Received: 8 October 2023 | Revised: 7 April 2024 | Accepted: 10 July 2024

DOI: 10.1002/hsr2.2277

ORIGINAL RESEARCH

Health Science Reports Open Access WILEY

Investigating hemolysis, elevated liver enzymes and low platelet count in preeclampsia: A case-control study in Ghana

Martin Awe Akilla[1] | Ignatius Abowini Nchor Awinibuno[1] | Moses Banyeh[1] | Benjamin N. Mayeem[2] | Gabriel Sakyi Kwofie[3] | Stephen Adoko[4] | Ruth Nimota Nukpezah[5] | Augusta S. Kolekang[6] | Clement Binwatin Dagungong[1] | Nafiu Amidu[7]

[1]Department of Biomedical Laboratory Science, University for Development Studies, Tamale, Ghana

[2]Department of Medical Laboratory, Living Waters Hospital, Kumasi, Ghana

[3]Department of Family Medicine, Living Waters Hospital, Kumasi, Ghana

[4]Department of Clinical Diagnostics, Shalina Diagnostics, Kumasi, Ghana

[5]Department of Preventive Health Nursing, University for Development Studies, Tamale, Ghana

[6]Department of Epidemiology, Biostatistics and Disease Control, University for Development Studies, Tamale, Ghana

[7]Department of Clinical Chemistry, University for Development Studies, Tamale, Ghana

Correspondence

Moses Banyeh, Department of Biomedical Laboratory Science, University for Development Studies, Tamale, Ghana.
Email: mosesbanyeh@gmail.com

Abstract

Background and Aims: Preeclampsia poses a heightened risk for women, particularly in the development of hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome, leading to adverse outcomes for both mothers and newborns. The incidence of HELLP syndrome tends to be notably higher among women with preeclampsia compared with those with normotensive pregnancies. However, there is a dearth of research on the frequency of HELLP syndrome within the context of preeclampsia specifically in Ghana. Furthermore, the potential predictive value of serum erythrocyte adenylate kinase (EAK), a marker of hemolysis, in anticipating the onset of preeclampsia remains largely unexplored.

Methods: Conducted between May 2020 and April 2022, this research employed a case-control methodology at the War Memorial and Upper East Regional Hospitals. A total of 291 pregnant women participated, comprising 111 diagnosed with preeclampsia and 180 control subjects, aged between 18 and 43 years. Venous blood samples were collected and subjected to analysis for platelet count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), and EAK, utilizing automated analyzers, alongside the ELISA technique. Diagnosis of HELLP syndrome was established using the Mississippi triple-class definition.

Results: The median serum ALT level (with interquartile range) was significantly elevated in the preeclampsia group compared with controls [20.0 (13.7–27.0) vs. 13.0 (9.4–18.6); $p < 0.001$]. Moreover, the frequency of Mississippi class 3 HELLP syndrome was notably higher among preeclampsia cases (2/111; 1.8%) compared with controls (1/180; 0.6%). Serum ALT emerged as the superior predictor of preeclampsia, outperforming LDH (with an area under the curve of 0.73 compared

with 0.58). The sensitivity and specificity of ALT were measured at 47.8% and 87.2%, respectively.

Conclusion: Although the occurrence of HELLP syndrome in preeclampsia cases appears relatively low, it may escalate as the prevalence of preeclampsia is anticipated to rise in low and middle-income nations.

KEYWORDS

adenylate kinase, erythrocytes, Ghana, HELLP syndrome, hemolysis, preeclampsia

1 | INTRODUCTION

Hemolysis, elevated liver enzymes, and low platelet (HELLP) syndrome represent a significant complication of pregnancy. Its prevalence in pregnancy ranges from 0.2% to 0.8%, contributing to approximately 1%–25% of maternal mortality and up to 34% of perinatal mortality.[1] While the exact pathophysiology remains elusive, preeclampsia stands out as a primary predisposing factor. Notably, 10%–20% of severe preeclampsia cases progress to HELLP syndrome, with 80% of all HELLP cases being preceded by preeclampsia.[2] However, it's crucial to note that although there are similarities, the pathophysiology of preeclampsia and HELLP syndrome only partially overlap, given that approximately 15% of HELLP patients present without proteinuria or hypertension.[3,4]

HELLP syndrome manifests through a spectrum of pathological mechanisms including impaired placentation, endothelial dysfunction, oxidative stress, immune maladaptation, and elevated placental cytokines.[5,6] Notably, the syndrome is characterized by Sinusoidal Obstruction Syndrome (SOS), precipitating hepatic injury, alongside microangiopathic hemolytic anemia (MAHA), thrombotic microangiopathy (TMA), and/or disseminated intravascular coagulation. Additionally, there's an association between HELLP syndrome and Antiphospholipid Antibody Syndrome (APLS).[5] The integration of placental, hepatic, endothelial, and immune system dysfunctions suggests the involvement of a "placenta-immune system-endothelium-liver axis" in the pathophysiology of HELLP syndrome.[1]

Hemolysis serves as a key diagnostic feature of HELLP syndrome, which often presents with MAHA. This condition can be identified through elevated serum lactate dehydrogenase (LDH) levels, the presence of burr cells and/or schistocytes, and reduced serum haptoglobin levels due to the binding of free hemoglobin to haptoglobin.[6] Studies indicate that hepatic function typically improves within 6 weeks postdelivery in HELLP syndrome patients, suggesting the involvement of the placenta-liver axis in its pathophysiology.[7]

Women with HELLP syndrome commonly experience a significant decrease in hepatic blood flow, particularly during the third trimester, possibly due to sustained inflammation and endothelial dysfunction. This can lead to SOS, characterized by hepatocyte ischemia, microthrombi formation, and subsequent liver malfunction or failure.[7] Research also suggests that placental-derived substances such as FasL (CD95L) possess hepatotoxic properties, inducing hepatocyte necrosis and apoptosis through increased TNF-α production.[5,8]

Diagnosing HELLP syndrome relies on laboratory assessments focusing on indicators of hemolysis, elevated liver enzymes, and decreased platelet counts. Two primary laboratory-based diagnostic methods exist: the Mississippi triple-class method and the Tennessee method.[9–11] In the Mississippi triple-class method, serum LDH, aspartate or alanine aminotransferase (AST or ALT), and platelet count serve as markers for hemolysis, hepatic injury, and thrombocytopenia, respectively.[10] Conversely, the Tennessee method incorporates additional parameters such as peripheral blood smear examination for burr cells and schistocytes, as well as serum bilirubin and/or haptoglobin concentration alongside LDH, AST, and platelet count.[9] HELLP syndrome is categorized as complete when all three indicators of HELLP counts are present, while partial HELLP syndrome may manifest when only one or two of these indicators are observed.[12] Although there exist alternative markers of hemolysis, such as serum erythrocyte adenylate kinase (EAK) levels, these are typically not included in HELLP syndrome diagnostic panels.[13]

Recent advancements in molecular biology have uncovered certain genetic variants or combinations associated with HELLP syndrome.[14,15] The interplay between genetics, environmental factors, and potential interactions may contribute to variations in the prevalence of HELLP syndrome among different populations or ethnic groups.[16] For instance, a meta-analysis revealed a HELLP syndrome prevalence of 13.0% among hypertensive disorders of pregnancy in Ethiopia.[17] However, it is speculated that the incidence of HELLP among women with preeclampsia could be higher in Ghana, given the scarcity of studies focusing on HELLP syndrome and preeclampsia within the Ghanaian population.[18] The burden of pregnancy-related conditions, including preeclampsia, is anticipated to rise in low and middle-income countries like Ghana.[19] Despite their significance for maternal and perinatal health, there remains a paucity of research examining the prevalence of HELLP syndrome and preeclampsia specifically within the Ghanaian demographic.

2 | MATERIALS AND METHODS

2.1 | Study design and settings

This study was conducted from May 2020 to April 2022 and employed an unmatched case-control design at two healthcare institutions: the War Memorial Hospital (WMH) and the Upper East Regional Hospital (UERH). The WMH functions as a primary healthcare center, catering to the healthcare needs of residents in Navrongo and nearby areas. On the other hand, the UERH operates as a secondary healthcare facility, serving as a referral center for primary healthcare establishments such as the WMH, as well as some from neighboring Burkina Faso.

2.2 | Study population and selection

The study comprised 291 pregnant women aged 18–43 years. Among them, 111 (38.1%) were diagnosed with preeclampsia (cases), while the remaining 180 exhibited normotensive pregnancies (controls). Within the normotensive group, 73 women were in the second trimester, and 107 were in the third trimester. Among those diagnosed with preeclampsia, 51 were in the second trimester, and 60 were in the third trimester. Preeclamptic participants were consecutively recruited from the antenatal clinic, while controls, pregnant women without preeclampsia, were similarly chosen from the same clinic attendees. Preeclampsia diagnosis adhered to the American College of Obstetrics and Gynecology (ACOG) guidelines,[20] defined as new-onset hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg) after 20 weeks of gestation, confirmed at two separate occasions with at least 4 h apart, or single measurements showing higher thresholds (systolic blood pressure of ≥160 mmHg or diastolic blood pressure of ≥110 mmHg). Additionally, proteinuria (spot urine protein of at least +1 on dipstick) or other signs of organ damage unrelated to pre-existing conditions were required. HELLP syndrome diagnosis followed the Mississippi triple-class system,[11] with partial HELLP syndrome (ELLP) defined by the presence of any two of the definitive criteria[12] as shown in Table 1. Participants with chronic hypertension, diabetes mellitus, hepatitis, fatty liver disease, or other chronic illnesses were excluded from the study.

TABLE 1 The Mississippi triple-class system for HELLP syndrome diagnosis.

Class	Criterion
1	PLT ($\times 10^3/\mu L$) ≤ 50 AST or ALT (IU/L) ≥ 70 LDH (IU/L) ≥ 600
2	50 < PLT ($\times 10^3/\mu L$) ≤ 100 AST or ALT(IU/L) ≥ 70 LDH (IU/L) ≥ 600
3	100 < PLT ($\times 10^3/\mu L$) ≤ 150 AST or ALT (IU/L) ≥ 40 LDH (IU/L) ≥ 600

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; PLT, platelet.

2.3 | Sample size determination

The sample size was determined using an online EPI tool (https://epitools.ausvet.com.au/casecontrolss), referencing a prior study by Malmström and Morken[21] which examined the frequency of HELLP syndrome in normotensive pregnancies versus preeclampsia. Kelsey's formula for unmatched case-control studies was used based on the following variables:

Study type: Unmatched case-control;
Case/control 1.0;
Power 0.8;
Alpha 5%;
Confidence interval 95%;
Odds ratio 4.0;
Minimum sample size per group 98;
Minimum total sample size 196.

2.4 | Data collection and measurements

2.4.1 | Sociodemographic and anthropometric data

Sociodemographic information was gathered through an interviewer-administered questionnaire, while clinical data were extracted from the women's medical records stored at the health facility. Body weight and standing height were measured with precision using a body scale and stadiometer, respectively, recorded to the nearest 0.1 kg and 0.01 cm. Subsequently, body mass index (BMI) was calculated in kg/m^2 by established guidelines.[22]

2.5 | Laboratory analysis

A single venous blood sample was collected and divided into K_3EDTA anticoagulant and gel-separator vacutainer tubes. Within an hour of collection, a full blood count (FBC) analysis was conducted using the anticoagulated blood sample on a 5-part automated hematology analyzer (Sysmex America, Inc). The blood in the gel-separator tube was left to clot before undergoing centrifugation at 3000*g* for 5 min to obtain serum. The serum samples were then aliquoted in duplicates and stored at −20°C until analysis, without undergoing thawing and refreezing cycles. Subsequent analysis included measuring serum levels of LDH, AST, and ALT using the BT 5000 automated Biochemistry analyser (Biotecnica). In contrast, EAK levels were determined using the enzyme-linked immunosorbent assay (ELISA) technique.

2.6 | Statistical analysis

The data were initially compiled into an Excel spreadsheet and subsequently analyzed using statistical software packages including SPSS (v26), GraphPad Prism (v8), and MedCalc. The Shapiro–Wilk test was employed to assess data normality. Categorical variables were presented as frequencies (percentage), while nonparametric continuous variables were summarized using median and interquartile range (IQR). Differences in the distribution of continuous nonparametric data between two or multiple groups were evaluated using the Mann–Whitney *U* test or the Kruskal–Wallis test, respectively. Significance values in the Kruskal–Wallis test were adjusted using the Bonferroni correction for multiple tests. For categorical data, differences between groups were assessed using the χ^2 test (or Fisher's exact test when applicable) and/or logistic regression analyses. Partial correlation analysis was conducted to explore relationships between variables, adjusting for covariates. The predictive abilities of serum markers for preeclampsia were assessed using receiver operator characteristic (ROC) curve analysis, following the Hanley and McNeil method. All statistical analyses were two-sided, with significance set at $p < 0.050$.

2.7 | Ethics approval statement

The research adhered to the guidelines outlined in the Declaration of Helsinki (1964) or its subsequent revisions regarding human subject studies. Approval for the study was granted by the institutional review board of Navrongo Health Research Center (NHRC) under the ethical approval number NHRCIRB378. Before participation, written informed consent was obtained from all women included in the study. Participation was voluntary, and individuals had the option to withdraw from the study at any point. The authors did not have access to information that could identify individual participants during or after data collection.

3 | RESULTS

3.1 | Sociodemographic characteristics

Table 2 summarizes the sociodemographic and obstetric characteristics of the study sample. Cultural affiliation and pregnancy trimester distribution among participants were not uniform. Predominantly, individuals identified with the Mole-Dagomba cultural group (90.4%) and were in their third trimester of pregnancy ($p = 0.003$ and <0.001,

TABLE 2 The sociodemographic and obstetric characteristics of the study population.

Variable	NP	PE	Total	χ^2	*p* Value
Cultural affiliation				11.729	0.003
Mole-Dagomba	171 (95.0)	92 (82.9)	263 (90.4)		
Akan	4 (2.2)	7 (6.3)	11 (3.8)		
Others	5 (2.8)	12 (10.8)	17 (5.8)		
Marital status				1.710	0.43
Married	174 (96.7)	107 (96.4)	281 (96.6)		
Co-Habitation	4 (2.2)	4 (3.6)	8 (2.7)		
Single	2 (1.1)	0 (0.0)	2 (0.7)		
Employment status				1.019	0.60
Unemployed	28 (15.6)	19 (17.1)	47 (16.2)		
Self-employed	92 (51.1)	50 (45.0)	142 (48.8)		
Salary worker	60 (33.3)	42 (37.8)	102 (35.0)		
Educational status				4.541	0.20
None	5 (2.8)	4 (3.6)	9 (3.2)		
Basic	57 (31.7)	38 (34.2)	95 (32.6)		
Secondary	52 (28.9)	20 (18.0)	72 (24.7)		
Tertiary	66 (36.7)	49 (44.1)	115 (39.5)		
Pregnancy trimester				291	<0.001
Second	73 (40.6)	50 (45.0)	123 (42.3)		
Third	107 (59.4)	61 (55.0)	168 (57.7)		

Note: The results are summarized as frequency (%). The differences between proportions were determined using χ^2 or Fisher's exact test as appropriate.
Abbreviations: NP, normotensive pregnancy; PE, preeclampsia.

respectively). The majority of pregnant women were married (96.6%), and a significant portion were self-employed (48.8%) or had attained tertiary education (39.5%). However, no statistically significant variances were observed between groups with or without preeclampsia.

3.2 | Comparison of variables between normotensive and preeclamptic pregnancies

According to Table 3, preeclampsia exhibited notably elevated serum ALT levels ($p < 0.001$) and significantly lower serum LDH levels ($p = 0.028$) compared with normotensive pregnancy.

3.3 | Changes in variables by the trimester of pregnancy

A comparison between the normotensive and preeclamptic groups was conducted across pregnancy trimesters (Table 4). Notably, the hemoglobin levels were higher in preeclampsia compared with normotensive pregnancy, while the EAK levels were lower in the third trimester compared with the second trimester of pregnancy. Additionally, within the preeclampsia cohort, serum ALT and EAK activity were higher in the third trimester compared with the second trimester of pregnancy.

TABLE 3 A summary of the variables of the study population stratified by the presence or absence of preeclampsia.

Variable	NP	PE	*p* Value
Age (years)	29 (26–33)	31 (27–35)	0.005
BMI (kg/m2)	27.9 (24.2–31.5)	27.7 (23.8–29.7)	0.44
RBC × (10^6/μL)	3.7 (3.5–4.0)	3.8 (3.5–4.0)	0.11
HGB (g/dL)	10.8 (10.1–11.3)	10.5 (9.7–11.2)	0.09
PLT (10^3/μL)	204 (157–249)	198 (142–250)	0.58
AST (IU/L)	24.7 (18.6–31.1)	22.0 (18.0–34.0)	0.31
ALT (IU/L)	13.0 (9.4–18.6)	20.0 (13.7–27.0)	<0.001
LDH (IU/L)	540.7 (467.2–594.0)	490.9 (370.0–620.1)	0.03
EAK (IU/L)	367.6 (252.8–542.6)	420.3 (279.5–646.9)	0.06

Note: The variables are summarized as median (interquartile range-IQR). The differences in the distribution of the data between the groups for each variable were compared using the Mann-Whitney U test.

Abbreviations: NP, normotensive pregnancy; PE, preeclampsia.

TABLE 4 Comparison of normotensive and preeclamptic pregnant women by the trimester of pregnancy.

Variable	2 TNP	3 TNP	2TPE	3TPE	*p* Value
RBC × (106/μL)	3.7 (3.4–4.0)	3.7 (3.5–4.0)	3.8 (3.6–4.0)	3.9 (3.4–4.1)	0.39
HGB (g/dL)	10.4 (9.8–11.1)	11.0 (10.2–11.5)*	10.4 (9.9–11.0)#	10.6 (9.2–11.6)	0.009
PLT (103/μL)	204 (148–247)	208 (166–251)	207 (147–250)	187 (139–258)	0.89
AST (IU/L)	27.8 (20.4–33.6)	24.0 (17.0–28.7)	24.0 (16.0–25.0)	21.5 (19.0–33.8)	0.07
ALT (IU/L)	12.2 (7.3–16.4)	14.0 (10.3–20.6)	18.0 (14.0–25.0)***,##	21.6 (13.8–27.0)***,###	<0.001
LDH (IU/L)	557.0 (475.0–602.2)	536.4 (465.0–592.9)	446.1 (357.4–620.1)	512.7 (371.3–620.1)	0.06
EAK (IU/L)	432.8 (264.0–587.9)	318.3 (252.8–542.6)*	340.7 (277.8–508.6)	542.6 (285.1–775.0)##	0.003

Note: The results are summarized as median (IQR). The differences in the distribution of the data between the groups for each variable were determined using the nonparametric ANOVA test (Kruskal–Wallis test). The significance values were adjusted using the Bonferroni correction for multiple tests.

Abbreviations: NP, normotensive pregnancy; PE, preeclampsia; 2T, second trimester; 3T; third trimester.

*$p < 0.050$, **$p < 0.010$ and ***$p < 0.001$ compared with 2TNP.

#$p < 0.050$, ##$p < 0.010$, and ###$p < 0.001$ compared with 3NTP.

^$p < 0.050$, ^^$p < 0.010$, ^^^$p < 0.001$ compared with 2TPE.

3.4 | Correlation between variables

Table 5 displays the partial correlation matrix. Within the pre-eclampsia group, serum LDH exhibited significant and inverse partial correlations with RBC ($r = -0.280$, $p < 0.010$), HGB ($r = -0.208$, $p < 0.050$), and PLT number ($r = -0.219$), with a small effect size ($0.20 < r \leq 0.30$). This correlation pattern was not observed among normotensive pregnant women.

3.5 | Association of preeclampsia and hemolysis, elevated liver enzymes and low platelets

Table 6 presents the associations between preeclampsia and the presence of HELLP counts. There was no significant association observed between preeclampsia and low platelet counts (<50 × 10^3/μL) or hemolysis (LDH ≥ 600 IU/L). None of the pregnant women exhibited serum AST or ALT levels ≥70 IU/L. Although the proportion of women

TABLE 5 Correlation between study variables in normotensive pregnancy and preeclampsia.

Variable	RBC	HGB	PLT	AST	ALT	LDH	EAK
RBC × (10^6/μL)	1	**0.232****	0.137	0.033	0.079	0.051	−0.012
HGB (g/dL)	**0.634****	1	−0.027	**−0.222****	0.075	0.027	−0.031
PLT (10^3/μL)	**0.237***	0.146	1	0.012	0.078	−0.062	−0.056
AST (IU/L)	0.065	0.151	−0.043	1	0.070	−0.120	−0.087
ALT (IU/L)	−0.064	−0.062	−0.170	0.064	1	0.042	0.133
LDH (IU/L)	**−0.280****	**−0.208***	**−0.219***	0.021	0.002	1	−0.052
EAK (IU/L)	−0.060	−0.062	−0.073	−0.117	−0.058	0.083	1

Note: The results are presented as partial correlation coefficients controlling for cultural affiliation, pregnancy trimester, and age. Top (normotensive pregnancy) and bottom (preeclampsia).

r = correlation coefficient with negligible effect size ($r < 0.20$), **Boldface *r*** = correlation coefficient with small effect size ($0.20 \leq r \geq 0.30$), ***Boldface r*** = correlation coefficient with a medium effect size ($0.30 \leq r \geq 0.50$), **boldface and underlined r** = correlation coefficient with a large effect size ($r > 0.50$).

*Correlation is significant at the 0.050 level (two-tailed).

**Correlation is significant at the 0.010 level (two-tailed).

TABLE 6 The association of preeclampsia and hemolysis, elevated liver enzymes and low platelets.

Variable	NP	PE	χ^2, *df*	*p* Value	AOR (95%CI)
PLT × 10^3/μL			4.754, 3	0.191	
>150	145 (80.6)	79 (71.2)			1
100 < PLT ≤ 150	25 (13.9)	23 (20.7)			1.606 (0.848–3.043)
50 < PLT ≤ 100	7 (3.9)	4 (3.6)			0.831 (0.229–3.021)
≤50	3 (1.7)	5 (4.5)			2.539 (0.777–11.184)
AST or ALT (IU/L)			N/A	N/A	
<70	180 (100)	111 (100)			
≥70	0 (0.0)	0 (0.0)			
AST or ALT (IU/L)			0.164, 1	0.725	
<40	157 (87.2)	95 (85.6)			1
≥40	23 (12.8)	16 (14.4)			1.127 (0.560–2.268)
LDH (IU/L)			2.213, 1	0.168	
<600	139 (77.2)	77 (69.4)			1
≥600	41 (22.8)	34 (30.6)			1.420 (0.827–2.438)

Note: The results are summarized as frequency (%). The associations between variable were determined using χ^2 and logistic regression analyses. The logistic regression models were adjusted for age, cultural affiliation, and pregnancy trimester.

Abbreviations: AOR, adjusted odds ratios; NP, normotensive pregnancy; PE, preeclampsia.

with preeclampsia having AST or ALT levels ≥40 IU/L was slightly higher (14.4%) compared with those with normotensive pregnancy (12.8%), this difference did not reach statistical significance (p value < 0.050).

3.6 | The frequency of HELLP syndrome

Table 7 displays the occurrence of HELLP syndrome. In preeclampsia, the frequency of pregnant women with Mississippi class 3 HELLP syndrome was higher (1.8%) compared with the normotensive pregnancy (NP) group (0.6%). Similarly, the proportion of individuals with Mississippi class 3 HELLP syndrome was higher in the preeclampsia group (5.4%) compared with the normotensive group (0.6%).

3.7 | Predicting preeclampsia with study variables

Figure 1 illustrates the predictive capacities of the study variables for preeclampsia (PE). Serum ALT levels ($p < 0.001$) and LDH levels ($p = 0.046$) emerged as the sole significant predictors of PE, with respective areas under the curve (AUC) of 0.73 and 0.58. Serum ALT and LDH levels demonstrated predictive sensitivities of 47.8% and 44.1% and specificities of 87.2% and 80.6%, respectively.

4 | DISCUSSION

The occurrence of HELLP syndrome may be higher in preeclampsia when compared with normotensive pregnancies. Despite this observation, studies to ascertain the frequency of HELPP in preeclampsia are limited in Ghana although the incidence of preeclampsia is said to increase in low and middle-income countries. The objective of the study was to compare the occurrence of HELLP syndrome in pregnant women with preeclampsia versus those with normotensive pregnancy. It was noted that the number of pregnant women with Mississippi class 3 HELLP syndrome in the preeclampsia group was double that of those in the normotensive pregnancy group.

TABLE 7 The proportion of the participants with ELLP and HELLP syndrome.

Mississippi classification	NP ($n = 180$)	PE ($n = 111$)
ELLP		
Class 1	0 (0.0)	0 (0.0)
Class 2	0 (0.0)	0 (0.0)
Class 3	1 (0.6)	6 (5.4)
HELLP		
Class 1	0 (0.0)	0 (0.0)
Class 2	0 (0.0)	0 (0.0)
Class 3	1 (0.6)	2 (1.8)

Note: The results are presented as frequency (%).
Abbreviations: NP, normotensive pregnancy; PE, preeclampsia.

In preeclampsia, the prevalence of Mississippi class 3 HELLP syndrome among pregnant women was found to be higher compared with those with normotensive pregnancy. Previous research, including studies by Petca et al.[5] and von Salmuth et al.,[1] supports this observation, indicating a higher frequency of HELLP syndrome in preeclampsia than in normal pregnancy. Both HELLP syndrome and preeclampsia fall under the category of "placental syndromes" in pregnancy and share bidirectional pathophysiology. Although the prevalence of HELLP syndrome during pregnancy is generally low (0.2%–0.8%), it escalates to approximately 10%–20% among women with preeclampsia, with about 80% of all HELLP syndrome cases preceded by preeclampsia.[1,2]

The pathogenesis of preeclampsia lays the groundwork for the development of HELLP syndrome. A dysfunctional or impaired placenta emerges as a significant precipitating factor in the pathophysiology of both conditions.[23,24] Placental ischemia in preeclampsia results in hypoperfusion, leading to the release of placenta-derived syncytiotrophoblast particles (STBM), antiangiogenic factors, and pro-inflammatory cytokines.[1] These placental antiangiogenic factors, such as endoglin, have the potential to activate endothelial cells, consequently altering their function.[1,25]

Endothelial cell dysfunction can lead to irregularities in the vascular endothelial lining, causing it to become discontinuous and patchy as the basement membrane is stripped away. When platelets traverse this irregular endothelial lining, they become activated, releasing vasoconstrictors like endothelin-1.[2,26,27] Vasoconstriction intensifies the mechanical strain on circulating red blood cells, potentially triggering hemolysis.[28] Moreover, preeclampsia (PE) is associated with an elevated procoagulant and antifibrinolytic state, characterized by increased interactions between components of the hemostatic and fibrinolytic systems, as well as tissue factor, leading to hypercoagulability and thrombocytopenia.[28]

Placental antiangiogenic factors have been found to activate Liver sinusoidal endothelial cells (LSECs), prompting the release of pro-inflammatory mediators that could induce TMA. Activated LSECs may also attract blood cells into the hepatic space of Disse, leading to congestion in hepatic sinusoids due to fibrin deposition and microthrombi formation in the sinusoidal microcirculation. This process may result in hepatocyte damage and liver dysfunction.[1] The cascade of events in preeclampsia increases the likelihood of HELLP syndrome compared with uncomplicated pregnancies.

The present study stands out as one of the few attempts to assess the prevalence of HELLP syndrome among pregnant women with preeclampsia in Ghana, a topic that is scarcely addressed in the existing literature. However, it is noteworthy that the study was constrained by its failure to account for parity, as HELLP syndrome might be more prevalent in primiparous women

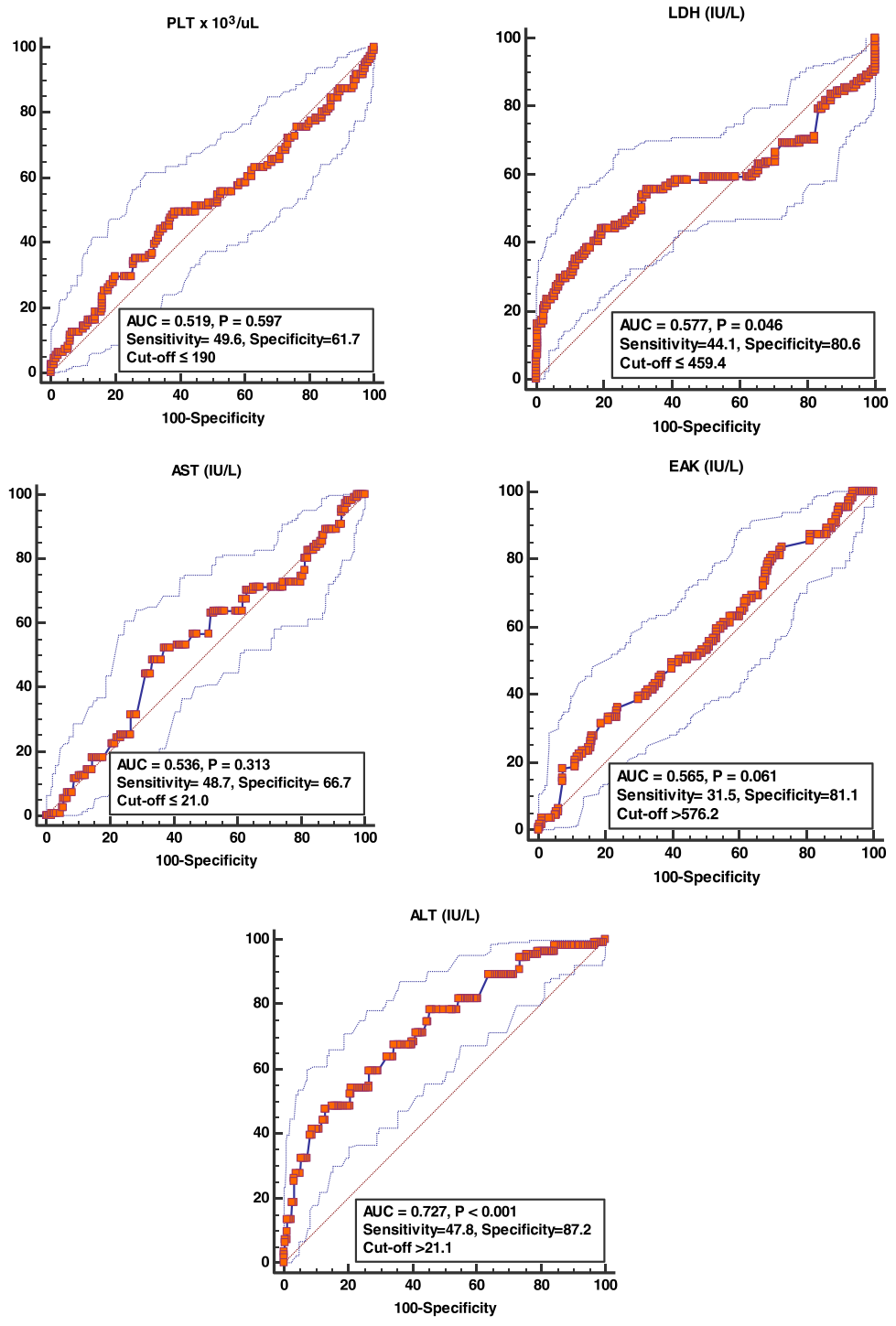

FIGURE 1 Receiver operator characteristics curves showing the predictive abilities of serum variables for preeclampsia. ALT, alanine aminotransferase; AST, aspartate aminotransferase; EAK, erythrocyte adenylate kinase; LDH, lactate dehydrogenase; PLT, platelet.

compared with multiparous ones.[21] Additionally, it is important to acknowledge that the Mole-Dagomba cultural affiliation is prominently represented in the geographical area where the hospital conducting the study is situated, whereas the Akan cultural group constitutes the largest cultural demographic in Ghana. Despite this discrepancy, the significance of the study remains valid. Future research endeavors should strive to address the limitations identified in this study.

5 | CONCLUSION

HELLP syndrome, although observed in both preeclampsia and normotensive pregnancies, appears to be more prevalent in the former. Despite the relatively low numbers of pregnant women affected by HELLP syndrome, stakeholders should remain vigilant, particularly considering the anticipated rise in the incidence and prevalence of preeclampsia in low and middle-income countries.[19]

Furthermore, serum LDH may continue to be favored over EAK for early prediction of preeclampsia.

AUTHOR CONTRIBUTIONS

Martin Awe Akilla: Conceptualization; writing—review and editing; investigation; methodology; data curation. **Ignatius Abowini Nchor Awinibuno**: Data curation; writing—review and editing; investigation; methodology. **Moses Banyeh**: Writing—original draft; writing—review and editing; formal analysis; validation. **Benjamin N. Mayeem**: Writing—review and editing. **Gabriel Sakyi Kwofie**: Writing—review and editing. **Stephen Adoko**: Writing—review and editing. **Ruth Nimota Nukpezah**: Writing—review and editing. **Augusta S. Kolekang**: Writing—review and editing. **Clement Binwatin Dagungong**: Writing—review and editing. **Nafiu Amidu**: Conceptualization; writing—review and editing; methodology.

ACKNOWLEDGMENTS

The authors wish to acknowledge the staff of the antenatal clinics of the War Memorial and the Upper East Regional Hospitals for their support. All the participants in this study are hereby acknowledged for consenting to the study.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data supporting these findings can be obtained from the corresponding author upon a reasonable request. All authors have read and approved the final version of the manuscript. The corresponding author had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis

TRANSPARENCY STATEMENT

The lead author Moses Banyeh affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

ORCID

Martin Awe Akilla http://orcid.org/0000-0001-7447-3933
Moses Banyeh http://orcid.org/0000-0003-3594-6077
Ruth Nimota Nukpezah http://orcid.org/0000-0002-4560-3329
Augusta S. Kolekang http://orcid.org/0000-0002-3600-3217

REFERENCES

1. Von Salmuth V, Van Der Heiden Y, Bekkers I, et al. The role of hepatic sinusoidal obstruction in the pathogenesis of the hepatic involvement in HELLP syndrome: exploring the literature. *Pregnancy Hypertens*. 2020;19:37-43.
2. Baxter JK, Weinstein L. HELLP syndrome: the state of the art. *Obstet Gynecol Surv*. 2004;59:838-845.
3. Haram K, Svendsen E, Abildgaard U. The HELLP syndrome: clinical issues and management. A review. *BMC Pregnancy Childbirth*. 2009;9:8.
4. Mihu D, Costin N, Mihu CM, Seicean A, Ciortea R. HELLP syndrome-a multisystemic disorder. *J Gastrointestin Liver Dis*. 2007;16:419-424.
5. Petca A, Miron BC, Pacu I, et al. HELLP syndrome—holistic insight into pathophysiology. *Medicina*. 2022;58:326.
6. Sibai BM. Diagnosis, controversies, and management of the syndrome of hemolysis, elevated liver enzymes, and low platelet count. *Obstet Gynecol*. 2004;103:981-991.
7. Van Lieshout LCEW, Koek GH, Spaanderman MA, Van Runnard Heimel PJ. Placenta derived factors involved in the pathogenesis of the liver in the syndrome of haemolysis, elevated liver enzymes and low platelets (HELLP): a review. *Pregnancy Hypertens*. 2019;18:42-48.
8. Halim A, Kanayama N, El Maradny E, et al. Immunohistological study in cases of HELLP syndrome (hemolysis, elevated liver enzymes and low platelets) and acute fatty liver of pregnancy. *Gynecol Obstet Invest*. 1996;41:106-112.
9. Erkılınç S, Eyi E. Factors contributing to adverse maternal outcomes in patients with HELLP syndrome. *J Matern Fetal Neonatal Med*. 2018;31:2870-2876.
10. Martin Jr. JN, Brewer JM, Wallace K, et al. Hellp syndrome and composite major maternal morbidity: importance of Mississippi classification system. *J Matern Fetal Neonatal Med*. 2013;26:1201-1206.
11. Rimaitis K, Grauslyte L, Zavackiene A, Baliuliene V, Nadisauskiene R, Macas A. Diagnosis of HELLP syndrome: a 10-year survey in a perinatology centre. *Int J Environ Res Public Health*. 2019;16:109.
12. Liu CM, Chang SD, Cheng PJ, Chao AS. Comparisons of maternal and perinatal outcomes in Taiwanese women with complete and partial HELLP syndrome and women with severe pre-eclampsia without HELLP. *J Obstet Gynaecol Res*. 2006;32:550-558.
13. Fujisawa K. Regulation of adenine nucleotide metabolism by adenylate kinase isozymes: physiological roles and diseases. *Int J Mol Sci*. 2023;24:5561.
14. Hupuczi P, Rigó B, Sziller I, Szabó G, Szigeti Z, Papp Z. Follow-up analysis of pregnancies complicated by HELLP syndrome. *Fetal Diagn Ther*. 2006;21:519-522.
15. Sørensen KK, Simon-Santamaria J, Mccuskey RS, Smedsrød B. Liver sinusoidal endothelial cells. *Compr Physiol*. 2015;5:1751-1774.
16. Oliveira N, Poon LC, Nicolaides KH, Baschat AA. First trimester prediction of HELLP syndrome. *Prenat Diagn*. 2016;36:29-33.
17. Mersha AG, Abegaz TM, Seid MA. Maternal and perinatal outcomes of hypertensive disorders of pregnancy in Ethiopia: systematic review and meta-analysis. *BMC Pregnancy Childbirth*. 2019;19:458.
18. Adwoa N, Kunfah JA, Akayuure CA, Kappiah J, Kampo S. Prevalence and demographic distribution associated with pre-eclampsia among pregnant women at a local Teaching Hospital in Ghana. *medRxiv* 2022.05.18.2227525.
19. Hussein J. Non-communicable diseases during pregnancy in low and middle income countries. *Obstet Med*. 2017;10:26-29.
20. Bouter AR, Duvekot JJ. Evaluation of the clinical impact of the revised ISSHP and ACOG definitions on preeclampsia. *Pregnancy Hypertens*. 2020;19:206-211.
21. Malmström O, Morken NH. HELLP syndrome, risk factors in first and second pregnancy: a population-based cohort study. *Acta Obstet Gynecol Scand*. 2018;97:709-716.
22. Olfert M, Barr M, Charlier C, et al. Self-reported vs. measured height, weight, and BMI in young adults. *Int J Environ Res Public Health*. 2018;15:2216.
23. Gude NM, Roberts CT, Kalionis B, King RG. Growth and function of the normal human placenta. *Thromb Res*. 2004;114:397-407.

24. Velicky P, Knöfler M, Pollheimer J. Function and control of human invasive trophoblast subtypes: intrinsic vs. maternal control. *Cell Adh Migr*. 2016;10:154-162.
25. Taché V, Lacoursiere DY, Saleemuddin A, Parast MM. Placental expression of vascular endothelial growth factor receptor-1/soluble vascular endothelial growth factor receptor-1 correlates with severity of clinical preeclampsia and villous hypermaturity. *Hum Pathol*. 2011;42:1283-1288.
26. Ali SM, Khalil RA. Genetic, immune and vasoactive factors in the vascular dysfunction associated with hypertension in pregnancy. *Expert Opin Ther Targets*. 2015;19:1495-1515.
27. Kazmi RS, Cooper AJ, Lwaleed BA. Platelet function in pre-eclampsia. *Semin Thromb Hemost*. 2011;37(2):131-136.
28. Fang CJ, Richards A, Liszewski MK, Kavanagh D, Atkinson JP. Advances in understanding of pathogenesis of aHUS and HELLP. *Br J Haematol*. 2008;143:336-348.

How to cite this article: Akilla MA, Nchor Awinibuno IA, Banyeh M, et al. Investigating hemolysis, elevated liver enzymes and low platelet count in preeclampsia: a case-control study in Ghana. *Health Sci Rep*. 2024;7:e2277. doi:10.1002/hsr2.2277