International Journal of General Medicine

Dovepress
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ORIGINAL RESEARCH

Detecting Preeclampsia Severity Using Maternal-Obstetrical Characteristics and Complete Blood Cell Counts

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Purpose: This study aimed to use the combination of maternal-obstetrical characteristics (MOCs) and complete blood cell counts (CBCs) with different red blood cell (RBC) indices as an alternative tool to detect preeclampsia (PE) severity immediately before delivery.

Patients and Methods: This retrospective study included all singleton pregnancies delivered after 24 weeks of gestation from April 2016 to April 2020. Patients were divided into four different groups: non-hypertensive (NH), gestational hypertension (GH), PE, and severe PE (SPE). Univariate and forward stepwise multivariate logistic regression analysis was conducted using MOCs, CBCs, and RBC indices. The calculation was performed between SPE and other non-hypertensive and hypertensive (GH, PE) groups. Moreover, the area under the curve (AUC) for the receiver operating characteristic curve, sensitivity, and specificity were estimated.

Results: The combined variables for differentiating SPE from NH were maternal age >29.5 years, weight >27.24, gestational age <272 days at the time of blood withdrawal, platelet count <217.5×103/μL, Srivastava indices <6.35, and Siradah indices <43.02 (AUC, 0.834; 95% confidence interval [CI], 0.773–0.895). The combined variables for differentiating SPE from GH were maternal age >29.5 years, body mass index >25.28, gestational age <268.5 days at the time of blood withdrawal, mean corpuscular volume <78.85 fL, and platelet count <234.5×103/μL (AUC, 0777; 95% CI, 0.703–0.852). The combined variables for differentiating SPE from PE were maternal age >32.5 years, mean corpuscular hemoglobin concentration >34.55 g/dL, and Siradah indices <40.05 (AUC, 0.745; 95% CI, 0.656–0.833).

Conclusion: The combination of selected variables from MOCs and CBCs with RBC indices before delivery showed satisfactory results for detecting PE severity.

Keywords: hypertension, pregnancy, preeclampsia, preeclampsia severity, complete blood counts

Introduction

The progression of preeclampsia (PE) severity is subtle and unpredictable Severe features of the PE (SPE) may represent the most critical form of hypertension during pregnancy and can result in maternal and fetal complications or mortality if not immediately treated.[1] Several methods focus on early trimester screening, such as those of angiogenic factors or biomarkers.[2,3] However, the recent pandemic outbreaks and the isolation policies hindered blood pressure tracking throughout prenatal visits.[4] Therefore, more emphasis has been placed on instant treatment or management protocols for the sudden incidence of previously undetected SPE.[5] The urge to recognize SPE further emphasizes the importance of the Committee Opinion of the American College of Obstetricians and Gynecologists (ACOG) in 2019. The ACOG recommended that antihypertensive treatment be initiated within 30–60 min of systolic blood pressure (SBP) exceeding 160 mmHg or diastolic blood pressure (DBP) exceeding 110 mmHg.[6]

The current guideline for immediately diagnosing preeclampsia severity depends mainly on blood pressure levels and proteinuria,[7] which wavered its accuracy. Several reasons support this apprehension of blood pressure assessment during

Received: 17 October 2022
Accepted: 18 December 2022
Published: 23 December 2022

pregnancy, including the measurement technique, maternal position, labor pain, wrong cuff size, food intake, white coat syndrome, and many other factors.[8,9] Proteinuria accuracy may also be influenced by many factors, such as dehydration and stress during pregnancy.[10] In this regard, alternative predictive tools have been designed to improve the accuracy of diagnosis of the severity of preeclampsia.[11,12]

Our study was focused on hypertensive pregnancies immediately before delivery that corresponds well with those without routine prenatal visits during the pandemic. In order to adapt to the recent change in ACOG treatment guidelines and the wavering blood pressure or proteinuria accuracy, we aimed to use an efficient alternative method of combining maternal-obstetrical characteristics (MOCs) and complete blood cell counts (CBCs) with different red blood cell (RBC) indices[13] to evaluate and further confirm PE severity immediately.

Materials and Methods

Study Design and Setting

This retrospective cohort study was conducted at the Cardinal Tien Hospital, a regional teaching hospital in Taiwan. The corresponding data from April 1, 2016, to April 30, 2020, were retrieved from electronic medical records or delivery report books, manually recorded according to the patient chart identification number, and revised twice by two reviewers before being included. This study was conducted following the provisions outlined in the Declaration of Helsinki and was approved by the Institutional Review Board of the Cardinal Tien Hospital (approval number: CTH-109-3-5-019). Patient rights were protected during the collection of medical records, and all personal identifiers were anonymized prior to analysis.

Participants and Variables

The population comprised singleton pregnancies delivered at gestational age (GA) more than 24 weeks. The exclusion criteria were as follows: patients with precipitated labor, missing values, maternal body mass index (BMI) >40, maternal pre-existing hematological and oncological diseases that may affect the hematological profile, active infection or fever at the time of blood collection, blood transfusion within two weeks of current pregnancy, drug abuse, fetal anomaly, fetal death, and maternal death.

The total population was categorized into four different groups: non-hypertensive (NH), gestational hypertension (GH), PE, and SPE (Figure 1). The diagnosis of PE was based on the criteria of the ACOG guidelines for hypertension during pregnancy (Supplementary Table 1). Gestational hypertension is defined as SBP ≥140 mmHg or DBP ≥90 mmHg. Preeclampsia is defined as SBP ≥140 mmHg or DBP ≥90 mmHg with urinary protein ≥300 mg/24 h, protein-to-creatinine

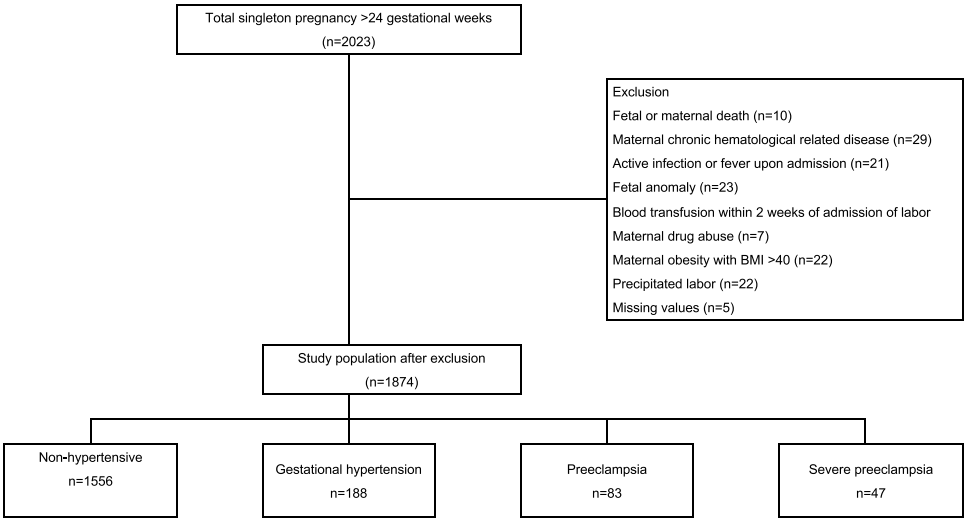

Figure 1 Flow diagram of the total population.

ratio ≥0.3, or dipstick ≥2+ or, in the absence of proteinuria with thrombocytopenia, renal insufficiency (creatinine >1.1 mg/dL or doubling), liver dysfunction (liver transaminase level twice that of the normal range), pulmonary edema, new-onset headache unresponsive to medication, or visual symptoms. Severe PE is defined as SBP ≥160 mmHg or DBP ≥110 mmHg, with symptoms similar to PE.[7]

Data Measurement and Study Size

The hematology tests, blood pressure, and urine protein are routinely performed in our hospital at the time of admission for delivery according to our hospital's healthcare policy. Before recording the blood pressure, the delivery ward nurses measure the blood pressure twice with a 4-h interval if the blood pressure is higher than 140/90 mmHg (for either SBP or DBP). For severely elevated blood pressure (either SBP >160 mmHg or DBP >110 mmHg), measurements are performed twice within 30 min. All measurements are performed according to the ACOG guidelines.

The collection of MOCs included maternal age, weight, height, GA at delivery, the status of pregestational diabetes, previous uterine surgery, parity, the number of abortions, epidural analgesia use, delivery mode, and meconium staining after membrane rupture. In addition, newborn characteristics were recorded, including birth weight, height, 1-min APGAR score, 5-min APGAR score, and whether the newborn was admitted to the neonatal intensive care unit. The CBC included white blood cells, RBCs, hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration (MCHC), and platelet count. The different RBC indices were calculated according to individual formulas listed in Supplementary Table 2.[13]

Statistical Analyses

All statistical analyses were performed using IBM SPSS Statistics for Macintosh version 27.0 (IBM Corp., Armonk, NY, USA). Data normality was analyzed using the Kolmogorov–Smirnov test. For continuous data, the Kruskal–Wallis test and the Mann–Whitney *U*-test were used for multiple group comparison and binary group comparison for baseline characteristics, respectively. The calculation was analyzed between SPE and PE, GH, and NH, with all data presented as medians (interquartile ranges). Categorical data were analyzed using Pearson's chi-squared test. All the statistical significance was set at $p<0.05$. Univariate and multivariate logistic regression models were used to test all variables in MOCs and CBCs with RBC indices to predict SPE based on NP, GH, and PE, respectively. The forward stepwise multivariate logistic regression analysis was calculated using univariate logistic models with $p<0.10$. The area under the curve (AUC) for the receiver operating characteristic curve was used to analyze the cut-off value selected by the Youden index for each variable of MOCs, CBCs, and RBC indices in each binary group comparison, with the sensitivity and specificity noted. The final predictive value combining all probabilities of significant variables from the MOCs, CBCs, and RBC indices was calculated with AUC and the sensitivity and specificity for each comparison group.

Results

The total number of participants was 1874 after the exclusion, including those with NH (n=1556), GH (n=188), PE (n=83), and SPE (n=47). The population, exclusion criteria, and sample size for each group are shown in Figure 1. The general MOCs and newborn characteristics with CBCs and RBC indices are presented in Table 1. Multiple group comparisons showed that the SPE group had significantly higher maternal age, BMI, and RBC levels than the other groups. On the other hand, the SPE group had a significantly lower GA at the time of blood withdrawal, Mentzer, Srivastava, and Ehsani RBC indices. The pairwise comparisons performed in each variable between SPE and other groups are also shown in Table 1. The result revealed that the NH and SPE groups show significant differences in pregestational diabetic status, APGAR score in the first minutes, the newborn's weight, RBC, MCV, platelet counts, and all RBC indices except Shine and Lal. Comparison between the GH and SPE groups showed a significant difference in the MCV, platelet count, Mentzer, Siradah, and Ehsani RBC indices. The MCHC, platelet count, and Siradah RBC indices significantly differed between the PE and SPE groups (Table 1).

Table 1 Maternal-Obstetrical and Newborn Characteristics and Complete Blood Cell Counts

Variables	NH (n=1566)	GH (n=188)	PE (n=83)	SPE (n=47)	*p-value	**Pairwise Comparison		
						NH Vs SPE	GH Vs SPE	PE Vs SPE
Maternal characteristics								
Age (years)	32 (7)	33 (7)	32 (8)	34 (7)	0.006	<0.001	0.008	0.003
BMI	26.4 (4.5)	28.5 (7.5)	29.3 (6.6)	29.9 (6.7)	<0.001	<0.001	0.042	0.326
Pregestational Diabetes					0.006	0.004	0.314	0.109
Present	48 (3.1)	12 (6.4)	3 (4.4)	5 (10.6)				
Absent	1508 (96.9)	176 (93.6)	80 (96.4)	42 (89.4)				
UWPS					0.251	0.272	0.062	0.400
Present	77 (4.9)	5 (2.7)	4 (4.8)	4 (8.5)				
Absent	1479 (95.1)	183 (97.3)	79 (95.2)	43 (91.5)				
Obstetrical characteristics								
Parity					0.604	0.313	0.737	0.136
Primigravida	811 (52.1)	117 (62.2)	60 (72.3)	28 (59.6)				
Multigravida	752 (47.9)	71 (37.8)	22 (27.7)	19 (40.4)				
Abortion					0.604	0.758	0.669	0.558
≤3	1474 (94.7)	177 (94.1)	81 (97.6)	45 (95.7)				
>3	82 (5.3)	11 (5.9)	2 (2.4)	2 (4.3)				
GA at the time of blood withdrawal (days)	271 (10)	272 (10)	270 (10)	268 (14)	0.001	<0.001	<0.001	0.105
Delivery mode					0.021	0.002	0.005	0.060
Vaginal delivery	1292 (83.0)	158 (84.0)	67 (80.7)	31 (66.0)				
Cesarean section	264 (17.0)	30 (16.0)	16 (19.3)	16 (34.0)				
Epidural analgesia					0.285	0.929	0.866	0.219
No	1266 (81.4)	154 (81.9)	59 (71.1)	38 (80.9)				
Yes	292 (18.6)	34 (18.1)	24 (28.9)	9 (19.1)				
Meconium stain					0.958	0.432	0.130	0.266
Positive	38 (2.4)	2 (1.1)	1 (1.2)	2 (4.3)				
Negative	1518 (97.6)	186 (98.9)	82 (98.8)	45 (95.7)				
Newborn characteristics								
Sex					0.712	0.410	0.328	0.535
Female	801 (51.5)	93 (49.5)	43 (51.8)	27 (57.4)				
Male	755 (48.5)	95 (50.5)	40 (48.2)	20 (42.6)				
APGAR score 1st minute					0.002	0.003	0.106	0.792
Normal (≥7)	1523 (97.9)	182 (96.8)	77 (92.8)	43 (97.5)				
Low (<7)	32 (2.1)	6 (3.2)	6 (7.2)	4 (8.5)				
APGAR score 5th minute					0.588	0.581	0.728	0.450
Normal (≥7)	1545 (99.4)	187 (99.4)	82 (98.8)	46 (97.9)				
Low (<7)	10 (0.6)	1 (0.6)	1 (1.2)	1 (2.1)				
Weight (grams)	3030 (475)	3020 (545)	3025 (580)	2870 (625)	0.077	0.015	0.055	0.201
Height (cm)	49.5 (3)	49.5 (2.5)	49.5 (3.0)	48.5 (4.0)	0.151	0.044	0.199	0.214
Admission to NICU					0.378	0.085	0.258	0.266
No	1536 (98.7)	185 (98.4)	82 (98.8)	45 (95.7)				
Yes	20 (1.3)	3 (1.6)	1 (1.2)	2 (4.35)				
Complete blood cell counts								
WBC ($\times 10^3/\mu L$)	9.22 (3.18)	9.44 (2.82)	9.82 (3.23)	9.39 (2.90)	0.257	0.791	0.866	0.351
RBC ($\times 10^6/\mu L$)	4.03 (0.51)	4.16 (0.52)	4.09 (0.50)	4.24 (0.68)	<0.001	0.003	0.373	0.337
Hemoglobulin (g/dL)	11.5 (1.8)	12.1 (1.6)	11.7 (1.3)	11.9 (2.0)	<0.001	0.075	0.462	0.435
Hematocrit (%)	33.8 (4.4)	35.7 (3.8)	34.6 (4.0)	34.6 (5.0)	<0.001	0.202	0.123	0.902
MCV (fL)	84.7 (8.9)	85.0 (7.4)	83.2 (8.8)	83.6 (11.1)	0.094	0.050	0.024	0.378
MCH (pg)	28.9 (4.3)	29.2 (3.6)	28.2 (3.5)	28.8 (5.6)	0.282	0.612	0.367	0.670
MCHC (g/dL)	34.0 (1.9)	34.0 (1.8)	33.7 (1.8)	34.5 (2.4)	0.074	0.059	0.201	0.023
Platelet ($10^3/\mu L$)	235 (84)	243 (92)	241 (70)	213 (78)	0.093	0.020	0.014	0.025

(*Continued*)

Table 1 (Continued).

Variables	NH (n=1566)	GH (n=188)	PE (n=83)	SPE (n=47)	*p-value	**Pairwise Comparison		
						NH Vs SPE	GH Vs SPE	PE Vs SPE
Different RBC indices (mathematical formulas)								
Mentzer Index (MCV/RBC)	20.97 (4.05)	20.44 (3.60)	19.94 (4.42)	18.91 (5.40)	<0.001	0.003	0.038	0.187
Shine and Lai (MCV^2xMCH/100)	2076 (723)	2119 (637)	1973 (660)	2054 (879)	0.182	0.169	0.084	0.740
Sirvastava (MCH/RBC)	7.15 (1.54)	6.93 (1.34)	6.87 (1.62)	6.45 (2.20)	0.004	0.037	0.193	0.602
Siradah (MCV-RBC-3Hb)	45.47 (7.74)	44.34 (7.17)	44.17 (7.52)	41.83 (9.09)	<0.001	<0.001	0.006	0.040
Ehsani (MCV – 10RBC)	44.1 (11.6)	43.3 (10.4)	41.2 (12.5)	40.0 (15.7)	0.003	0.004	0.024	0.194

Notes: Data are expressed as median (interquartile range); number (percentage%). *P*-value <0.05 considered significant. *Kruskal Wallis for the multiple comparisons. **Mann–Whitney *U*-test for the pairwise comparison.

Abbreviations: NH, non-hypertensive; GH, gestational hypertension; PE, preeclampsia; SPE, severe preeclampsia; UWPS, uterus with previous surgery; GA, gestational age; NICU, neonatal intensive care unit; WBC, white blood cell; RBC, red blood cell; MCV, mean corpuscular volume; MCH, mean cell hemoglobin; MCHC, mean corpuscular hemoglobin concentration.

SPE and NH

The univariate and forward stepwise multivariate logistic regression comparison results for the MOC, CBC, and RBC indices variables between SPE and NH are shown in Table 2. The forward stepwise multivariate logistic regression model

Table 2 Comparison of Maternal-Obstetrical Characteristics and Complete Blood Cell Indices Between Severe Preeclampsia and Non-Hypertensive Patients

Variables	Univariate OR (95% CI)	p-value	Forward Stepwise Multivariate OR (95% CI)	p-value
Maternal characteristics				
Age (years)	1.100 (1.038–1.166)	0.001	1.092 (1.022–1.167)	0.009
BMI	1.234 (1.150–1.324)	<0.001	1.259 (1.167–1.358)	<0.001
Pregestational Diabetes		0.008		
Present	3.740 (1.417–9.873)			
Absent	0.267 (0.101–0.706)			
UWPS		0.279		
Present	1.787 (0.625–5.105)			
Absent	0.560 (0.196–1.599)			
Obstetrical characteristics				
Parity		0.315		
Primigravida	1.354 (0.750–2.445)			
Multigravida	0.739 (0.409–1.334)			
Abortion		0.759		
≤3	0.799 (0.190–3.351)			
>3	1.252 (0.298–5.250)			
GA at the time of blood withdrawal (days)	0.970 (0.952–0.988)	0.002	0.962 (0.940–0.985)	0.002
Epidural analgesia		0.929		
No	1.034 (0.495–2.162)			
Yes	0.967 (0.462–2.022)			
Meconium stain		0.439		
Positive	1.775 (0.415–7.588)			
Negative	0.563 (0.132–2.407)			
Complete blood cells (CBCs)				
WBC ($\times10^3/\mu L$)	0.993 (0.889–1.107)	0.899		
RBC ($\times10^6/\mu L$)	2.713 (1.515–4.857)	<0.001		

(*Continued*)

Table 2 (Continued).

Variables	Univariate OR (95% CI)	p-value	Forward Stepwise Multivariate OR (95% CI)	p-value
Hemoglobulin (g/dL)	1.300 (1.050–1.610)	0.016		
Hematocrit (%)	1.091 (1.003–1.187)	0.042		
MCV (fL)	0.971 (0.937–1.006)	0.106		
MCH (pg)	0.980 (0.902–1.065)	0.641		
MCHC (g/dL)	1.261 (1.017–1.565)	0.035		
Platelet ($10^{\wedge}3/\mu L$)	0.993 (0.988–0.998)	0.006	0.992 (0.986–0.998)	0.006
Different RBC indices (mathematical formulas)				
Mentzer index (MCV/RBC)	0.889 (0.818–0.967)	0.006		
Shine and Lal (MCV^2xMCH/100)	1.000 (0.999–1.000)	0.193		
Srivastava (MCH/RBC)	0.804 (0.646–0.999)	0.049	2.479 (1.214–5.062)	0.013
Siradah (MCV-RBC-3Hb)	0.929 (0.893–0.967)	<0.001	0.758 (0.685–0.899)	<0.001
Ehsani (MCV-10xRBC)	0.968 (0.945–0.992)	0.010		

Note: Univariate logistic models with p<0.01 were included in the forward stepwise multivariate logistic regression analysis.
Abbreviations: UWPS, uterus with previous surgery; GA, gestational age; WBC, white blood cell; RBC, red blood cell; MCV, mean corpuscular volume; MCH, mean cell hemoglobin; MCHC, mean corpuscular hemoglobin concentration.

showed that maternal age, BMI, GA at the time of blood withdrawal, platelet, Srivastava, and Siradah RBC indices were significant. However, the greatest odds ratio (OR) observed was for the Srivastava RBC indices before delivery (2.479; 95% CI, 1.214–5.062, p=0.013), and the smallest OR observed was for GA at the time of blood withdrawal (0.962; 95% CI, 0.940–0.985, p=0.002).

SPE and Hypertensive Pregnancy (GH and PE)

The forward stepwise multivariate logistic regression was performed between SPE and other hypertensive groups (GH and PE) for comparisons (Tables 3 and 4). The maternal age, BMI, GA at the time of blood withdrawal, MCV, and

Table 3 Comparison of Maternal-Obstetrical Characteristics and Complete Blood Cell Indices Between Severe Preeclampsia and Gestational Hypertension

Variables	Univariate OR (95% CI)	p-value	Forward Stepwise Multivariate OR (95% CI)	p-value
Maternal characteristics				
Age (years)	1.084 (1.016–1.158)	0.015	1.101 (1.021–1.188)	0.013
BMI	1.078 (1.002–1.159)	0.043	1.116 (1.026–1.213)	0.010
Pregestational diabetes		0.319		
Present	1.746 (0.583–5.226)			
Absent	0.319 (0.191–1.714)			
UWPS		0.077		
Present	3.405 (0.877–13.213)			
Absent	0.294 (0.076–1.140)			
Obstetrical characteristics				
Parity		0.737		
Primigravida	1.118 (0.582–2.148)			
Multigravida	0.894 (0.465–1.718)			
Abortion		0.670		
≤3	0.715 (0.153–3.342)			
>3	1.398 (0.299–6.534)			
GA at the time of blood withdrawal (days)	0.935 (0.902–0.969)	<0.001	0.928 (0.890–0.966)	<0.001

(*Continued*)

Table 3 (Continued).

Variables	Univariate OR (95% CI)	p-value	Forward Stepwise Multivariate OR (95% CI)	p-value
Epidural analgesia use		0.866		
No	1.073 (0.474–2.426)			
Yes	0.932 (0.412–2.108)			
Meconium staining		0.162		
Positive	4.133 (0.567–30.142)			
Negative	0.242 (0.033–1.764)			
Complete blood cells				
WBC ($\times 10^3/\mu L$)	0.978 (0.856–1.117)	0.743		
RBC ($\times 10^6/\mu L$)	1.516 (0.765–3.003)	0.233		
Hemoglobulin (g/dL)	0.999 (0.811–1.231)	0.993		
Hematocrit (%)	0.978 (0.900–1.062)	0.593		
MCV (fL)	0.995 (0.914–0.997)	0.038	0.946 (0.897–0.998)	0.041
MCH (pg)	0.951 (0.863–1.048)	0.308		
MCHC (g/dL)	1.215 (0.947–1.560)	0.126		
Platelet ($10^3/\mu L$)	0.993 (0.987–0.998)	0.007	0.990 (0.983–0.996)	0.002
Different RBC indices (Mathematical formulas)				
Mentzer index (MCV/RBC)	0.913 (0.821–1.015)	0.092		
Shine and Lal (MCV^2xMCH/100)	0.999 (0.999–1.000)	0.083		
Srivastava (MCH/RBC)	0.854 (0.650–1.123)	0.259		
Siradah (MCV-RBC-3Hb)	0.938 (0.891–0.988)	0.015		
Ehsani (MCV-10RBC)	0.968 (0.925–0.998)	0.037		

Notes: Univariate logistic models with p-value <0.10 were considered in forward stepwise multivariate logistic regression analysis.
Abbreviations: UWPS, uterus with previous surgery; GA, gestational age; WBC, white blood cell; RBC, red blood cell; MCV, mean corpuscular volume; MCH, mean cell hemoglobin; MCHC, mean corpuscular hemoglobin concentration.

Table 4 Comparison of Maternal-Obstetrical Characteristics and Complete Blood Cell Indices Between Severe Preeclampsia and Preeclampsia

Variables	Univariate OR (95% CI)	p-value	Forward Stepwise Multivariate OR (95% CI)	p-value
Maternal characteristics				
Age (years)	1.099 (1.024–1.179)	0.009	1.114 (1.030–1.204)	0.007
BMI	1.052 (0.965–1.146)	0.250		
Pregestational diabetes		0.126		
Present	3.175 (0.723–13.936)			
Absent	0.315 (0.072–1.383)			
UWPS		0.406		
Present	1.837 (0.438–7.714)			
Absent	0.544 (0.130–2.285)			
Obstetrical characteristics				
Parity		0.138		
Primigravida	1.770 (0.832–3.767)			
Multigravida	0.565 (0.265–1.202)			
Abortion		0.563		
≤3	0.556 (0.076–4.079)			
>3	1.800 (0.245–13.21)			
GA at the time of blood withdrawal (days)	0.970 (0.936–1.006)	0.098		

(*Continued*)

Table 4 (Continued).

Variables	Univariate OR (95% CI)	p-value	Forward Stepwise Multivariate OR (95% CI)	p-value
Epidural analgesia use		0.222		
No	1.718 (0.721–4.091)			
Yes	0.582 (0.244–1.387)			
Meconium staining		0.296		
Positive	3.644 (0.322–41.31)			
Negative	0.442 (0.127–1.864)			
Complete blood cells				
WBC ($\times 10^3/\mu L$)	0.922 (0.814–1.045)	0.206		
RBC ($\times 10^6/\mu L$)	1.583 (0.716–3.452)	0.248		
Hemoglobulin (g/dL)	1.148 (0.899–1.466)	0.267		
Hematocrit (%)	1.017 (0.926–1.117)	0.723		
MCV (fL)	0.974 (0.925–1.026)	0.326		
MCH (pg)	1.011 (0.903–1.132)	0.851		
MCHC (g/dL)	1.412 (1.071–1.132)	0.015	1.586 (1.153–2.181)	0.005
Platelet ($10^3/\mu L$)	0.992 (0.986–0.998)	0.014		
Different RBC indices (mathematical formulas)				
Mentzer index (MCV/RBC)	0.941 (0.838–1.056)	0.299		
Shine and Lai ($MCV^2xMCH/100$)	1.000 (0.999–1.001)	0.631		
Srivastava (MCH/RBC)	0.948 (0.707–1.272)	0.723		
Siradah (MCV-RBC-3Hb)	0.945 (0.891–1.002)	0.057	0.898 (0.837–0.964)	0.003
Ehsani (MCV-10RBC)	0.976 (0.940–1.014)	0.209		

Notes: Univariate logistic models with p-value <0.10 were considered in forward stepwise multivariate logistic regression analysis.
Abbreviations: UWPS, uterus with previous surgery; GA, gestational age; WBC, white blood cell; RBC, red blood cell; MCV, mean corpuscular volume; MCH, mean cell hemoglobin; MCHC, mean corpuscular hemoglobin concentration.

platelet count were significantly different between SPE and GH. Simultaneously, a comparison between SPE and PE showed that maternal age, MCHC, and Siradah RBC indices were significantly different. The greatest OR of 1.116 (95% CI, 1.026–1.213) was observed when comparing SPE to GH for maternal BMI and a lower OR of 0.928 (95% CI, 0.890–0.966) was observed with the same comparison for GA at the time of blood withdrawal. On the other hand, the highest OR of 1.568 (95% CI, 1.153–2.181) was for the MCHC level, and the lowest OR of 0.898 (95% CI, 0.837–0.964) was for Siradah RBC indices when comparing SPE to PE.

Diagnostic Accuracy

The AUC which was performed on the significant variables ($p<0.05$) in the forward stepwise multivariate logistic regression analysis for each binary group comparison between SPE, and others is summarized in Table 5. The AUC for SPE prediction from NH was 0.834 (95% CI, 0.773–0.895) for the combined variables from MOCs, CBCs, and RBC indices. The AUC for the combined variables was 0.777 (95% CI, 0.703–0.852) for the prediction of SPE from GH and 0.745 (95% CI, 0.656–0.833) for the prediction of SPE from PE. The cut-off values for each significant variable of MOCs and CBCs are shown in Table 6.

Discussion

Principal Findings

This study showed that combining MOCs, CBCs, and RBC indices can efficiently differentiate SPE from hypertension (PE and GH groups) and NH groups. An AUC value is considered acceptable when it is greater than 0.7, and values between 0.8 and 1.0 represent excellent diagnostic potential. The AUC values in our study for distinguishing SPE from NH, PE, and GH were 0.83, 0.78, and 0.75, respectively. Thus, combining certain variables from MOCs, CBCs, and RBC indices can effectively predict PE severity. The following metrics can be used:

Table 5 The Area Under the Curve for Maternal-Fetal Characteristics and Complete Blood Cell Counts in Each Binary Group Comparison

	Severe preeclampsia vs non-hypertension				
MOCs	**AUC (95% CI)**	**p-value**	**Cut-off**	**Specificity (%)**	**Sensitivity (%)**
Age (years)	0.642 (0.563–0.721)	0.001	>29.5	32.0	89.4
BMI	0.728 (0.652–0.804)	<0.001	>27.24	59.5	77.3
GA at the time of blood withdrawal (days)	0.642 (0.564–0.719)	0.001	<272	49.7	72.3
Complete blood cell counts					
Platelet (10^3/μL)	0.600 (0.515–0.683)	0.020	<217.5	62.9	55.3
Different RBC indices (mathematical formulas)					
Srivastava (MCH/RBC)	0.589 (0.501–0.678)	0.037	<6.35	74.4	48.9
Siradah (MCV-RBC-3Hb)	0.663 (0.580–0.746)	<0.001	<43.02	67.5	61.7
Combination	†0.834 (0.773–0.895)	<0.001		84.3	70.5
	Severe preeclampsia vs gestational hypertension				
MOCs	**AUC**	**p-value**	**Cut-off**	**Specificity (%)**	**Sensitivity (%)**
Age (years)	0.619 (0.529–0.710)	0.011	>29.5	89.4	39.2
BMI	0.600 (0.511–0.687)	0.042	>25.28	39.3	90.0
GA at the time of blood withdrawal (days)	0.665 (0.580–0.749)	<0.001	<268.5	68.6	57.4
Complete blood cell counts					
MCV (fL)	0.606 (0.514–0.698)	0.024	<78.85	83.5	40.4
Platelet (10^3/μL)	0.616 (0.526–0.706)	0.014	<234.5	54.3	68.1
Combination	‡0.777 (0.703–0.852)	<0.001		77.0	65.9
	Severe preeclampsia vs preeclampsia				
MOCs	**AUC**	**p-value**	**Cut-off**	**Specificity (%)**	**Sensitivity (%)**
Age (years)	0.656 (0.559–0.753)	0.003	>32.5	58.8	66
Complete blood cell counts					
MCHC (g/dL)	0.620 (0.516–0.724)	0.023	>34.55	75.9	48.9
Different RBC indices (mathematical formulas)					
Siradah (MCV-RBC-3Hb)	0.608 (0.505–0.712)	0.040	<40.05	68.77	55.3
Combination	§0.745 (0.656–0.833)	<0.001		61.2	78.7

Notes: †AUC for the combination of predicted probability of maternal age, weight, BMI, GA at the time of blood withdrawal, platelet, Srivastava and Siradah RBC indices in severe preeclampsia from non-hypertensive. ‡AUC for the combination of predicted probability for maternal age, BMI, GA at the time of blood withdrawal, MCV, and platelet in severe preeclampsia and gestational hypertension. §AUC for the combination of predicted probability for maternal age, MCHC, and Siradah RBC indices in severe preeclampsia and preeclampsia. *p*-value <0.05 is considered significant.

Abbreviations: GH, gestational hypertension; MOCs, maternal-obstetrical characteristics; GA, gestational age; MCV, Mean corpuscular volume; MCHC, mean corpuscular hemoglobin concentration AUC; area under the curve.

1. To differentiate between SPE and PE (sensitivity, 78.7%; specificity, 61.2%): maternal age >32.5 years, MCHC >34.55 g/dL, and Siradah index <40.5
2. To differentiate between SPE and GH (sensitivity, 65.9%; specificity, 77%): maternal age >29.5 years, BMI>25.28, GA <268.5 days at blood withdrawal, MCV <78.85 fL, and platelet count <234.5×10^3/μL
3. To differentiate between SPE and NH (sensitivity, 70.5%; specificity, 84.3%): maternal age >29.5 years, BMI>27.24, GA <272 days at blood withdrawal, platelet count <217.5×10^3/μL, Srivastava index <6.35, and Siradah index <43.02

Comparison with Other Studies in the Literature

Some studies have relied purely on CBCs to predict PE, such as Kirabas et al[14] and Örgül et al,[15] who mainly analyzed the early-trimester CBCs. Both studies differ from ours since we have compared the CBCs and RBC indices obtained just

Table 6 Cut-off Values from the Significant Variables in Maternal-Obstetrical Characteristics and Complete Blood Cell Counts for Each Severity Comparison Groups

	SPE and NH	SPE and GH	SPE and PE
Maternal-obstetrical characteristics			
Age (years)	> 29.5	> 29.5	> 32.5
BMI	> 27.24	>25.28	
GA at the time of blood withdrawal (days)	< 272	< 268.5	
Complete blood cell counts			
MCV (fL)		<78.85	
MCHC (g/dL)			> 34.55
Platelet ($10^3/\mu L$)	< 217.5	< 234.5	
Different RBC indices (mathematical formulas)			
Srivastava (MCH/RBC)	<6.35		
Siradah (MCV-RBC-3Hb)	<43.02		<40.05

Abbreviations: SPE, severe preeclampsia; NH, non-hypertensives; GH, gestational hypertension; PE, preeclampsia; GA, gestational age; MCV, Mean corpuscular volume; MCHC, mean corpuscular hemoglobin concentration.

before delivery (late trimester). Jeon et al[16] used modified CBCs from the late trimester to differentiate between PE and GH; however, our study was able to define metrics that differentiate SPE from PE, GH, or NH. Recently, Bulbul et al[17] analyzed CBC metrics for differentiation between SPE and NH in each trimester. Similarly, they only compared NH with SPE, whereas our study also compared hypertension (PE and GH) with SPE. In addition, their CBC parameters are quite different from ours because they did not include RBC or MCV or different RBC indices, which were significant predictors of SPE in our study. Many studies have been conducted on the neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and platelet-to-neutrophil ratio in PE.[18–20] Our study utilized pure CBCs and different RBC indices from calculation without differential counts because they may be affected by a calibration reference error or lipidemia.[21,22] Maternal characteristics have also been used to predict PE alone or in combination with other serum markers.[23,24] Overall, our study is the first to use different RBC indices in comparison. On the contrary, most studies used RBC or RBC volume distribution width (RDW) to detect PE. We used a combination of MOCs with CBCs and RBC indices to evaluate SPE from other groups.[25,26]

Clinical Implications

Blood pressure screening in the early trimester is critical in diagnosing preeclampsia and its severity. However, due to the recent pandemic outbreak, routine prenatal visits or regular blood pressure monitoring are impeded by quarantine or isolation policy.[27] Concerning this, unpredicted hypertensive or preeclamptic pregnancy cases have emerged,[28] implying that more alternative or adjunctive diagnostic methods are needed. Due to the recent guideline of immediate treatment for severe preeclampsia, a rapid and efficient method of detecting this is also crucial. All of the above can be answered by our study, which uses the simple method of combing the MOCs, CBCs, and RBC indices to detect preeclampsia severity. Furthermore, solely relying on blood pressure measurement to determine PE severity may be challenging and sometimes may bring about over or under-treatment.[29] A recent expert review has stated that many factors would affect blood pressure during the peripartum period.[9] Therefore, much other literature has brought about alternative predicting methods that use biomarkers and angiogenic factors that have shown promising results in predicting early trimester PE;[30,31] however, each has shortcomings regarding clinical implications and availability. A fluorescence immunoassay device takes 7–14 days to process the diagnostic results for this test; therefore, it is neither simple nor efficient.[32] Markers such as this can be used to screen for PE but are not rapid enough to detect sudden-onset late SPE. Our method of combining MOCs, CBCs, and RBC indices which are measured in the late trimester is easy to comprehend and interpret by almost all physicians in different specialties and allows multidisciplinary cooperation without delay. Moreover, it is much more cost-effective than other biomarkers or angiogenic factors. All the above statements support that our detection method addresses the clinical ambiguity on whether to continue antihypertensive agents or initiate magnesium sulfate during emergency treatment. Considering that several drugs have side

effects on pregnancy, over-treatment or under-treatment should be avoided.[33,34] The implication of using the combination of variables from MOCs, CBCs, and RBCs indices is also applicable and available in every healthcare institution.

Strengths and Limitations

The strength of our study is that we characterized PE severity based on the comparison of SPE with NH and hypertension (PE and GH). In contrast to previous studies that only used a single parameter to measure the accuracy of diagnosis, we combined the MOCs, CBCs, and RBC indices parameters to increase the diagnostic accuracy.

This study had some limitations. First, it was a retrospective study, and some missing data or maternal clinical symptoms could not be included or obtained. Second, this study only analyzed data from a single hospital. In the future, we may propose a prospective study to reduce the incidence of missing data, expand the research to include multiple hospitals, and include patients' clinical features in the design.

Conclusion

Although all efforts are aimed at introducing alternative or adjunctive methods for predicting PE, there is a need for a simple and easily performed method. In an event of SPE crisis or emergency, time is the most crucial factor. We need the diagnostic studies that can instantly obtain results and are comprehensible by physicians in every field are vital. Our study revealed that complex biomarkers for assessing PE severity are unnecessary, as simple MOCs and blood cell parameters can easily achieve this.

Acknowledgments

We thank Dr. Lu Sung-Kuei for his valuable and constructive suggestions during the planning and development of this study. We also acknowledge the work of Tsai Yi-Chun, a nurse, for her assistance in the study.

Author Contributions

All authors made significant contributions to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article, and gave final approval of the version to be published. Further, all authors have agreed on the journal to which the article has been submitted and agree to be accountable for all aspects of the work.

Funding

There is no funding to report.

Disclosure

The authors report no conflicts of interest in this work.

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