited for this study. The mean age of normotensive pregnant women was 25.76 ± 5.3 years while it was 29.33 ± 4.89 years for preeclamptic patients. The numbers of gravidity among normotensive and preeclamptic pregnant women were 2.33 ± 1.39 and 3.15 ± 1.75 pregnancies respectively (Table 1).

3.2. Hematological characteristics of pregnant women

The complete blood cell count analysis of each study participants result showed that the means of most of the hematological parameters were not statistically different except relative lymphocyte count ($p < 0.047$), Red blood cell distribution width (RDW-SD) ($p < 0.036$) and neutrophil to lymphocyte ratio (NLR) ($p < 0.016$) even though numerical differences were evident (Table 2).

3.3. Potential predictors for preeclampsia

From the hematological parameters evaluated, variables which show statistically significant difference between study groups (Normotensive and preeclamptic pregnant women) were assessed for their potential diagnostic value of preeclampsia using Receiver Operating Curve (ROC) and Area Under the Curve (AUC) analysis. The analysis output for RDW-SD, NLR and relative lymphocyte count showed AUC of 0.607, 0.609 and 0.600 respectively (Table 3, Figs. 1 and 2).

4. Discussion

The diagnosis of preeclampsia is routinely made by evaluation of blood pressure and protein urea after 20th week of gestation. Although pathophysiological changes (e.g. inadequate placentation) exist from very early stages of the pregnancy, hypertension and proteinuria usually become apparent in the second half of pregnancy and are present in 2%–8% of all pregnancies overall [10]. This makes the current available methods for diagnosis, screening and classification controversial. Therefore, this study tried to investigate the potential diagnostic and screening capability of hematological parameters that can be performed easily with readily available resources.

The findings of this study showed that the means of RDW ($p = 0.036$), NLR ($p = 0.016$), and relative Lymphocyte count ($p = 0.047$) had differences between pregnant women with and without preeclampsia. Thus, some hematological parameters were considered potential candidates for ROC analysis and resulted AUC of 0.607, 0.609, and 0.600 for RDW, NLR and Relative Lymphocyte count respectively. The potential cut-off points greater than or equal to 16.4 % and 3.80 for RDW and NLR while less than or equal to 18.50 % for Relative Lymphocyte count (%) were capable of classifying 61.76 %, 56.62 %, 56.62 % of pregnant women into PE and non-PE respectively.

Different studies had reported that platelet count and platelet indices like MPV, PDW and Plateletcrit were statistically different between PE and non-PE pregnant women and can be used as diagnostic and screening test [11–15]. While we couldn't find supporting evidence from our study as there were no statistical difference of the mentioned hematological parameters between the groups.

On the other hand, there were evidence of increased RDW and NLR but decreased relative lymphocyte count in PE women compared with non-PE pregnant women were found to be the potential diagnostic hematological markers of preeclampsia. This result

Table 1
Maternal and clinical characteristics of pregnant women who attended ANC at Arba Minch General Hospital.

Characteristics	Groups					
	Non-preeclamptic (control) groups (N = 90)			Preeclamptic (case) groups (N = 46)		
	Mean ± SD	Min	Max	Mean ± SD	Min	max
Age (Years)	25.76 ± 5.3	17	40	29.33 ± 4.89	20	40
Gravidity	2.33[a] ± 1.39	1	6	3.15 ± 1.75	1	8
Parity	1.32[a] ± 1.38	0	5	2.15 ± 1.80	0	7
Weeks of gestation	23.84 ± 6.48	13	38	34.30 ± 2.71	28	39
Years between previous and current pregnancy	1.66 ± 1.64	0	7	2.28 ± 1.64	0	7
Mean Arterial pressure	86.8 ± 4.46	74.55	96.44	119.76 ± 6.51	107.33	132.00

[a] The values are proportion.

Table 2
Hematological characteristics of pregnant women who attended ANC at Arba Minch General Hospital,2021.

Characteristics	Groups						Mean difference	P value
	Non-preeclamptic (control) groups (N = 90)			Preeclamptic (case) groups (N = 46)				
	Mean ± SD	95 % CI		Mean ± SD	95 % CI			
		Min	Max		Min	Max		
Total White Blood Cell count (x10^9/L)	8.31 ± 2.65	4.10	17.50	9.30 ± 3.30	4.60	18.00	−0.998	0.059
Relative Lymphocyte Count (%)	22.91 ± 9.24	5.10	59.20	19.73 ± 7.70	6.70	41.10	3.18	**0.047**
Relative Mixed cells count (%)	10.95 ± 3.75	5.80	25.60	11.16 ± 4.31	5.10	27.10	−0.204	0.776
Absolute Neutrophil (x10^9/L)	5.67 ± 2.45	1.18	14.02	6.60 ± 2.93	1.83	15.10	−0.932	0.052
Absolute Lymphocyte (x10^9/L)	1.780.51	0.32	2.84	1.72 ± 0.67	0.61	4.65	0.061	0.555
Absolute Mixed cells (x10^9/L)	0.87 ± 0.28	0.24	1.66	0.99 ± 0.397	0.3	2.44	−0.112	0.058
Neutrophil-lymphocyte ratio (%)	3.50 ± 2.12	0.06	2.42	4.33 ± 2.44	0.09	1.03	−0.869	**0.016**
RBC (x10^{12}/L)	4.28 ± 0.59	2.27	5.49	4.20 ± 0.80	1.74	6.82	0.071	0.594
Hemoglobin (g/dl)	12.61 ± 2.10	6.0	17.30	12.09 ± 2.44	5.70	19.80	0.517	0.201
Hematocrit (%)	40.03 ± 6.04	21.0	52.60	38.25 ± 7.83	10.50	61.10	1.77	0.146
MCH (pg)	29.41 ± 2.72	17.80	34.10	28.75 ± 3.44	16.50	33.00	−0.658	0.554
MCHC (mg/dl)	31.27 ± 1.42	25.90	34.40	31.02 ± 1.81	25.40	34.70	0.252	0.374
MCV (fl)	94.19 ± 6.48	68.90	107.10	93.36 ± 9.38	64.40	125.00	1.37	0.546
RDW-SD (%)	16.21 ± 1.77	12.10	23.50	17.04 ± 2.82	12.50	26.50	−0.835	**0.036**
Platelet count (x10^9/L	202.20 ± 90.12	52.00	580.00	178.00 ± 61.81	68.00	387.00	24.20	0.105
MPV (fl)	10.71 ± 1.50	7.60	14.60	10.97 ± 1.57	7.80	13.60	−0.256	0.353
PDW (%)	14.12 ± 2.52	8.30	22.30	14.48 ± 2.50	8.90	19.20	−0.353	0.439
PCT	0.21 ± 0.085	0.06	0.54	0.192 ± 0.63	0.08	0.35	0.019	0.177
PLR	127.24 ± 92.07	27.57	718.22	118.09 ± 61.58	30.96	354.61	9.15	0.544

Abbreviations. RBC: Red Blood cells, MCH, mean cell volume; MCHC, Mean corpuscular hemoglobin concentration; MCV, Mean corpuscular volume, RDW-SD; Red cell distribution width (Standard deviation), PDW: platelet distribution width, MPV: mean platelet volume, PCT: Plateletcrit, PLR: platelet –Lymphocyte ratio, CI: Confidence interval.

Table 3
ROC analysis of AUC for hematological parameters showing diagnostic importance for preeclampsia.

Test variables	AUC	95 % CI		Cut off point	Sensitivity (%)	Specificity (%)	Correctly classified (%)
		LB	UB				
RDW-SD	0.607	0.507	0.707	≥16.4	54.35 %	65.56 %	61.76 %
NLR	0.609	0.508	0.710	≥3.80	52.17 %	58.89 %	56.62 %
Relative Lymphocyte count (%)	0.600	0.496	0.699	≤18.50	50.00 %	60.00 %	56.62 %

Abbreviations. AUC, Area Under the Curve; RDW-SD, red cell distribution width; NLR, Neutrophil-Lymphocyte ratio.

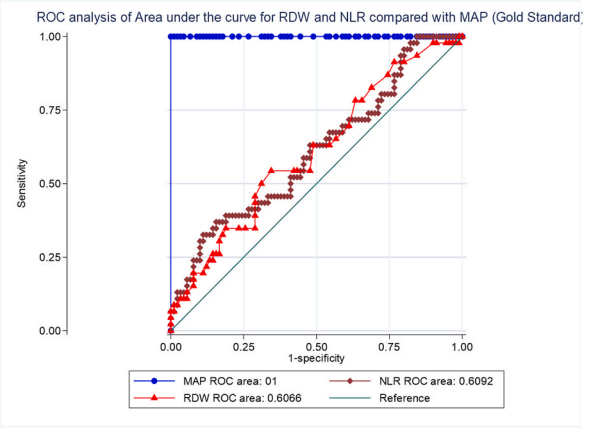

Fig. 1. Area Under the Curve of the ROC analysis for diagnostic value of RDW and NLR for preeclampsia in pregnant women.

is supported by evidences from studies reported by different authors which showed that PE pregnant women had significantly higher values of RDW and NLR while in some women relative lymphocyte counts were significantly decreased [16–19]. Apart from classification of pregnant women in to PE and non-PE, RDW has also shown a relationship with the severity of preeclampsia [20]. It is well recognized that abnormalities in the functional and physicochemical properties of red blood cells (RBCs) may underlie the defects that

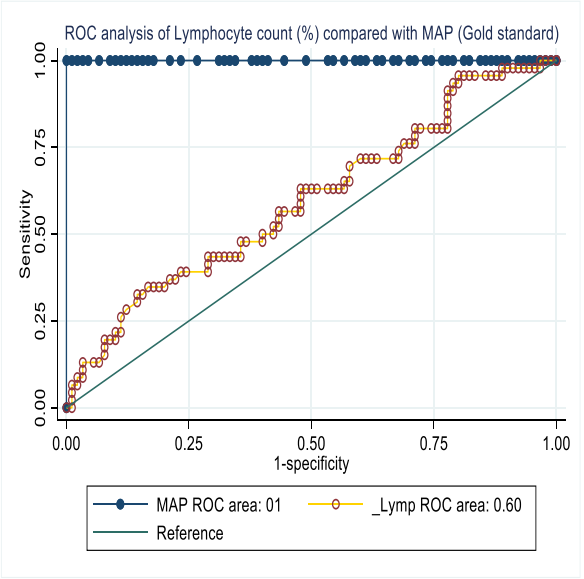

Fig. 2. AUC of the ROC analysis for diagnostic value of relative Lymphocyte count (%) for preeclampsia in pregnant women.

are strongly linked to hypertension, stroke, and other cardiovascular diseases. The underlying mechanisms responsible for the association between high RDW and hypertension are uncertain [21]. Similarly, Neutrophil/lymphocyte ratio (NLR) is a marker of systemic inflammation and endothelial dysfunction which is recently being reported as a potential utility to predict/diagnose preeclampsia. A systematic review and meta-analysis showed NLR has a predictive role for preeclampsia since inflammation response is suggested to be an important process in preeclampsia [22]. Researchers have found that the severe inflammation in PE is often accompanied by the neutrophil activation and develops simultaneously with the clinical symptoms in a patient [23].

Regarding lymphocyte count, there is a decrease during pregnancy through the first and second trimesters and but increases during the third trimester as there is inactivation of the innate immunity specially lymphocytes [24,25]. Similarly, in this study there were pronounced statistically significant lymphocyte count decrement among PE groups compared with non-PE pregnant women.

5. Limitation of the study

This study tried to find the best clinically applicable diagnostic and screening hematological parameter whereas, due to cross-sectional nature of the study design, it couldn't analyze each pregnant women's hematological parameters and show whether there were changes through trimesters. Additionally, the AUC of the results were not such good (it falls within the poor for AUC range) [26].

6. Conclusion and recommendation

RDW, NLR and Lymphocyte count can be potential candidate for the diagnosis and screening of preeclampsia as these tests can be easily available and cost-effective tests performed routinely in the laboratory. However, the robustness of the utilities should be tested with prospective long run studies assessing changes present in each trimester.

Ethical considerations and approvals

The study was approved by Arba Minch University Institutional review Board and Informed consent was obtained from each study participant.

Consent for publication

NA.

Funding opportunity

Financial support to conduct this study was obtained from Arba Minch University Research and Development Office. But the office doesn't have any role in the designing, conducting and analysis of this study.

CRediT authorship contribution statement

Woldeteklehaymanot Kassahun: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Aschalew Kidanewold:** Conceptualization, Data curation, Funding acquisition, Investigation, Resources, Supervision, Writing – original draft. **Getahun Koira:** Funding acquisition, Investigation, Resources, Supervision, Validation. **Gelila Biresaw:** Funding acquisition, Investigation, Resources, Supervision, Validation. **Mulu Shiferaw:** Formal analysis, Methodology, Resources, Software, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

All authors have declared that they don't have any competing interest in this publication.

Data availability

Data will be made available on request.

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Abbreviations and acronyms

AMGH	Arba Minch General Hospital
ANC	Ante-natal Care
AUC	Area under the curve
CI	Confidence interval
HDP	hypertensive disorders of pregnancy
ISSH	International Society for Study of Hypertension in Pregnancy)
Lymp%	Relative lymphocyte count
MAP	Mean arterial pressure
MCH	mean cell hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean cell volume
MPV	mean platelet volume
NLR	Neutrophil-Lymphocyte ratio
PCT	Plateletcrit
PDW	platelet distribution width
PE	Preeclampsia
PIH	Pregnancy Induced Hypertension
PLR	platelet –Lymphocyte ratio
RBC	Red Blood cells
RDW	red cell distribution width
RDW-SD	Red cell distribution width (Standard deviation)
ROC	Receiver Operating Characteristics
SD	Standard Deviation
WBC	White Blood Cells

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