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Assessment efficacy of neutrophil-lymphocyte ratio and monocyte-lymphocyte ratio in preeclampsia

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ABSTRACT

Objective: Abnormal changes in immune-mediated inflammation contribute to the pathogenesis of preeclampsia (PE). We aim to investigate the value of systemic immune inflammation indices—neutrophil-lymphocyte ratio (NLR) and monocyte-lymphocyte ratio (MLR)—to identify and evaluate the prognosis of patients with PE.

Methods: This study reviewed clinical records of 367 PE patients (162 with mild PE and 205 with severe PE), in addition to a control group of 172 normal pregnancies. Blood cell counts were performed at the first diagnosis of PE, and NLR and MLR were calculated by absolute cell count.

Results: Absolute neutrophil, lymphocyte, and monocyte counts and NLR and MLR values in PE were significantly different from controls, although monocyte counts did not significantly differ between mild and severe PE. Receiver operating characteristics curve (ROC) analysis showed NLR and MLR had better diagnostic accuracy in distinguishing PE from controls [NLR area under the curve (AUC) = 0.70; MLR AUC = 0.78]. Further, NLR was the best predictor of disease severity (AUC = 0.71). Cutoff values of NLR > 4.198 or MLR > 0.325 for control and PE groups or a cutoff value of NLR > 4.182 for PE groups indicated that patients were more likely to encounter preterm delivery, have shorter admission-to-delivery interval, and develop maternal and neonatal complications.

Conclusion: Secondary analyses of white blood cell differential count parameters effectively evaluate the systemic inflammatory/immune state. Compared with absolute cell counts, NLR and MLR offer more effective indicators of clinical assessment, disease severity evaluation, and prognosis evaluation of PE.

1. Introduction

Preeclampsia (PE) is an idiopathic multisystem disorder of unknown etiology that affects ˜2%–8% of pregnancies. It usually occurs after 20 weeks of pregnancy and affects both the mother and fetus, resulting in increased maternal and neonatal mortality and morbidity. PE is defined as the combination of high blood pressure, swelling, and albuminuria in a pregnant woman. In severe cases, PE may lead to maternal end-organ dysfunction, systemic disease (hemolysis, thrombocytopenia, and high liver transaminase), negative long-term maternal outcomes, and adverse perinatal outcomes of early and late onset intrauterine growth restriction (Milosevic-Stevanovic et al., 2016; Dacaj et al., 2016). The main causes of PE are unclear, although recent studies have confirmed that PE is associated with excessive inflammation and abnormal immune responses (Visser et al., 2007; Staff et al., 2014).

A normal pregnancy can be considered a successful semi-allograft reaction. Suitable inflammatory state of the maternal (maternal-fetal interface) and systemic immune system induces blastocyst implantation; induces trophoblast cell proliferation, differentiation, and infiltration; and promotes placental growth and development (Mor and Kwon, 2015; Laresgoiti-Servitje, 2013). Thus, the balance between immune and inflammatory responses might be an important determinant in maintaining pregnancy. PE can be considered an over-activated inflammatory response of abnormal maternal immune tolerance to

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accept the fetal semi-allograft. Changes in peripheral blood inflammatory cells (Harmon et al., 2016), T lymphocyte subsets (Toldi et al., 2015), acute reactive protein (Stubert et al., 2016), plasma inflammatory cytokine factors (Das, 2015), complement activity, and coagulation system-induced systemic inflammatory response may be specific manifestations of PE (Pinheiro et al., 2013).

Systemic immune inflammation indices derived from peripheral blood cells have recently attracted much attention because they are easily measurable and available. These combined indices are calculated based on basic parameters, such as neutrophil-lymphocyte ratio (NLR) and monocyte-lymphocyte ratio (MLR), and have been widely applied to diagnose and treat patients with septic shock (Hwang et al., 2017), axial spine arthritis (Seng et al., 2018), chordoma (Hu et al., 2018), and hepatocellular carcinoma (Ji et al., 2016). Abnormal changes in white blood cell counts have been observed in PE (Elgari et al., 2018), although the role of these systemic inflammatory indicators in clinical assessment, differential diagnosis, and prognosis evaluation of PE remains unclear.

PE is a progressive, unpredictable, and incurable disease, and the only current treatment is timely termination of pregnancy. Therefore, early identification of PE is beneficial for close clinical monitoring of patients and can safely extend pregnancy through effective nursing. In this study, our goal was to investigate the value of systemic inflammatory indices (NLR and MLR) as indicators for disease and as a theoretical basis for early diagnosis, assessment of severity, and prognosis of PE.

2. Methods

2.1. Study participants

A total of 367 women with PE [162 with mild PE (MPE) and 205 with severe PE (SPE)] were recruited from the Department of Obstetrics at the Nantong Women and Children Health Care Hospital during January 2014–July 2018. There were no significant differences between the two groups in terms of maternal and gestational ages. Diagnoses of PE were based on reported American Congress of Obstetricians and Gynecologists (ACOG) clinical criteria. In brief, PE diagnoses meet the following criteria: systolic blood pressure (SBP) of ≥140 mm Hg and/or diastolic blood pressure (DBP) of ≥90 mm Hg on two occasions at least 4 h apart; and proteinuria (> 0.3 g per day) after 20 weeks gestation. SPE was diagnosed based on further elevated blood pressure (SBP ≥ 160 mm Hg or DBP ≥ 110 mm Hg) or at least one of the following clinical symptoms: pulmonary edema, microvascular disease, thrombocytopenia, impaired liver function, and peripheral severe organ involvement (visual impairment and headache). Patients who had other obstetric medical complications or histories of autoimmune disorders were excluded from the study.

As a control group, we enrolled 172 women with a normal pregnancy who had no maternal medical complications or histories of autoimmune disorders during the same period. Use of patient medical record data was approved by the Nantong Women and Children Health Care Hospital Ethics Committee, and written informed consent was obtained for all individuals. 170 non-pregnancy women who received health examination were included to explore normal pregnancy systemic inflammatory/immune response.

Specific indices were defined as follows: “adverse pregnancy frequency” was the frequency of miscarriage, intrauterine fetal death, or arrested embryonic development; “maternal morbidity” referred to any physical illness directly related to pregnancy; “adverse neonatal outcome” referred to respiratory distress syndrome, intrauterine growth retardation, acute and chronic hypoxia, preterm delivery, or stillbirth; and “preterm delivery” was defined as delivery at < 34.0 weeks.

2.2. Blood sample counts

We collected 2-mL venous blood samples with EDTA-K-2 anticoagulant, and whole blood counts were performed on a Beckman Coulter LH 750 hematology analyzer (Beckman Coulter Inc., Brea, CA, USA). Each sample was tested twice, and the average value of the two readings was used for analysis. NLR was calculated by dividing absolute blood neutrophil count by absolute lymphocyte count. MLR was calculated by dividing absolute monocyte count by absolute lymphocyte count.

2.3. Statistical analysis

All statistical analyses and graphical presentations were performed using Prism 5.0 software (GraphPad, San Diego, CA, USA). Data are presented as mean ± standard deviation (SD) for continuous variables and number of subjects (n) and percentage (%) for categorical variables. Two-sample t-tests and multiple comparisons were conducted using one-way analysis of variance (ANOVA). If significant heterogeneity of variance was detected, the Welch’s ANOVE test was performed. Chi-squared test was used to compare categorical variables. Optimal cut-off values, defined as points with maximal sum of sensitivity and specificity, were calculated using receiver operating characteristic (ROC) curves. ROC curves were used to evaluate diagnostic value of novel inflammatory markers NLR and MLR in PE diagnosis, and area under the curve (AUC) was compared to determine the discriminative ability of a parameter. Binary logistic regression was used to assess the magnitude of association between biomarkers and pregnancy outcomes. Magnitude of associations of biomarkers with maternal morbidity, adverse neonatal outcome, and preterm delivery were adjusted for potential confounders in multiple logistic regression models. All potentially confounding factors (age, BMI, gravidity, highest SBP at triage, highest DBP at triage, gestational age at triage, twins) were entered into a full model. Potentially confounding factors whose relationship with the dependent variable was ≥0.01 were excluded from model reduction.

3. Results

Baseline patient characteristics are summarized in Table 1. Maternal clinical examinations indicated that PE and control groups significantly differed in gravidity, mean arterial pressure, gestational age at hospitalization time and delivery, interval to delivery, and maternal morbidity (renal dysfunction, liver dysfunction, and coagulopathy) ($P < 0.01$). Adverse pregnancy frequency significantly differed between control and PE groups, although no significant difference was observed between MPE and SPE groups. Neonatal clinical characteristics, birth weight, neonatal intensive care unit admission, preterm birth, and APGAR score at 1 and 5 min were significantly different between PE and control groups ($P < 0.01$).

Blood count parameters are shown in Table 2. Absolute neutrophil and monocyte counts and NLR and MLR values were significantly lower in non-pregnancy than those in control group, along with higher lymphocyte counts ($P < 0.01$). Compared with the control group, the PE group had significantly higher absolute neutrophil and monocyte counts and NLR and MLR values, along with significantly lower lymphocyte counts ($P < 0.01$). The SPE group had significantly higher absolute neutrophil counts, NLR ($P < 0.01$), and MLR ($P < 0.05$) than the MPE group, along with significantly decreased lymphocyte counts ($P < 0.01$). Absolute monocyte counts were not significantly different between MPE and SPE groups. Eosinophil and basophil counts did not significantly differ among any groups.

ROC analysis of disease diagnosis was plotted to determine optimal cutoff values for neutrophil, lymphocyte, and monocyte counts and NLR and MLR values (Table 3). MLR and NLR had good diagnostic accuracy to distinguish between normal pregnancy and PE (MLR, sensitivity:

Table 1
Clinical characteristics of control pregnant women and preeclamptic patients (mild preeclampsia and severe preeclampsia).

Variable	Control(n = 161)	PE (n = 302)	*P**	PE group		*P***
				Mild PE (n = 147)	Severe PE (n = 155)	
Maternal						
Age (y)	27.88 ± 4.32	27.95 ± 4.39	0.873	27.7 ± 4.14	28.2 ± 4.62	0.365
BMI (kg/m^2)	29.48 ± 4.03	30.08 ± 3.82	0.111	30.42 ± 3.81	29.77 ± 3.80	0.133
Gravidity	0.29 ± 0.63	0.67 ± 0.98	< 0.01	0.52 ± 0.88	0.83 ± 1.06	< 0.01
Adverse pregnancy frequency	0.17 ± 0.46	0.31 ± 0.66	< 0.05	0.26 ± 0.64	0.35 ± 0.67	0.274
Highest SBP at triage (mmHg)	122.88 ± 12.57	149.66 ± 15.08	< 0.01	141.9 ± 9.66	157.04 ± 15.64	< 0.01
Highest DBP at triage (mmHg)	81.72 ± 4.96	95.97 ± 11.02	< 0.01	91.9 ± 9.09	99.8 ± 11.3	< 0.01
Gestational age at triage (wks)	38.53 ± 0.56	35.58 ± 2.89	< 0.01	36.74 ± 2.35	34 ± 2.9	< 0.01
Gestational age at delivery (wks)	38.81 ± 0.64	36.59 ± 2.70	< 0.01	38.2 ± 1.52	35.1 ± 2.74	< 0.01
Interval to delivery	2.87 ± 0.64	7.26 ± 8.54	< 0.01	10.6 ± 10.7	4.03 ± 3.45	< 0.01
Renal dysfunction, n (%)	2 (1.24)	84 (27.81)	< 0.01	12 (8.16)	72 (46.45)	< 0.01
Liver dysfunction, n (%)	1 (0.62)	29 (9.60)	< 0.01	4 (2.72)	25 (16.13)	< 0.01
Coagulopathy, n (%)	13(8.07)	103 (34.11)	< 0.01	41 (27.89)	62 (40.00)	< 0.01
Infant						
Twins, n (%)	14 (8.70)	33(10.93)	0.336	11(7.48)	22(14.19)	0.148
Birth weight (g)	3302.5 ± 504.2	2811.1 ± 875.3	< 0.01	3267.6 ± 658.1	2375.1 ± 835.1	< 0.01
Neonatal intensive care unit admission, n (%)	2 (1.24)	103 (34.11)	< 0.01	26 (17.69)	77 (49.68)	< 0.01
Preterm (< 34 wks), n (%)	0 (0.00)	61 (20.20)	< 0.01	5 (3.40)	56 (36.13)	< 0.01
IUGR, n(%)	0 (0.00)	13 (4.30)	< 0.01	2 (1.36)	11 (7.10)	< 0.01
APGAR score at 1 min	9.25 ± 0.18	7.28 ± 0.25	< 0.01	8.00 ± 1.28	6.67 ± 1.53	< 0.01
APGAR score at 5 min	9.55 ± 0.14	8.03 ± 0.21	< 0.01	8.83 ± 0.20	7.33 ± 0.25	< 0.01

PE, preeclampsia; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

64.57%; specificity: 80.75%; AUC: 0.78; NLR, sensitivity: 53.31%; specificity: 83.22%; AUC: 0.70), in accordance with the likelihood ratio (LR) for positive test results (MLR LR = 3.35; NLR LR = 3.17). In contrast, lymphocyte count had no diagnostic efficacy (AUC < 0.50) to distinguish normal pregnancy and PE (data not shown). ROC curve analysis between PE groups (MPE and SPE) identified NLR as the best predictor of disease severity (sensitivity: 69.68; specificity: 63.95; AUC: 0.71). A cutoff value of NLR > 4.182 indicated the best positive test (LR = 1.93). Although absolute lymphocyte counts were significantly different between the two groups, ROC curves of these parameters did not show useful values (AUC < 0.5, data not shown).

We performed Kaplan-Meier survival analysis of NLR and MLR with the time interval from admission to delivery. As shown in Fig. 1, patients were divided into negative or positive groups based on whether their index values were below or above, respectively, the cut-off values determined by ROC analysis. In PE and control groups, NLR- and MLR-negative groups had significantly longer admission to delivery intervals when compared to NLR-positive (median: 8.00 vs 3.00 days; log rank: $P < 0.001$; Fig. 1A) and MLR-positive (median: 7.00 vs 5.00 days; log rank, $P < 0.001$; Fig. 1B) groups. In MPE and SPE groups only, the NLR-positive group had a significantly shorter admission to delivery interval than the NLR-negative group (median: 9.00 vs 4.00 days; log rank, $P < 0.001$; Fig. 1C). The MLR-positive group had a shorter admission to delivery interval than the MLR-negative group, but the difference was not significant (median: 9.00 vs 6.00 days; log rank, $P = 0.087$; Fig. 1D).

Multivariate analysis was performed to evaluate the relationship between outcomes according to NLR or MLR cut-off values. Among all women who participated in this study, after adjustment for potential confounders, MLR > 0.325 was significantly associated with maternal morbidity, while NLR > 4.198 was significantly associated with maternal morbidity, adverse neonatal outcome, and preterm delivery (Table 4). Between MPE and SPE groups, multivariate analysis further showed that NLR > 4.182 was significantly associated with severe maternal morbidity, adverse neonatal outcome, and preterm delivery after adjustment for potential confounders.

4. Discussion

PE is a progressive and incurable disease that seriously endangers the health of pregnant mothers and fetuses. Early diagnosis is helpful for clinical monitoring and effective nursing to control the disease to

Table 2
Blood count parameters of control pregnant women and preeclamptic patients (mild preeclampsia and severe preeclampsia).

Parameter	Non pregnancy (n = 170)	Control(n = 161)	PE (n = 302)	*P**	*P***	PE group		*P****
						Mild PE (n = 147)	Severe PE (n = 155)	
Neutrophil count (×10^9/L)	4.14 ± 1.46	6.16 ± 1.51	6.80 ± 2.13	< 0.01	< 0.01	6.43 ± 1.94	7.16 ± 2.24	< 0.01
Lymphocyte count (×10^9/L)	1.97 ± 0.55	1.80 ± 0.43	1.58 ± 0.47	< 0.01	< 0.01	1.69 ± 0.45	1.47 ± 0.47	< 0.01
Monocyte count (×10^9/L)	0.35 ± 0.10	0.46 ± 0.13	0.58 ± 0.21	< 0.01	< 0.01	0.60 ± 0.19	0.59 ± 0.43	0.926
Eosinophil count (×10^9/L)	0.10 ± 0.09	0.09 ± 0.03	0.08 ± 0.04	0.61	0.68	0.09 ± 0.06	0.08 ± 0.04	0.47
Basophil count (×10^9/L)	0.02 ± 0.01	0.02 ± 0.02	0.02 ± 0.02	0.22	0.81	0.02 ± 0.01	0.02 ± 0.02	0.13
NLR	2.17 ± 0.75	3.51 ± 0.82	4.60 ± 1.83	< 0.01	< 0.01	3.94 ± 1.20	5.22 ± 2.09	< 0.01
MLR	0.18 ± 0.05	0.26 ± 0.76	0.39 ± 0.23	< 0.01	< 0.01	0.37 ± 0.14	0.40 ± 0.16	< 0.05

PE, preeclampsia; NLR, neutrophil-lymphocyte ratio; MLR, monocyte-lymphocyte ratio.
*P** Non pregnancy women *vs* Control pregnancy women.
*P*** Control pregnancy women *vs* PE.
*P**** Mild PE *vs* Severe PE.

Table 3
Diagnostic performance of blood parameters to distinguish preeclampsia from controls or distinguish severe preeclampsia from mild preeclampsia.

Parameter	AUC (95%CI)[a]	Cut-off value ($\times 10^9$/L)[a]	Sensitivity	Specificity	LR for positive test (95%CI)	Positive predictive value (95%CI)	LR for negative test (95%CI)	Negative predictive value (95%CI)
Normal pregnancy as control								
Neutrophil	0.57(0.52–0.62)	7.65	38.98%	78.89%	1.84(1.26–2.72)	85.71%(79.13–90.54)	0.77(1.71–0.84)	28.48%(23.53–33.98)
Monocyte	0.68(0.63–0.73)	0.535	54.97%	73.91%	2.11(1.59–2.79)	79.81%(73.58–84.91)	0.60(0.54–0.69)	46.67%(40.45–52.99)
NLR	0.70(0.66–0.75)	4.198	53.31%	83.22%	3.17(2.21–4.56)	85.64%(79.61–90.16)	0.56(0.49–0.63)	48.73%(42.70–54.79)
MLR	0.78(0.74–0.83)	0.325	64.57%	80.75%	3.35(2.41–4.65)	86.28%(80.94–90.35)	0.43(0.38–0.51)	54.85%(48.28–61.27)
Mild preeclampsia as control[b]								
Neutrophil	0.60(0.54–0.67)	6.875	46.45%	71.43%	1.62(1.20–2.21)	63.16%(53.56–71.85)	0.75(0.64–0.87)	55.85%(48.44–63.02)
NLR	0.71(0.66–0.77)	4.182	69.68%	63.95%	1.93(1.52–2.45)	67.08%(59.18–74.15)	0.47(0.37–0.61)	66.67%(58.17–74.24)
MLR	0.58(0.51–0.64)	0.340	67.10%	48.30%	1.29(1.07–1.57)	57.78%(50.20–65.02)	0.68(0.54–0.87)	58.20%(48.92–66.95)

AUC, area under the curve; LR, likelihood ratio ; 95%CI, 95% confidence interval; NLR, neutrophil-lymphocyte ratio; MLR, monocyte-lymphocyte ratio.
[a] AUC and cut-off value determined by receiver operating characteristic (ROC) curve.
[b] ROC analysis with absolute monocyte count as the variable indicated no diagnostic efficacy, AUC < 0.5 (data not shown).

prolong pregnancy and improve pregnancy outcomes. In the past several years, some biomarkers of maternal plasma have been identified as predictors of PE, such as plasma placental protein 13 (De Villiers et al., 2017), soluble tyrosine kinase 1 (Burke et al., 2016), and placental growth factor (Lecarpentier et al., 2016), but predictability of these biomarkers still needs to be verified. NLR and MLR are ratio indices calculated by inflammatory activators (neutrophils/monocytes) and inflammatory regulators (lymphocytes) that are considered effective indicators of systemic inflammation and immune balance and play an important role in diagnosis, prognosis, and therapeutic evaluation of several diseases.

In this study, we determined that differential leukocyte count significantly changes in PE, as PE patients had significantly higher MLR and NLR values than control women with normal pregnancies. Further, higher NLR values had better diagnostic performance in distinguishing PE severity. Patients with higher NLR values were at higher risk of short admission to delivery intervals, whether the study populations included all pregnant women or were limited to only those with PE. Higher NLR and MLR values were significantly associated with severe maternal morbidity, adverse neonatal outcomes, and preterm delivery.

Previous studies demonstrate that increased number and surface marker activation of monocytes and neutrophils in normal pregnancy imply that a moderate but significant systemic inflammatory/immune response is important to maintain a successful pregnancy (Palm et al., 2013). However, the response is exacerbated in PE and can account for its clinical features (Germain et al., 2007), as neutrophil and monocyte cells activated by inflammatory cytokines overproduced by placenta cells (stromal and trophoblast cells) have abnormal biological functions (Díaz et al., 2009). For example, chemoattractants cytokine IL-8 and MCP-1 attract circulating monocytes/macrophages and neutrophils to

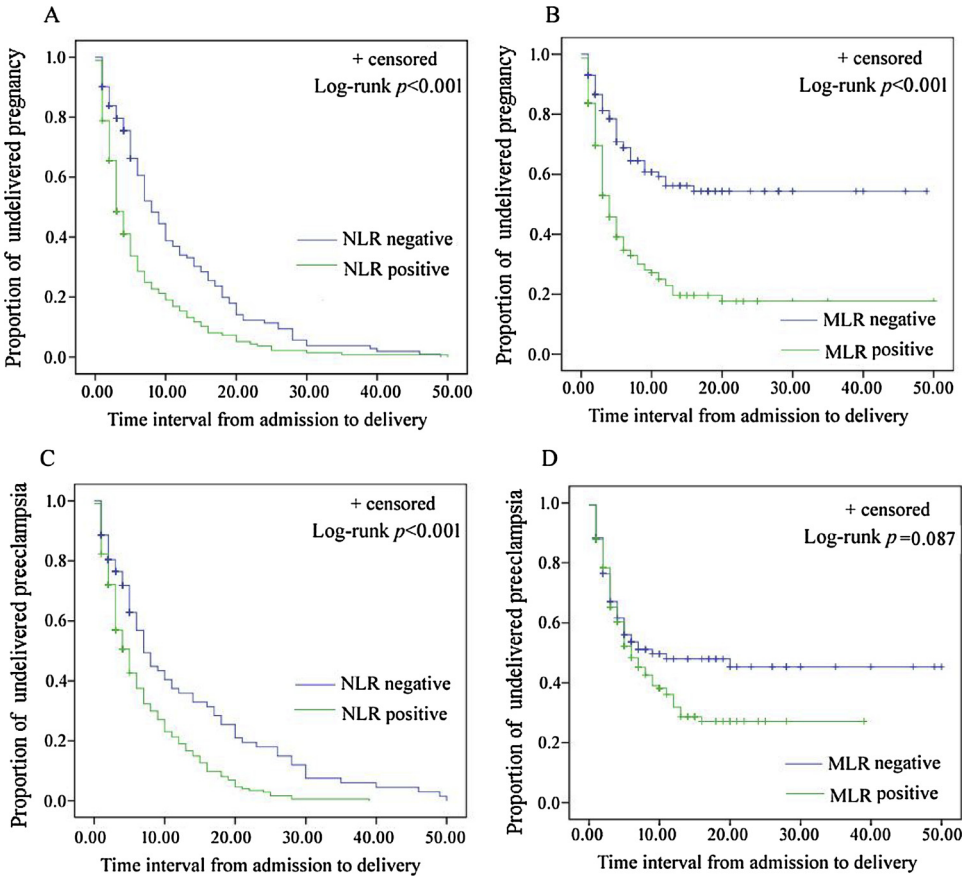

Fig. 1. Kaplan-Meier survival curves using cut-off values determined by ROC analysis. Estimation of admission to delivery intervals in all pregnant women (NP, MPE, and SPE) with (A) NLR > 4.198 and (B) MLR > 0.325. Estimation of admission to delivery interval in women with PE (MPE and SPE) with (C) NLR > 4.182 and (D) MLR > 0.340.

Table 4
Likelihood analysis (unadjusted and adjusted) of cut-off values associated with pregnancy outcomes.

Outcome	Outcome				Unadjusted		Adjusted-I (full)[a]		Adjusted-II (reduced)[b]	
	No		Yes		OR[c]	95%CI	OR[c]	95%CI	OR[c]	95%CI
	n/N	%	n/N	%						
All studied populations										
Maternal morbidity										
NLR > 4.198	28/161	17.39	161/302	53.31	5.74	3.59-9.20	3.73	1.88-7.39	3.62*	1.86-7.02
MLR > 0.325	31/161	19.25	195/302	64.57	7.64	4.84-12.07	15.75	4.74-52.36	15.50**	4.78-50.22
Adverse neonatal outcome										
NLR > 4.198	124/366	33.88	65/97	67.01	4.21	2.61-6.79	3.03	1.62-5.65	2.69#	1.47-4.92
MLR > 0.325	164/366	44.81	62/97	63.92	2.18	1.37-3.47	1.23	0.63-2.32	1.370#	0.73-2.57
Preterm delivery										
NLR > 4.198	113/341	33.14	76/122	62.30	3.50	2.27-5.39	1.91	0.85-4.26	1.87##	0.85-4.10
MLR > 0.325	145/341	42.52	81/122	66.39	2.67	1.73-4.12	1.12	0.51-2.48	1.13##	0.52-2.48
Mild preeclampsia and severe preeclampsia[d]										
Maternal morbidity										
NLR > 4.182	53/147	36.05	108/155	69.68	4.07	2.52-6.58	4.16	2.23-7.76	3.91**	2.12-7.20
Adverse neonatal outcome										
NLR > 4.182	101/210	48.10	60/92	65.22	2.10	1.27-3.49	2.22	1.16-4.25	2.34#	1.27-4.33
Preterm delivery										
NLR > 4.182	84/179	46.93	77/123	62.60	1.98	1.24-3.17	2.10	0.96-4.56	2.02##	0.95-4.33

OR, odds ratio; 95%CI, 95% confidence interval; NLR, neutrophil-lymphocyte ratio; MLR, monocyte-lymphocyte ratio.

[a] Adjusted-I (full) models include age, BMI, gravidity, adverse pregnancy frequency, highest SBP at triage, highest DBP at triage, gestational age at triage, and twins.

[b] Adjusted-II (reduced) models exclude factors not significantly associated with outcome from the full model. Variables included are: *adjusted for highest SBP at triage and highest DBP at triage; **adjusted for highest SBP at triage, highest DBP at triage, gravidity, and gestational age at triage; # adjusted for gravidity and gestational age at triage; or ##adjusted for highest SBP at triage, gestational age at triage, and twins.

[c] OR represents mean—among observed subjects, the likelihood of an outcome exhibiting ratio above cutoff value relative to the likelihood at or below cutoff.

[d] In preeclampsia group, likelihood of outcome exhibiting MLR $>$ 0.340 relative to likelihood of outcome exhibiting MLR $\leq$ 0.340 is $<$ 1, indicating lower risk in the observed group; result is not statistically significant (data not shown).

inflammatory sites, enhance phagocytosis, and upregulate the inflammatory response, promoting release of inflammatory mediators (Zurek et al., 2015; Deshmane et al., 2009). Immunoglobulin superfamily members (ICAM-1, VCAM-1) promote migration of neutrophils from the vascular lumen into the interstitial space and stimulate endothelial cells and macrophages to secrete MCP-1 to further induce monocyte recruitment (Lyck and Enzmann, 2015; Mishra et al., 2016).

Increased numbers of macrophages in the decidua of PE has been proved, inhibiting invasion of trophoblast cells and inducing apoptosis of trophoblast cells by secreting TNF-α, forming positive feedback that finally induces full-blown PE (Allaire et al., 2000). Placental mesenchymal stem cells from PE patients also suppress lymphocyte proliferation, affecting the maternal immune system and altering immune balance by secreting soluble factors (Liu et al., 2014). Inconsistent absolute lymphocyte counts have been observed in previous studies, including reports of elevated lymphocyte counts in PE patients (Kim et al., 2018). Therefore, secondary analyses of white blood cell differential count parameters could effectively provide a more accurate method for doctors to judge the clinical condition of patients and to reduce the impact of inconsistent collection times of blood specimens or sampling bias. MLR is a subclinical indicator of inflammation and is a prognostic factor for several diseases, including colorectal cancer and lung cancer. Further, low MLR is associated with longer relapse-free survival time, indicating that MLR level can reflect the body's immune status (Stotz et al., 2014; Jiang et al., 2015).

PE is new onset (or worsening of preexisting) hypertension accompanied by chronic inflammation that occurs during pregnancy. Infiltration of monocyte phagocytes presents a clinical aspect of chronic inflammation (LaMarca et al., 2016), and increased PGE2 production by CD83+ monocyte to further inhibit T-Cell proliferation through NF-κB pathway (Chen et al., 2011). In this study, monocyte cell counts were increased in the PE group compared to control normal pregnancies, although we detected no significant differences between MPE and SPE. Lymphocyte counts were decreased in PE, and more serious disease was associated with greater count reduction. MLR values differed among all groups. Although ROC curve analysis showed better diagnostic performance of MLR than absolute monocyte or lymphocyte counts in distinguishing PE from control pregnancies, the sensitivity and specificity are too low. As control group, normal pregnancy is associated with a moderate systemic inflammatory/immune response (Granne et al., 2011), elevated base values were primarily responsible for it (Date shown in Table 2). Kaplan-Meier survival analysis showed that MLR-positive results were associated with shorter admission to delivery interval. An index value of MLR $>$ 0.325 was significantly associated with maternal morbidity, adverse neonatal outcome, and preterm delivery after adjusting for potential confounders. These results indicate that monocyte was a good indices to indicate chronic inflammation, compared with absolute cell counts, MLR is a prognostic factor of poor outcome and may more fully reflect the state of the body.

Syncytiotrophoblast microparticles released from the placenta can effectively activate neutrophils and trigger formation of neutrophil extracellular traps, further damaging vascular endothelial cells (Gupta et al., 2005). Therefore, neutrophils may be considered an important bridge to connect syncytic trophoblast cells and vascular endothelial cells, thus inducing systemic inflammatory responses in PE (Reister et al., 2001). Previous studies have shown acute inflammation-induced intrauterine stress in severe PE. During acute inflammation, a rapid and robust increase in neutrophil numbers (Fredman et al., 2012), inflammation induce a subset of neutrophil ($CD11c^{bright}$/$CD62L^{dim}$/$CD11b^{bright}$/$CD16^{brigh}$t) mature and futher inhibits T cell proliferation through Mac-1(Pillay et al., 2011). IL-1, IL-6, IL-8, TNF, and protease released from activated neutrophils induce an inflammatory cascade reaction, damage the extracellular matrix, promote lymphocyte apoptosis, and release nitric oxide, oxygen free radicals, and suppressor cytokine-inhibited T lymphocyte activation (Bogdan, 2011). Therefore, NLR represents the balance between inflammatory activators and inflammatory regulators and is an effective indicator of acute systemic inflammation. Research on inflammatory diseases, such as Henoch-

Schönlein purpura and asthma, reveals higher sensitivity of NLR compared to cell absolute counts (Park et al., 2016; Dogru and Yesiltepe Mutlu, 2016). In this study, NLR was significantly increased in PE and was related to disease severity. Compared with MLR, it exhibited better diagnostic performance in distinguishing SPE from MPE. Further, NLR-positive results were more significantly associated with adverse neonatal outcome and preterm delivery after adjusting for potential confounders.

In conclusion, while white blood cell count is a traditional method to clinically monitor inflammatory diseases, MLR and NLR are secondary analyses that can more effectively judge the balance between inflammation and immune regulation. Our results also show that MLR and NLR values, as markers of inflammation, are more valuable in early diagnosis and prognostic evaluation of PE than absolute white blood cell counts. Meanwhile, with advantages of convenience, simplicity, sensitivity, versatility, and speed, MLR and NLR indices have the prospect of wide clinical application.

Conflict of interest statement

The authors declared that they have no conflicts of interest to this work.

We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

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