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ORIGINAL ARTICLE

Combined Immature Platelet Fraction and Schistocyte Count to Differentiate Pregnancy-Associated Thrombotic Thrombocytopenic Purpura from Severe Preeclampsia/Haemolysis, Elevated Liver Enzymes, and Low Platelet Syndrome (SPE/HELLP)

Rasha A. El-Gamal[1] · Mohamed A. Mekawy[1] · Ayman M. Abd Elkader[2,3] · Haitham M. Abdelbary[4] · Mary Z. Fayek[5]

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Abstract The occurrence of thrombotic microangiopathy (TMA) in pregnancy is an unfortunate emergency condition. Proper diagnosis is mandatory which requires the consideration of two overlapping diagnoses: severe preeclampsia/haemolysis, elevated liver enzymes, and low platelet syndrome (SPE/HELLP) and thrombotic thrombocytopenic purpura (TTP). The long turn-around times of ADAMTS13 testing precludes the timely distinction between the two conditions. We aimed at evaluating schistocyte counts and immature platelet fraction (IPF%), as both increase in TMAs, to discriminate between TTP and SPE/HELLP of pregnancy. IPF% was measured using Sysmex XE-2100 automated hematology analyzer, and schistocyte counts were estimated microscopically as per the International Council for Standardization in Hematology-Schistocyte Working Group guidelines. The study included 30 pregnant patients with SPE/HELLP, 13 pregnant patients with TTP, and 30 women with normal pregnancy. The discrimination between the two patient categories was based on clinical judgment and TTP cases were identified using the PLASMIC score. TTP patients had higher values of IPF% than SPE/HELLP [19.5% (16.9–27.1) vs 13% (9.5–23.25); $p < 0.001$]; similar results were revealed regarding schistocyte counts [6.5% (3.9–8.6) vs 2.1% (1.6–3.5); $p < 0.001$]. IPF% and schistocyte counts were able to discriminate between TMA patients and normal pregnant women, and between and SPE/HELLP and TTP patients. Moreover, the discriminatory function of each was improved when the two parameters were used in combination. IPF% analysis should be used in conjunction with manual schistocyte counting in TMA cases to distinguish TTP pregnant patients from patients having SPE/HELLP.

Keywords HELLP · Immature platelet fraction · Pregnancy · Schistocytes · TTP

Introduction

Thrombotic microangiopathies (TMAs) occurring during pregnancy is a distressing event which mandates immediate response to save maternal and fetal lives. Diverse clinical syndromes might be the underlying cause. However, the possibility of the presence of severe preeclampsia or its microangiopathic hemolytic anemia (MAHA)-related subtype, haemolysis elevated liver enzymes and low blood platelet count syndrome (SPE/HELLP), or thrombotic thrombocytopenic purpura (TTP), should always be considered [1, 2].

HELLP syndrome and TTP might share some clinical and laboratory findings, and because the definite diagnosis of TTP (in the form of ADAMTS13 activity level $\leq 10\%$) is usually not available for a timely diagnosis, the distinction between the two conditions becomes more challenging [3, 4]. Essentially, the exact diagnosis of either condition is required because the management plan differs:

✉ Rasha A. El-Gamal
rashaelgamal@hotmail.com

1 Hematology Unit, Department of Clinical Pathology, Ain Shams University, Cairo, Egypt

2 Department of Obstetrics and Gynaecology, Ain Shams University, Cairo, Egypt

3 Present Address: Frimley Park Hospital, Frimley, UK

4 Clinical Hematology and Bone Marrow Transplantation Unit, Department of Internal Medicine, Ain Shams University, Cairo, Egypt

5 Department of Clinical Pathology, Misr University for Science and Technology (MUST), Giza, Egypt

while therapeutic plasma exchange (TPE) is the treatment of choice for TTP, termination of pregnancy remains the definitive treatment in HELLP syndrome and fails to ameliorate the condition of TTP [5, 6]. Adding another level of complexity, some cases of SPE/HELLP syndrome don't improve after intervention [7].

Certain laboratory parameters were introduced to make up for the delayed ADAMTS13 results. For example, higher LDH/AST ratios were suggested to favor the diagnosis of TTP [8], and the PLASMIC scoring system to predict ADAMTS13 activity $\leq 10\%$ [9].

The value of schistocyte counts in TTP diagnosis has been repeatedly evaluated and a general cutoff value of 1% was concluded to diagnose TTP [10, 11]. More recently, a consensus report was published by Schistocyte Working Group of the International Council for Standardization in Hematology (ICSH), which was directed to standardize schistocyte identification, enumeration, and reporting in TMA conditions [12].

Different platelet indices were employed to differentiate thrombocytopenic disorders, among which is the relatively high RNA content of platelets found in the immature platelet fraction (IPF%) [13]. IPF% was found to reflect the level of platelet production in the bone marrow, showing higher values in consumptive thrombocytopenia [14–16].

Our plan in this study was to evaluate the two important signs of MAHA in pregnancy-associated TMA conditions: IPF%, reflecting a consequence of thrombocytopenia, and schistocyte count that represents the harmful effect of TMA. We aimed at assessing their combined effect in discriminating TTP from cases of SPE/HELLP syndrome.

Materials and Methods

The Study sample included 73 pregnant women admitted to Ain Shams University Maternity Hospital over a period of 2.25 years (from 2016 till 2018) with a maternal age older than 20 years. Exclusion criteria included multiple pregnancies, pregnancies of congenital malformations, recent blood transfusion, and history of liver, kidney, or autoimmune diseases.

Subjects included in the study comprised a control pregnant group (n = 30) having normal pregnancy with normal blood pressure and platelet count, and TMA group (n = 43) presenting with thrombocytopenia and/or hypertension. Subjects of the latter group were subclassified into 2 subgroups: SPE/HELLP subgroup (n = 30), and TTP subgroup (n = 13).

SPE/HELLP syndrome was provisionally diagnosed by the presence of one or more specific findings (hypertension ($> 160/110$ mmHg), platelet count $< 100 \times 10^9$/L, increased liver enzymes (twice normal concentrations) with severe upper quadrant or epigastric pain, serum creatinine > 1.1 mg/dL, pulmonary edema, cerebral or visual symptoms) in women meeting the basic criteria of preeclampsia (i.e. blood pressure $> 140/90$ mmHg and proteinuria) [17]. The development of MAHA (marked by peripheral blood (PB) schistocytes) in the setting of thrombocytopenia, increased indirect bilirubin, and elevated AST (twice normal concentrations), were used to indicate the presence of HELLP syndrome [18]. TTP was suspected when patients presented with severe thrombocytopenia (typically $< 30 \times 10^9$/L) and MAHA, in addition to symptoms of organ ischemia/infarction mostly neurologic [19].

According to presenting symptoms and laboratory tests results, termination of pregnancy after trial of proper control of the patients' conditions was the treatment option for those with a provisional diagnosis of SPE/HELLP, whereas TPE was done for suspected TTP diagnosis. In case of recovery after delivery, TTP was excluded and the diagnosis of SPE/HELLP syndrome was given. The suspected TTP patients, as well as patients who showed progression of symptoms despite delivery, were subjected to applying the PLASMIC score [9] where one point was assigned for each of the following data if met: no active cancer, no history of solid-organ or stem-cell transplant, platelets $< 30 \times 10^9$/L, mean corpuscular volume < 90 fL, creatinine < 2.0 mg/dL, INR < 1.5, and a hemolysis variable (reticulocyte count $> 2.5\%$, indirect bilirubin > 2.0 mg/dL, or undetectable haptoglobin). Those who scored 7 were diagnosed as TTP, followed by initiation or continuation of TPE. Confirmation of the diagnosis of TTP by ADAMTS13 assay couldn't be afforded for all patients enrolled in the study.

An informed consent was taken from all subjects with clear explanation of the aim of the research.

Laboratory Investigations

EDTA-anticoagulated venous PB samples were obtained after preliminary diagnosis of TMA and before TPA or pregnancy termination was done. CBC testing was performed using XE-2100® (Sysmex Corporation, Kobe, Japan). Estimation of IPF% was done within 4 h of collection, employing an upgraded software (XE-Pro Series; Sysmex). IPF absolute count (A-IPF) was calculated by multiplying optical platelet count by IPF%. Microscopic counting of schistocytes was done using Romanwsky-stained PB smears, in at least 1000 RBCs in optimal areas of the film at 100× power magnification, with interpretation of results following the ICSH recommendations [12]. The counts were blindly reviewed by two competent morphologists. Manual reticulocyte count was estimated by examination of brilliant cresyl blue-stained blood films.

Citrated samples were tested for prothrombin time and international normalized ratio (INR) values using STAGO

COMPACT CT ST4 analyzer (Diagnostica Stago, France). Assessment of serum lactate dehydrogenase (LDH), serum bilirubin, liver enzymes (ALT & AST), serum uric acid, and kidney function tests was done using HITACHI 912 automatic analyzer (Roche Diagnostics GmbH., Germany).

Statistical Methods

Data were analyzed using IBM© SPSS© Statistics version 22 (IBM© Corp., Armonk, NY, USA) and MedCalc© version 14 (MedCalc© Software bvba, Ostend, Belgium).

The normality of numerical data was tested by the Shapiro–Wilk test. Parametric numerical variables were presented as mean ± SD and groups were compared using one-way analysis of variance (ANOVA) with application of the Schéffé test for post hoc pair-wise comparison. Non-parametric numerical variables were presented as median (interquartile range) and groups were compared using the Kruskal–Wallis test; post hoc comparisons were done using the Conover test.

Categorical variables were presented as number (%) and differences were compared using Fisher's exact test. Correlations among numerical variables were tested using the Spearman rank correlation. Receiver-operating characteristic (ROC) curve analysis was used to examine the value of the IPF or the schistocyte count in discrimination different study groups. The DeLong method was used to compare the areas under ROC curves.

Multivariable binary logistic regression analysis was used to examine the value of the IPF or schistocyte count in discrimination between patients with SPE/HELLP and TTP patients with adjustment for the possible confounding effect of the gestational age. A two sided p value < 0.05 was considered statistically significant.

Results

Demographic and Laboratory Data of the Study Groups

The distribution of different parities and previous abortions were comparable among the three groups (Table 1).

All subjects in the study were enrolled after 20 weeks of pregnancy. On comparing the gestational ages of the two patient groups, no statistical significant difference was revealed (31.4 ± 2.3 vs 32.5 ± 2.8 weeks in SPE/HELLP and TTP, respectively; $p = 0.1$).

The two patient subgroups had significantly lower platelet count, higher IPF% and schistocyte counts, and lower A-IPC when compared with the control group; these changes were more pronounced in the TTP group than in the SPE/HELLP group. Prevalence of reduced platelet count, increased IPF% [20] and increased schistocyte count [12] in each group is shown in Table 2.

Correlation Between Platelet Counts, IPF%, and Schistocyte Count

In SPE/HELLP group, a moderate negative correlation was detected between platelet count and IPF% ($\rho = -0.522$, $p = 0.003$), and a weak negative one between platelet count and schistocyte count ($\rho = -0.27$, $p = 0.15$). In TTP group, weak negative correlations were detected between platelet count and each of IPF% and schistocyte count ($\rho = -0.436$, $p = 0.137$; $\rho = -0.49$, $p = 0.08$, respectively). Other weak correlations were found between the IPF% and schistocyte count in either patient group (rho values ranged from 0.058 to 0.231).

Evaluation of the Discriminating Power of IPF% and Schistocyte Count Between SPE/HELLP and TTP

The diagnostic ability of IPF% and schistocyte count to differentiate between SPE/HELLP and TTP groups and between TMA patients and healthy pregnant women was estimated using ROC curve analysis (Fig. 1; Table 3). Multivariable binary logistic regression analysis has shown that IPF% and schistocyte counts were independent predictors for TTP (Table 4).

The predicted probabilities estimated from multivariable binary logistic regression analysis were used in the design of a ROC curve using the IPF% and schistocyte count, combined. The model had a good predictive value to discriminate TTP from SPE/HELLP, as evidenced by increased AUC (0.827), with estimated sensitivity of 92.3% and specificity of 62.5%. However, there was no significant difference revealed on comparing the AUC value of the ROC curve of the combined use of both parameters to AUC values of either marker alone (Table 5).

Discussion

Previous studies that evaluated IPF% and schistocyte counts were primarily concerned with the value of either one, independently, in discriminating TMA conditions from normal states, and some included minor preeclamptic population as control subjects. In this study, our aim was to show if estimating IPF% combined with schistocyte counting, based on ICSH-Schistocyte Working group criteria, would positively contribute in discriminating TTP from cases of SPE/HELLP syndrome, with acceptable levels of sensitivity and specificity.

Table 1 Characteristics of SPE/HELLP and TTP patients and normal controls

Variable	SPE/HELLP (n = 30)	TTP (n = 13)	Control (n = 30)	F/χ^2	*p* value
Age (years)	28.24 ± 5.8	27.7 ± 5.2	26.0 ± 4.6	1.83	0.162
Parity					
P0	8 (26.7%)	2 (15.4%)	7 (23.3%)	7.3	0.504
P1	6 (20.0%)	7 (53.8%)	7 (23.3%)		
P2	10 (33.3%)	2 (15.4%)	9 (30.0%)		
P3	2 (6.7%)	1 (7.7%)	5 (16.7%)		
P4	3 (10%)	1 (7.7%)	2 (6.7%)		
P5	1 (3.33%)	0 (0.0%)	0 (0.0%)		
Previous abortions					
Nil	28 (93.3%)	12 (92.3.0%)	27 (90.0%)	1.47	0.83
One	2 (6.7%)	1 (7.7%)	1 (3.3%)		
Three	0 (0.0%)	0 (0.0%)	2 (6.7%)		
Systolic blood pressure (mmHg)	192 ± 17.5†	183 ± 7*†	109 ± 9	322.9	< 0.0001
Diastolic blood pressure (mmHg)	109 ± 14†	108 ± 9*†	78 ± 6	64.28	< 0.0001
LDH (IU/l)	720 ± 410†	893 ± 435.6*†	190.7 ± 25.3	12.72	0.003
Albuminuria					
3+	6 (20%)	7 (53.8%)	Absent	4.95	0.084
4+	13 (43.33%)	3 (23.08%)	Absent		
5+	11 (36.67%)	3 (23.08%)	Absent		
Hemoglobin (g/dl)	10.5 ± 1.6	11.1 ± 1.9	11.4 ± 1.2	1.773	0.180
Hematocrit (%)	32.3 ± 5.7	33.1 ± 6.5	34.9 ± 3.3	1.457	0.242
Platelet count ($\times 10^9$/L)	121 (73–188.5)†	21 (12–28)†‡	269.5 (235–337)	35.333	< 0.0001
Immature platelet fraction (%)	13 (9.5–23.25)†	19.5 (16.9–27.1)†‡	7.2 (6.2–11.1)	18.897	< 0.0001
Immature platelet count ($\times 10^9$/L)	14.9 (12–21.4)†	4.1 (2.3–5.6)†‡	21.9 (16.9–25.4)	10.362	0.006
Schistocyte count (%)	2.1 (1.6–3.5)†	6.5 (3.9–8.6)†‡	0.02 (0.0–0.2)	27.186	< 0.0001

Data presented as mean ± SD, or number (percentage)

SPE/HELLP severe preeclampsia/hemolysis, elevated liver enzymes, low platelet syndrome, *TTP* thrombotic thrombocytopenic purpura

*No statistically significant difference versus SPE/HELLP group (Student T test)

$^{\dagger}p$ value < 0.05 versus control group (Conover test)

$^{\ddagger}p$ value < 0.05 versus SPE/HELLP group (Conover test)

Table 2 Prevalence of low platelet count, high IPF%, or high schistocyte count among patients with SPE/HELLP or TTP and normal controls

Variable	SPE/HELLP n (%)	TTP n (%)	Control n (%)	*p* value
Low platelet count (< 140 × 10^9/L)	21 (70%)	13 (100%)	0 (0.0%)	< 0.001
High IPF% (> 7.4%)[a]	24 (80%)	11 (84.6%)	12 (40.0%)	0.001
High schistocyte count (> 1%)[b]	26 (86.7%)	13 (100%)	0.0 (0.0%)	< 0.001

IPF% immature platelet fraction, *SPE/HELLP* severe preeclampsia/hemolysis, elevated liver enzymes, low platelet syndrome, *TTP* thrombotic thrombocytopenic purpura

[a]Ko et al. [20]

[b]Zini et al. [12]

The inclusion of TTP cases in our study was done by careful selection of patients who met certain criteria that we believed to be adequate for an assured diagnosis in the absence of ADAMTS13 testing. The newly developed PLASMIC scoring was one fundamental criterion. Patients who were clinically suspected as having TTP (or those showing no improvement after pregnancy termination) and scored 7, were diagnosed as TTP. The choice of score 7 to identify TTP cases has relied on the results of previous studies, where Bendapudi et al. had shown that TTP cases

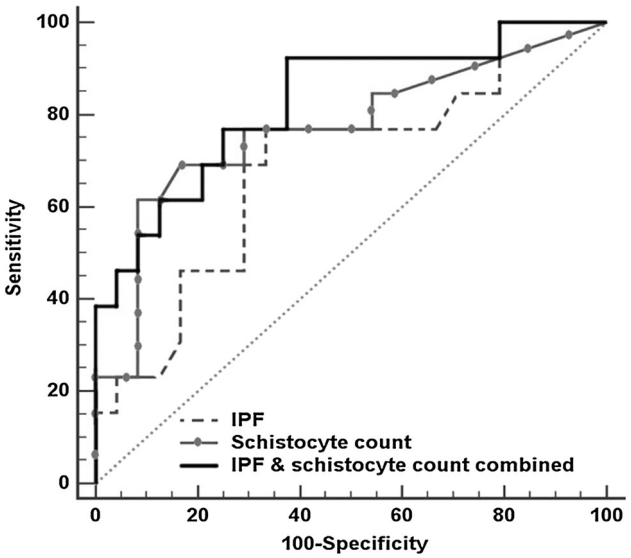

Fig. 1 Comparison of the ROC curves for discrimination between patients with TTP or SPE/HELLP using the IPF, schistocyte count, or IPF and schistocyte count

with ADAMTS13 activity levels < 10% (n = 200) had a median score of 7, whereas other TMA conditions scored 5 or less [9]. Another study had shown a specificity of 100% for TTP cases that scored 7, though number of patients were very limited (n = 7) [21].

Reference limits for IPF% were found highly dependent on the analyser used. The effect of ethnic background was questionable, but generally no differences between genders were found [20, 22–24]. In the study of Ko et al., conducted on 2104 healthy individuals using Sysmex XE-2100, an upper limit was determined at 7.4% [20]. Using their IPF% threshold level, our results have shown that 80% of SPE/HELLP patients and nearly 85% of TTP patients had high IPF% levels. Surprisingly, 40% of normally pregnant females have exceeded the value of 7.4%, and a cut off value of 8.1% was found reliable to define TMA patients. This can be explained by the fact that the threshold value of 7.4% was estimated in healthy non-pregnant subjects, while IPF% was reported to increase during normal pregnancy [25].

The increased IPF% in TTP and SPE/HELLP is consistent with the concept of increased thrombopoeisis occurring to compensate for the increased platelet consumption [16, 26]. The highest levels IPF% were detected in TTP patients (median 20%; range 8.6-39.7), who also had the lowest platelet and A-IPF counts. However, the value of comparing platelet count and A-IPC is limited by the selection criteria of TTP patients where only those with PLASMIC score 7 (i.e. platelet counts $< 30 \times 10^9$/L) were included, and consequently, A-IPF count was inevitably decreased by the marked thrombocytopenia.

Briggs et al. have reported similar results with a mean value of 17.2% for IPF% in TTP patients (range 11.2–30.9; n = 11), whilst their mean value of A-IPF was 5.4×10^9/L (range 1.2–9.1) which is merely comparable to our results [27]. The elevated IPF% values in the SPE/HELLP group were similar to the results of Everett et al. in which significantly higher IPF% were found in preeclamptic pregnant women than their normotensive counterpart [26].

In 2012, the ICSH Schistocyte Working Group has set definite criteria for identification of schistocytes in a

Table 3 Receiver-operating characteristic (ROC) curve analysis for discrimination between the study groups and subgroups using the IPF% or schistocyte count

Two groups for discrimination	Index	IPF-%	Schistocyte count
TMA versus normal controls	AUC	0.83 (0.728–0.932)	0.987 (0.979–0.995)
	p value	< 0.0001	< 0.0001
	Associated cut-off criterion	8.1%	0.6%
	Sensitivity (%)	86.49	100
	Specificity (%)	65	76.8
	PPV (%)	82.1	86
	NPV (%)	72.2	100
SPE/HELLP versus TTP	AUC	0.692 (0.519–0.833)	0.77 (0.603–0.893)
	p value	0.043	0.003
	Associated cut-off criterion	16.8	4.6
	Sensitivity (%)	76.92	69.23
	Specificity (%)	75	87.5
	PPV (%)	62.5	75
	NPV (%)	85.7	84

IPF% immature platelet fraction, *TMA* thrombotic microangiopathy, *AUC* area under the curve, *PPV* positive predictive value, *NPV* negative predictive value, *SPE/HELLP* severe preeclampsia/hemolysis, elevated liver enzymes, low platelet syndrome, *TTP* thrombotic thrombocytopenic purpura

Table 4 Multivariable binary logistic regression analysis for discrimination between SPE/HELLP and TTP using IPF% and schistocyte count, combined

Variable	Regression coefficient (B)	SE for B	Wald	*p* value	Odds ratio (OR)	95% CI for OR
IPF (%)	0.104	0.048	4.666	0.031	1.110	1.010–1.220
Schistocyte count (%)	0.107	0.046	5.283	0.022	1.113	1.016–1.219
Constant	− 3.251					

SPE/HELLP severe preeclampsia/hemolysis, elevated liver enzymes, low platelet syndrome, *TTP* thrombotic thrombocytopenic purpura, *IPF%* immature platelet fraction, *SE* standard error, *CI* confidence interval

Table 5 Comparison of the receiver-operating characteristic (ROC) curves for discrimination between patients with SPE/HELLP and TTP using the IPF%, schistocyte count, or IPF% and schistocyte count combined

Marker	AUC	95% CI
IPF%	0.692	0.519–0.833
Schistocyte count	0.771	0.603–0.893
IPF% and schistocyte count combined	0.827	0.667–0.931

Marker	Difference between AUCs	95% CI	Z statistic	*p* value
IPF% versus schistocyte count	0.079	− 0.171 to 0.328	0.617	0.537
IPF% versus IPF% and Schistocyte count combined	0.135	− 0.034 to 0.303	1.569	0.117
Schistocyte count versus IPF% and schistocyte count combined	0.056	− 0.085 to 0.197	0.780	0.435

SPE/HELLP severe preeclampsia/hemolysis, elevated liver enzymes, low platelet syndrome, *TTP* thrombotic thrombocytopenic purpura, *IPF%* immature platelet fraction, *AUC* area under the curve, *CI* confidence interval

standardized procedure [12]; the agreed-upon 1% of schistocyte count that would diagnose TMA was accepted by the Working Group. Several studies have validated the ICSH schistocyte guidelines [28, 29]. However, they were considered questionable by the French Group of Cellular Hematology [30]. Our study has followed the ICSH specific recommendations, and, indeed, schistocyte counts in most TMA patients were higher than 1%, and a discriminatory cutoff value to distinguish TMA cases was determined at the level of 0.6% (sensitivity: 100%, specificity: 76.8%). Also, we had considerably higher median values of schistocytes in TTP patients (6.5%, IQR: 3.9–8.6) when compared to schistocyte counts of either the SPE/HELLP patients (2.1%, IQR: 1.6–3.5) or healthy pregnant females (0.02%, IQR: 0.0–0.2). The study of Schapkaitz and Mezgebe has reported a mean schistocyte percentages of 3.51 ± 1.88% in TTP (n = 68), and 2.42 ± 1.6% in HELLP (n = 5) [29]. Another earlier study has reported mean values of 8.35% in TTP, 0.25% in preeclampsia, and 0.05% in healthy subjects, though their criteria for identifying and counting schistocytes were not elucidated [10].

A-IPF was not studied in terms of setting a cut off to differentiate between the two TMA conditions because, as previously mentioned, it's a calculated parameter dependent on platelet count. Meanwhile, because of the weak negative correlation between IPF% and platelet count in TTP patients, we considered IPF% a reliable differentiating marker. We evaluated the ability of IPF% to discriminate between TTP and SPE/HELLP at the determined optimal cutoff value of 16.8%; sensitivity and specificity were 76.92% and 75%, respectively. Likewise, a cut off value for schistocyte count of 4.6% was determined that showed a fair diagnostic efficiency marked by sensitivity and specificity of 69.23% and 87.5%, respectively.

Multivariate analysis of our results has confirmed that each of IPF% and schistocyte count can perform independently in discriminating TTP from SPE/HELLP. Nonetheless, their combined use in the differential diagnosis of the two conditions has relatively promoted the AUC, with general upgrading of the diagnostic specifications, affecting mainly sensitivity. Yet, this added value was not statistically significant.

We believe that using schistocytes percentage, following the recommendations of ICSH-Schistocyte Working group, together with the non-invasive indicator of real time thrombopoiesis, IPF%, might resolve the diagnostic obstacles in cases with severe microangiopathic hemolysis. We recommend examining the time-dependent changes in both parameters to monitor SPE/HELLP and TTP cases before and in response to proper treatment. Despite the measures made in our study to clearly classify patients into TTP and SPE/HELLP diseases in view of the inconvenient lack of ADAMTS13 results, still, evaluating the efficacy of IPF% and schistocyte count based on diagnosing TTP cases with < 10% ADAMTS13 activity is crucial. This would

allow the inclusion of different spectra of TTP syndrome, not only severely thrombocytopenic conditions, providing wider scope of using the two parameters in settings where TMA of pregnancy is an important diagnostic consideration.

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Compliance with Ethical Standards

Conflict of interest The authors report no declarations of interest.

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