Journal of Gynecology and Obstetrics
2021; 9(6): 217-223
http://www.sciencepublishinggroup.com/j/jgo
doi: 10.11648/j.jgo.20210906.16
ISSN: 2376-7812 (Print); ISSN: 2376-7820 (Online)

Comparative Analysis Between Invalidated Biochemical Markers and the Well-established Markers of HELLP Syndrome

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To cite this article:

Kinikanwo Green, Collins Amadi. Comparative Analysis Between Invalidated Biochemical Markers and the Well-established Markers of HELLP Syndrome. *Journal of Gynecology and Obstetrics*. Vol. 9, No. 6, 2021, pp. 217-223. doi: 10.11648/j.jgo.20210906.16

Received: October 20, 2021; **Accepted**: November 8, 2021; **Published**: November 17, 2021

Abstract: *Background*: The use of the well-established markers of the Hemolysis, Elevated Liver enzymes and Low Platelet (HELLP) syndrome is very limited in the resource-poor settings of the developing populations. This study aimed to compare the readily available but invalidated biochemical markers with the well-established markers of HELLP syndrome. *Methods*: This was a retrospective cross-sectional study conducted among women diagnosed with HELLP syndrome in the University of Port Harcourt Teaching Hospital (UPTH) from 2011 to 2020. Data of each eligible case was acquired from the laboratory and medical records using a well-structured template and analyzed by standardized protocols. *Results*: A total of 230 cases of HELLP syndrome was identified; 200 complete HELLP (cHELLP) and 30 partial HELLP (pHELLP) variants. The cHELLP variants presented at an older age, higher gestational age, and had higher plasma bilirubin (PB), lactate dehydrogenase (LDH), creatinine, and uric acid (UA) but lower albumin concentration compared to those with pHELLP variant ($p<0.05$). With worsening severity, there was an increasing trend of plasma creatinine and UA but a decreasing trend of albumin among the cHELLP variants ($p<0.05$). UA level exhibited the strongest positive correlation with PB, LDH, aspartate, and alanine aminotransferases and maintained the strongest negative correlation with platelet count among those with cHELLP variants ($p<0.05$). At a cut-off value of 1.5 mmol/L, plasma UA (AUC:0.968; 95%CI:0.913-1.000;$p<0.001$) level had the most robust ROC values compared to those of plasma creatinine and albumin among the cHELLP variants. *Conclusion*: From the foregoing, plasma UA should be considered as an adjunct marker of cHELLP syndrome. However, further studies are highly recommended to evaluate conclusions from this study.

Keywords: HELLP, Complete HELLP, Partial HELLP

1. Introduction

HELLP syndrome is a complication of pregnancy comprising triad of Hemolysis, Elevated Liver enzymes, and Low Platelet count [1]. It generally occurs in 0.5-0.9% of all pregnancies and 10–20% of cases with severe preeclampsia [1, 2]. The syndrome was originally described by Pritchard and associates in 1954, and the term was conceived in 1982 by Louis Weinstein [1, 2]. It is generally regarded as a variant or a complication of severe preeclampsia. The diagnosis of the complete form requires the presence of all the 3 aforementioned major triads, while partial or incomplete HELLP syndrome consists of only 1 or 2 elements of the triad [2].

The syndrome is an ill-defined pregnancy-related disorder with a rapid onset, mostly seen in patients with severe preeclampsia, although it can also manifest in the absence of preeclampsia in 10% of cases [3]. Excessive weight gain and generalized edema precede the syndrome in more than 50% of the cases.

It evolves with a peak frequency before delivery between the 27th and 37th gestational weeks [4]. The postpartum cases of the

syndrome usually develop within the first 48 h after delivery and these cases are at a higher risk of developing renal failure and pulmonary edema. The risk of recurrence of HELLP syndrome is 24% after previous pregnancy [5, 6].

The syndrome, in its complete form, is an alarming diagnosis, which brings in very high adverse maternal and perinatal outcomes [7-9]. For yet unknown reasons, the condition is more prevalent among the multiparous Caucasian women in the westernized developed populations [8-9]. However, it is rare but comes with massive devastating consequences among the women in the less-developed populations of Negroid race. In Nigeria, few reports have been documented about the syndrome in the literature in recent times despite a high incidence of its widely acclaimed precursor agents – severe preeclampsia [10, 11].

The diagnosis of HELLP syndrome may be challenging because the patients usually present with vague symptoms like generalized malaise, nausea/vomiting, headache, or flu-like symptoms which could lead to misdiagnosis of the syndrome with other conditions [2-5].

A comprehensive biochemical evaluation using the well-established markers is essential in the diagnosis of the syndrome; a factor that is not readily available in developing populations due to scarce resources [4-6]. This inherent limiting factor may well be responsible for the low incidence and devastating consequences of the syndrome reported within the developing populations [11].

Hence, the current study aimed to compare readily available but invalidated biochemical markers related to the pathophysiology of HELLP syndrome with the well-established markers of this syndrome among cases of complete and partial HELLP syndromes in Port Harcourt, Nigeria.

2. Materials and Methods

2.1. Study Design and Site

This was a retrospective cross-sectional comparative evaluation of common biochemical markers related to HELLP syndrome pathophysiology with the established markers of the syndrome among pregnant women of Nigerian origin who were diagnosed with the syndrome over ten years in the University of Port Harcourt Teaching Hospital (UPTH), Nigeria. UPTH is a tertiary (third-level) public medical facility located in Port Harcourt, River State, within the Southern zone of Nigeria. The hospital is a major referral center for all the private, primary, and secondary healthcare centers in Rivers State and the adjoining states in the region.

The hospital has well-equipped and adequately-staffed Departments where pregnant women with varied obstetric complications including HELLP syndrome are properly evaluated, diagnosed, managed, and their data properly archived.

The Department of Obstetrics and gynecology handles thousands of deliveries per year with some cases of those deliveries complicated with HELLP syndrome. The Department of Chemical Pathology and that of hematology and blood transfusion and other related Pathology Departments handles all the complex laboratory support during diagnostic evaluation and management of all the cases of HELLP syndrome in the hospital.

2.2. Ethical Considerations

No medical intervention was undertaken during the conduct of this research. Ethical approval to assess all medical data/records was sought and granted by the Institutional Research Ethics Committee in the study center (UPTH) before commencement of the study. The requirement for informed or oral consent was waived owing to the retrospective solely data-based design of the study. However, all data was anonymized and treated with utmost confidentiality. The conduct of the study was tailored towards the Institutional Ethics guidelines and the principles embodied in the Helsinki Declaration.

2.3. Study Instruments

The study utilized only hospital data in the records and Pathology Departments of all the eligible cases of HELLP syndrome managed in UPTH during the study period.

2.4. Eligibility Criteria

The criteria for inclusion were as follows: data at diagnosis of all the eligible booked (supervised) and un-booked (supervised) indigenous Nigerian cases of HELLP syndrome with singleton pregnancies and diagnosed and managed in UPTH over 10 years from the 1st January 2011 to the 31st December 2020.

The criteria for exclusion included the following pre-existing conditions: acute/chronic liver diseases, gallbladder diseases, diabetes mellitus, thyroid disorders, chronic renal diseases, hemoglobinopathies, thrombotic microangiopathies (idiopathic/autoimmune thrombocytopenic purpura, atypical hemolytic uremic syndrome, and disseminated intravascular coagulopathy), chronic and gestational hypertension, acute fatty liver disease of pregnancy, acute/chronic hepatitis, and those infected with HIV infection. Also excluded are those records with any of the followings: incomplete data and preeclamptic/eclamptic cases with multiple gestations, preeclamptic/eclamptic superimposed on chronic hypertension, renal transplant recipients, and those diagnosed outside the study period (2011–2020).

2.5. Data Acquisition

All relevant data was acquired anonymously without any distinguishing identifiers from the Departments of Records and Pathology using trained research assistants.

Key variables of which data was collected included the number of deliveries within the study period, the number of suspected HELLP precursor agents (e.g. preeclampsia, etc), and the number of cases of HELLP syndrome diagnosed within the study period.

Subsequently, the relevant socio-demographic (age), medical history review, clinical, gynecological, obstetric [gravidity, parity, gestation age (GA)], biochemical markers [Total plasma bilirubin (TPB), aspartate aminotransferase

(AST), alanine aminotransferase (ALT) and lactate dehydrogenase (LDH)] and hematological [platelet (PLT) count] data was abstracted from all the eligible HELLP syndrome cases at the point of diagnosis using a well-structured research pro forma.

2.6. Data Definitions

The syndrome was defined using the Mississippi triple-class classification as follows [3]:

Class 1 (severe):

a) TPB ≥ 1.2mg/dl (20.5 μmol/L) or LDH of ≥ 600 IU/L

b) Plasma AST and ALT activities ≥ 70 IU/L

c) PLT count < 50 x 10^9/L

Class 2 (moderate):

a) TPB ≥ 1.2mg/dl (20.5 μmol/L) or LDH of ≥ 600 IU/L

b) Plasma AST and ALT activities ≥ 70 IU/L

c) PLT count 50-100 x 10^9/L

Class 3 (mild):

a) TPB ≥ 1.2mg/dl (20.5 umol/L) or LDH of ≥ 600 IU/L

b) Plasma AST and ALT activities ≥ 40 IU/L

c) PLT count 100-150 x 10^9/L

Also, using the Memphis classification system:

1) Complete HELLP (cHELLP) syndrome: those with three aforementioned major components based on the Mississippi triple-class classification (severe, moderate, and mild) components.

2) Partial HELLP (pHELLP) syndrome: those with any two of the three components of the Mississippi triple-class classification system in addition to been diagnosed with severe preeclampsia.

2.7. Specimen Acquisition and Laboratory Analysis

During the study period, all specimen acquisition had been done while adhering to standard protocols. The laboratory analyses were carried out using fully automated chemistry and hematological analyzers in the study center by well-experienced analysts. At least two levels of commercial quality control materials were used to evaluate and monitor analytical errors during each run of analysis.

2.8. Data Management and Statistical Analysis

Data was initially inputted into Statistical Package for Social Science software version 25. Pattern of continuous data distribution was evaluated by the Shapiro-Wilk test. Data found not to be of normal distribution were subsequently log-transformed before analysis. Following analysis, derived continuous data were presented as mean ± standard deviation and comparison explored using the independent-samples t-test or one-way analysis of variance, where necessary. Correlations between the biochemical markers, as continuous data, were evaluated by the Pearson correlation coefficient (*r*). The predictive potentials of the biochemical markers for HELLP syndrome were explored by the receiver operating characteristic (ROC) curve. The area under the curve (AUC) was calculated to evaluate the predictive powers at 95% confidence intervals. Cut-off points were determined by searching for the maximum Youden's index (sensitivity + specificity – 1). A statistical significance was tested at a two-tailed p-value of < 0.05 (5%).

3. Results

During the study period (2011-2020), a total of 298 women of Nigeria origin were diagnosed with HELLP syndrome out of a total of 24,630 pregnancies. Out of the 298 diagnosed during the study period, 230 women met the inclusion criteria and were finally recruited for the study. Two hundred (n=200) of these cases of HELLP syndrome had complete HELLP syndrome (cHELLP) while 30 were diagnosed with partial HELLP (pHELLP) syndrome.

Table 1 depicts the distribution of key demographic, obstetric, clinical and HELLP-associated laboratory parameters obtained at diagnosis from the total (n=230), cHELLP (n=200), and pHELLP (n=30) HELLP syndrome subgroups. Those with cHELLP syndrome presented at an older age (28.07 ± 0.83 vs. 32.88 ± 4.42) and higher gestational age (33.15 ± 3.19 vs. 35.50 ± 0.56) compared with those with pHELLP ($p<0.05$). Furthermore, those with cHELLP had higher total plasma bilirubin (TPB), lactate dehydrogenase (LDH) activity, creatinine and plasma uric acid but lower plasma albumin concentration compared to those with pHELLP variant ($p < 0.05$) (Table 1).

Among the cHELLP syndrome subclasses as shown in Table 2, plasma creatinine and uric acid level showed an increasing trend with worsening severity from class 3 (mild) through to class 2 (moderate) and to class 1 (severe) cHELLP cases ($p < 0.05$). While a decreasing trend of plasma albumin was observed with increasing severity of the cHELLP cases from class 3 to class 1 ($p < 0.05$) (Table 2)

As depicted in Table 3, no significant correlation existed between the five HELLP established biochemical markers [Total plasma bilirubin (TPB), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), and platelet (PLT) count] and plasma creatinine, uric acid and albumin levels among the those with pHELLP syndrome ($p > 0.05$) (Table 3; Item A).

While among those with cHELLP variants, a significant correlation existed between the five established HELLP biochemical markers (TPB, AST, ALT, LDH, PLT count) and plasma creatinine, uric acid, and albumin levels among the those with pHELLP variants ($p < 0.05$) (Table 3; Item B). While positive associations were observed between TPB, AST, ALT, LDH and plasma creatinine and uric acid levels, a negative association existed between TPB, AST, ALT LDH and plasma albumin levels (Table 3; Item B).

However, PLT count maintained a positive correlation with plasma albumin levels (Table; Item B).

Plasma uric acid level exhibited the strongest positive correlation with TPB, AST, ALT and LDH and also maintained the strongest negative correlation with PLT count (Table 3; Item B).

As shown in Table 4, the ROC curve was used to explore the AUC of plasma creatinine, uric acid and albumin levels which were significantly associated with the five established

markers (TPB, AST, ALT, LDH, and PLT count) of HELLP syndrome ($p < 0.05$) among those with the cHELLP variant. At the uric acid cut-off value of 1.5 mmol/L, the plasma uric acid (AUC: 0.968; 95%CI: 0.913-1.000; $p<0.001$) level had the most robust AUC compared to those of plasma creatinine and albumin levels (Table 4).

Table 1. *Distribution of key demographic, obstetric, clinical, and HELLP-associated laboratory parameters obtained at diagnosis.*

Variables	Total HELLP n = 230 M±SD	Partial HELLP n = 30 M±SD	Complete HELLP n = 200 M±SD	p-value (Partial vs. Complete)
A. Demographic data				
Age (years)	31.47 ± 4.35	28.07 ± 0.83	32.88 ± 4.42	<0.001*
B. Obstetric data				
Gravidity	2.56 ± 1.411	2.55 ± 0.83	2.65 ± 1.42	0.226
Parity	1.82 ± 1.05	1.79 ± 0.95	1.85 ± 1.06	0.497
GA, weeks	33.38 ± 3.11	33.15 ± 3.19	35.50 ± 0.56	<0.001*
C. Clinical data				
SBP, mmHg	161.30 ± 6.76	161.96 ± 7.23	162.11 ± 6.65	0.132
DBP, mmHg	116.09 ± 7.34	115.66 ± 4.79	116.31 ± 2.03	0.117
D. HELLP-associated diagnostic markers				
TPB, µmol/L	71.95 ± 4.45	56.33 ± 3.33	74.30 ± 4.30	<0.001*
AST activity, IU/L	207.39 ± 7.46	207.44 ± 9.94	208.50 ± 7.82	0.163
ALT activity, IU/L	293.04 ± 8.85	279.59 ± 6.07	281.22 ± 5.58	0.342
LDH activity, IU/L	914.78 ± 14.83	537.33 ± 16.90	972.17 ± 12.30	<0.001*
PLT count, x 10^9/L	83.47 ± 12.23	86.66 ± 7.28	83.60 ± 8.28	0.530
E. Other biochemical markers under evaluation				
Plasma Sodium, mmol/L	138.13 ± 4.72	138.88 ± 2.66	138.95 ± 3.13	0.214
Plasma potassium, mmol/L	5.27 ± 0.62	4.98 ± 0.16	5.01 ± 0.32	0.167
Plasma HCO_3, mmol/L	19.08 ± 2.14	19.12 ± 1.96	19.11 ± 2.07	0.191
Plasma urea, mmol/L	7.78 ± 2.07	6.98 ± 0.59	7.12 ± 0.71	0.223
Plasma creatinine, umol/L	144.21 ± 5.15	143.95 ± 9.02	146.08 ± 8.71	<0.001*
RPG, mmol/L	9.90 ± 1.39	9.53 ± 0.67	9.61 ± 0.46	0.085
Plasma uric acid, mmol/L	2.25 ± 0.58	1.96 ± 0.57	2.66 ± 0.45	0.011*
Total plasma protein, g/L	60.17 ± 3.94	64.66 ± 2.90	59.50 ± 3.62	0.491
Plasma albumin, g/L	29.68 ± 3.52	34.33 ± 1.27	29.17 ± 3.22	<0.001*

*Statistically significant; M±SD: mean ± standard deviation; GA: gestation age; SBP: systolic blood pressure; DBP: diastolic blood pressure; mmHg: millimeter mercury; TPB: total plasma bilirubin; AST: aspartate aminotransferase enzyme; ALT: alanine aminotransferase enzyme; LDH: lactate dehydrogenase enzyme; PLT: platelet cell; HCO_3: bicarbonate; RPG: random plasma glucose

Table 2. *Comparison of other biochemical markers obtained at diagnosis among the three major HELLP subclasses.*

	Complete HELLP Syndrome Subclasses, n = 200			
Invalidated markers under evaluation	**Class 3 n = 70 M±SD**	**Class 2 n=110 M±SD**	**Class 1 n=30 M±SD**	**p-value**
Plasma sodium, mmol/L	138.28 ± 4.71	139.69 ± 6.63	138.66 ± 6.96	0.097
Plasma potassium, mmol/L	4.88 ± 0.53	5.31 ± 0.59	5.38 ± 0.96	0.245
Plasma bicarbonate, mmol/L	20.14 ± 2.04	18.76 ± 2.68	18.81 ± 2.66	0.098
Plasma urea, mmol/L	6.44 ± 1.94	8.98 ± 1.88	9.21 ± 2.01	0.106
Plasma creatinine, µmol/L	120.28 ± 4.07	146.46 ± 4.91	190.33 ± 4.07	<0.001*
RPG, mmol/L	9.60 ± 1.13	9.07 ± 1.37	9.98 ± 1.87	0.075
Plasma uric acid, mmol/L	1.96 ± 0.52	2.32 ± 0.57	2.93 ± 4.71	<0.001*
Total plasma protein, g/L	61.09 ± 4.56	60.93 ± 3.67	60.04 ± 2.90	0.078
Plasma albumin, g/L	30.57 ± 3.39	29.84 ± 3.69	27.21 ± 1.83	<0.001*

*Statistically significant; M±SD: mean ± standard deviation; RPG: random plasma glucose

Table 3. *Correlations of HELLP-defined biomarkers with other biochemical markers under evaluation among the partial and full HELLP syndrome cases.*

	Well-established markers of HELLP syndrome				
Invalidated markers under evaluation	**TPB r; p-value**	**AST r: p-value**	**ALT r; p-value**	**LDH r; p-value**	**PLT count r; p-value**
A. Incomplete HELLP					
Plasma creatinine	0.167; 0.085	0.131; 0.322	0.163; 0.513	0.043; 0.762	-0.216; 0.071
Plasma uric acid	0.116; 0.211	0.173; 0.382	0.227; 0.046	0.117; 0.075	-0.155; 0.063
Plasma albumin	-0.091; 0.354	-0.078; 0.101	-0.133; 0.366	-0.178; 0.088	0.097; 0.116
B. Complete HELLP					
Plasma creatinine	0.214; 0.031*	0.342; 0.011*	0.313; 0.043*	0.269; 0.032*	-0.311; 0.001*
Plasma uric acid	0.461;<0.001*	0.487;<0.001*	0.594; <0.001*	0.417; <0.001*	-0.503; 0.001*
Plasma albumin	-0.261; 0.001*	-0.218; 0.015*	-0.276; 0.002*	-0.361;<0.001*	0.167; 0.027*

*Statistically significant; r: Pearson's correlation coefficient; M±SD: mean ± standard deviation; GA: gestation age; SBP: systolic blood pressure; DBP: diastolic blood pressure; mmHg: millimeter mercury; TPB: total plasma bilirubin; AST: aspartate aminotransferase enzyme; ALT: alanine aminotransferase enzyme; LDH: lactate dehydrogenase enzyme; PLT: platelet cell; HCO_3: bicarbonate; RPG: random plasma glucose

Table 4. *ROC values of significant biomarkers of HELLP syndrome under evaluation among those with the complete HELLP syndrome.*

Invalidated markers under evaluation	Cut-off value	Sensitivity (%)	Specificity (%)	AUC	95% CI	p-value
Plasma creatinine	98 µmol/L	96.8	85.8	0.898	0.831 – 0.963	<0.001*
Plasma uric acid	1.5 mmol/L	100	88.9	0.968	0.913 – 1.000	<0.001*
Plasma albumin	32 g/L	98.5	87.5	0.924	0.892 – 0.996	<0.001*

*Statistically significant; AUC: area under the receiver operation characteristic curve; CI: confidence interval

4. Discussion

The study had evaluated and compared some invalidated biochemical markers related to the pathophysiology of HELLP syndrome with the well-established biochemical markers of this syndrome among women of Nigerian origin.

The study indicated that those with the complete HELLP syndrome presented at an older age and at higher gestational age compared to those with partial HELLP cases. Our findings concur with recent findings documented from two similar studies reported among pregnant women from Ethiopian and Canadian populations [12, 13]. However, Tyas and colleagues found no significant risk of HELLP syndrome with increasing maternal age among Indonesia women when compared with the younger age population [14].

The risk of HELLP with advancing maternal age has been adduced to the increased incidence of chronic hypertension, other comorbidities (e.g. diabetes, etc) and HELLP precursor agents (e,g. preeclampsia, etc) with increasing maternal age [12-14]. Genetic studies have shown that the pathogenesis of HELLP syndrome is hinged on placental dysfunction and the diminishing placental unit with advancing gestational may account for the increasing incidence of HELLP syndrome with advancing gestational age [15, 16].

In the current study, we also deduced that those diagnosed with the complete HELLP had higher total plasma bilirubin (TPB), lactate dehydrogenase (LDH) activity, creatinine, and plasma uric acid (UA) but lower plasma albumin concentration compared to those with the partial HELLP variant. These features are all factors related to the severity of the pathophysiologic basis of the complete HELLP variants of the syndrome compared to the partial variants [16-22]. Furthermore, these major characteristic findings could well be applied to distinguish these two variants of the syndrome in clinical practice.

The increased plasma creatinine and UA levels could be related to acute kidney injuries that often accompany HELLP syndrome and have also been reported in association with adverse outcomes of the syndrome [17, 19]. In a Chinese study, Ye and colleagues demonstrated that elevated creatinine level was an independent predictor of maternal/perinatal mortality in HELLP syndrome [17]. Meta-analysis of the role of serum UA levels among patients at risk of HELLP syndrome, reported by Bellos and colleagues, showed that the increased UA is associated with the incidence, prediction of adverse maternal/perinatal outcomes and the progression of the syndrome [19].

In a similar retrospective study documented in Turkey by Gedik and colleagues, the authors surmised that higher TPB levels and LDH activities, which are related to hemolytic episodes, reported among patients with HELLP syndrome are associated with high mortality risk and adverse complications of the syndrome [20]. Low plasma albumin levels have been reported to precede severe pregnancy-related hypertensive disorders (e.g. preeclampsia) known frequently to precipitate HELLP syndrome in the literature [21, 22]. Seong and colleagues had demonstrated that the risk of HELLP syndrome increases (OR: 12; CI: 3.1 - 45) in high-risk Korean women when the albumin levels fall below 25g/L [22].

Among those diagnosed with the complete HELLP syndrome, positive associations existed between the TPB, AST, ALT, LDH, and plasma creatinine and UA levels while a negative association was observed between TPB, AST, ALT LDH, and plasma albumin levels. However, PLT count maintained a positive association with plasma albumin levels. Similar observations had previously been documented by Duan and colleagues among severe preeclampsia patients in China [23]. These findings suggest that plasma creatinine, UA and albumin could complement the well-established markers of HELLP syndrome, especially the UA which had the strongest positive association and more robust ROC predictive values following analysis.

The study is limited by several factors that merit notification but do not in any way undermine its significance. Firstly, its retrospective design may have led to the under-reporting of the number of cases of HELLP syndrome identified. Secondly, as a single-centered and hospital-based study, its conclusions may not be representative of the entire population in the studied region. So, its findings should be interpreted and applied clinically with caution

5. Conclusion

The study had compared some invalidated biochemical markers related to the pathophysiology of HELLP syndrome with the well-established biochemical markers of this syndrome among black women of Nigerian origin. Among those diagnosed with the complete HELLP syndrome, a positive correlation existed between the TPB, AST, ALT, LDH and plasma creatinine and UA levels while a negative correlation was observed between TPB, AST, ALT LDH and plasma albumin levels. PLT count maintained a positive correlation with plasma albumin levels. This finding indicates that plasma creatinine, UA and albumin could complement the other established markers of HELLP syndrome. UA which had the strongest positive correlation with these established markers and more robust ROC area under the curve (AUC) characteristics may serve as an

adjunct marker to complement these well-established markers. However, further studies with more robust design are highly recommended to evaluate conclusions from this study.

Recommendations

Further investigations using more robust studies are highly recommended to evaluate the findings and conclusions from this current study.

Statement of Ethics

The ethical approval of the study was obtained from the Research Ethics Committee of UPTH following review of the study protocols.

Disclosure Statement

The authors declare that they have no competing interests.

Author Contributions

All the authors were involved substantially in the concept and design of the study, acquisition, analysis and interpretation of the data, drafting the article, revising the article critically for its intellectual content, and in the final approval of the version to be published.

Data Availability

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author (CA) upon reasonable request.

Acknowledgements

The authors appreciate all the efforts of the resident doctors for their professional assistance during the conduct of the study.

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