Pregnancy Hypertension 18 (2019) 29–34

Contents lists available at ScienceDirect

Pregnancy Hypertension

journal homepage: www.elsevier.com/locate/preghy

Platelet count and mean platelet volume predict atypical pre-eclampsia

Huale Zhang, Yulong Zhang, Zhenna Wang, Jianying Yan*

Fujian Provincial Maternity and Children's Hospital, Affiliated Hospital of Fujian Medical University, Fuzhou 350001, China

ARTICLE INFO

Keywords:
Pre-eclampsia
Platelet count
Mean platelet volume
Predictive value
Atypical pre-eclampsia

ABSTRACT

Objective: We aimed to analyze the role of platelet count (PC), mean platelet volume (MPV), and ratio of PC to MPV (PC/MPV) in predicting and/or diagnosing atypical pre-eclampsia (PE).

Study design: We performed a retrospective case–control analysis of these platelet parameters in healthy pregnant women with normal blood pressure (control) and the changes that occurred in patients with atypical PE and PE.

Main outcome measures: We performed statistical analysis to evaluate the prognostic and predictive significance of PC, MPV, and PC/MPV and the combined effects of these parameters in the parturient population ($N = 300$) composed of 100 controls, 100 atypical PE cases, and 100 PE cases.

Results: The PC, MPV, and PC/MPV in both atypical PE and PE were significantly different to that in the controls. After adjusting for confounding factors using the ordinal logistics regression model, we found that PC/MPV, N% and BMI were independent risk factors for PE and atypical PE(The odds ratio was 0.925, 1.028 and 1.071). The model's C-index is 0.684.

Conclusion: We found that the PC, MPV, and PC/MPV may be changed in atypical PE patients who did not have significant PE symptoms. Our results indicated that it could be a diagnostic method to predict atypical PE during pregnancy. PC/MPV and the other platelet parameters can play a role in predicting the development of atypical PE, leading to better diagnosis and management of atypical PE.

1. Introduction

The incidence of hypertensive disorders complicating pregnancy is about 3%–10%. Pre-eclampsia (PE) is one of the causes of maternal and fetal morbidity and mortality, and deaths associated with complications of PE account for 14% of maternal deaths [1,2]. The reasons for the high morbidity and mortality associated with PE are 1) a lack of complete understanding of the pathological mechanisms of PE and 2) the fact that some PE patients do not have high blood pressure and (or) albuminuria before developing severe PE complications, such as placental abruption, eclampsia, HELLP syndrome, and posterior reversible encephalopathy syndrome [3,4], which is now known as atypical PE. Early diagnosis of eclampsia, PE, and atypical PE can aid in reducing the maternal mortality by appropriate medication, effective care, or timely termination of the pregnancy. The ideal treatment for these three conditions is termination of pregnancy.

The term atypical PE was first proposed by Sibai and Stella [5] and was classified into four categories as follows: (1) parturients develop PE or eclampsia within 20 weeks of pregnancy; (2) parturients present with proteinuria after 20 weeks of pregnancy but do not have hypertension, with presence of microvascular disease/hemolytic symptoms or abnormal laboratory tests; (3) parturients have high blood pressure but no proteinuria, along with symptoms and/or signs of severe hypertension and/or microvascular hemolytic changes; (4) parturients have PE, eclampsia, or HELLP syndrome after 48 h postpartum. Rojas-Arias et al. studied 200 cases of atypical PE [6], and reported that the first sign seen in 96% patients was vasospasm, and postulated that the symptoms of vasospasm would be the key elements in detecting vasospasm. Among the 200 cases, 61.5% of those with atypical PE had proteinuria negative hypertension. In addition, the incidence of thrombocytopenia and liver diseases in patients with negative proteinuria was higher than that in the proteinuria positive group. However, many diseases can cause thrombocytopenia and elevated transaminase levels in pregnancy, and there are no accurate predictors or specific prediction methods for atypical PE at present.

Initial studies indicated that platelet activation occurred before the onset of PE [7]. Recent evidence confirmed that accumulation of activated maternal platelets within the placenta resulting in PE, and genetic

Abbreviations: PC, platelet count; MPV, mean platelet volume; PC/MPV, the ratio of PC to MPV; PE, pre-eclampsia; LSD-t, least-significant difference test

* Corresponding author at: Department of Obstetrics and Gynecology, Fujian Provincial Maternity and Children's Hospital, Affiliated Hospital of Fujian Medical University, No.18, Daoshan Rd., Gulou Dist., Fuzhou City, Fujian Province, China.

E-mail address: yanjy2004@126.com (J. Yan).

https://doi.org/10.1016/j.preghy.2019.08.003
Received 1 April 2019; Received in revised form 4 August 2019; Accepted 15 August 2019
Available online 17 August 2019

inhibition of maternal platelet activation abolished the PE-like phenotype [8]. Studies have shown that changes in platelet indices predated development of PE by 2–8 weeks [9]. Even at second trimester, MPV could be used as a useful biochemical marker for prediction of PE [10]. Furthermore, studies have also indicated that the ratio of PC to MPV (PC/MPV) has significance in the prediction of PE [11].

In the present study, we analyzed the changes in PC, MPV, and PC/MPV in atypical PE, and compared the predictive value of these parameters between the PE and atypical PE groups. We aimed to examine and develop a simple and easy-to-use prediction index to diagnose patients with atypical PE. As the platelet index has shown a high predictive value for PE, we propose that it can also be used to predict and diagnose atypical PE. This test is not only inexpensive and easy to operate, but also worth promoting in a low-resource setting.

2. Methods

2.1. Participant selection

To evaluate the predictive value of PC, MPV, and PC/MPV in atypical PE, we performed a retrospective case-control study in Fujian Provincial Maternity and Children's Hospital of China with the approval of our local ethics committee who deemed written informed consent was not required (Ethical approval number 17–20). The study population was selected from the parturients ($N = 300$) seen in our institute from April 2013 to April 2018, and consisted of 100 normal pregnant women (control), 100 women with atypical PE, and 100 women with PE. All the parturients were in the age group 21–42 and in the third trimester of a monocyesis pregnancy (28–41 weeks). Gestational age was determined by reference to the last menstrual period and the first trimester obstetric ultrasonographic data. The diagnosis of PE and atypical PE was based on the diagnostic criteria proposed by the ACOG (American Congress of Obstetricians and Gynecologists) [12] and Sibai and Stella [5], respectively. The control group and the PE group were matched for maternal age and gestational age against those diagnosed with atypical PE in the present study. When selecting the study samples, we ensured that none of the cases ($N = 300$) had diseases such as chronic kidney disease, thrombocytopenia, lupus nephritis, chronic hypertension, coagulation disorder, and diabetes mellitus of type 1 and 2 and none of them were on antiplatelet medications, anticoagulants, glucocorticoids, or any other drugs which may affect the PC. According to the hospital's routine, all the patients were followed-up for 42 days after delivery, and both blood pressure and platelet parameters were measured till the values reached the normal range.

2.2. Outcome definition

Patients with PE were diagnosed using the criteria of the ACOG (2013) Practice Bulletin. The diagnostic criteria for PE were onset of hypertension (a blood pressure of 140/90 mmHg or greater, measured twice at least 4 h apart) with consistent proteinuria (300 mg/day or more) after 20 weeks of gestation; or a protein (mg/dL)/creatinine (mg/dL) ratio 0.3 and serum creatinine 1.1 mg/dL; or a doubling of serum creatinine level in the absence of any other renal disease. Patients with atypical PE were diagnosed by the presence of one or more of the following three criteria: (1) parturients have proteinuria after 20 weeks of pregnancy but no hypertension, with microvascular disease/hemolytic symptoms or abnormal laboratory tests; (2) parturients have high blood pressure but proteinuria negative, with severe hypertension symptoms and/or signs and/or microvascular hemolytic changes; (3) parturients have PE, eclampsia, or HELLP syndrome after 48 h postpartum.

2.3. Method of measurement

The patients had undergone a routine blood test when hospitalized for other reasons (indications such as childbirth, abnormal fetal heart monitoring, etc.). All the blood tests were performed before the clinical diagnosis (2–7 days before delivery). The automated blood counter XE-5000 (Sysmex Corporation, Japan) was used to evaluate PC, MPV, and PC/MPV.

2.4. Sample size calculation

The sample size was calculated using PASS software, version 15.0.5. In a single factor ANOVA study, sample sizes of 97, 97, and 97 are obtained from the 3 groups whose means are to be compared. The total sample of 291 subjects achieves 82% power to detect a difference of at least 5.00 using the Tukey-Kramer (Pairwise) multiple comparison test at a 0.1000 significance level. The common standard deviation within a group is assumed to be 8.00.

2.5. Statistical methods

The data used in the present study were stored in a database of Microsoft ® Excel ® 2010 and analyzed using SPSS 22.0 and R 3.5.1. Data that were normally distributed were then assessed using 1-way ANOVA for continuous variables, while data that were still not normally distributed or heterogeneity variance were analyzed with a Kruskal-Wallis H test. The Fisher's exact test and Pearson's chi-squared test were used to compare qualitative data. Ordinal logistic regression (stepwise forward method) was used to screen for independent influencing factors of PE and atypical PE, and based on the selected independent factors, a nomogram prediction model was constructed to visually demonstrate the risk of PE and atypical PE. Finally, the predictive performance of the model is constructed using Harrell' concordance index (C-index). A level of $P \leq 0.05$ was accepted as statistically significant.

3. Results

3.1. Case description

All the 300 cases selected were in accordance with the inclusion and exclusion criteria. Baseline characteristics of the three groups are shown in Table 1. There was no statistical significance in the age of parturients ($p = 0.804$), gestational age at delivery ($p = 0.58$), and gender of the baby ($p = 0.936$) among the three groups. However, the Kruskal–Wallis test revealed a significant difference in the gestational age at delivery as well as BMI across patients with different clinical diagnoses ($P = 0.016$ and $P < 0.001$, respectively). Delivery time SBP (systolic blood pressure) and DBP (diastolic blood pressure) among the three groups showed significant differences (Table 1). Newborn weights in the atypical PE and PE groups were significantly lower than that in the control group (2731 g vs. 2813 g and 2492 g vs. 2813 g, respectively; $p = 0.011$). The incidence of 2-hour postpartum hemorrhage was also significantly higher in the atypical PE and PE groups than that in the control group (392 mL vs. 237 mL and 481 mL vs. 237 mL, respectively; $p < 0.001$). The cesarean section rates in the atypical PE and PE groups were also significantly higher than that in the control group (81% vs. 40% and 87% vs. 40%, respectively; $p < 0.001$).

4. PC and PC/MPV were decreased and MPV was increased in atypical PE patients

It is known that the platelet count (PC), mean platelet volume (MPV), and the ratio of PC to MPV (PC/MPV) can predict the risk and the prognosis of PE [11]. This prompted us to examine whether these parameters can also predict the risk of atypical PE. We considered the fact that the PC, MPV, and PC/MPV values in the atypical PE, PE, and control groups may not meet normal distribution, and this was confirmed by our results that the variance of PC, MPV, and PC/MPV was

Table 1
Clinical characteristics of the Atypical PE, PE, and control groups.

Variables	Mean ± SD			P-value
	Control	Atypical PE	PE	
Age(years)	29.63 ± 4.63	29.30 ± 5.18	29.18 ± 5.12	0.804[a]
Gestation(week)	36.14(34.71,37.57)	37.43(34.71,39.43)	37.43(33.57,38.28)	0.016[b]
BMI (kg/m^2)	26.50(24.63,28.47)	28.41(25.93,32.38)	27.38(25.80,30.74)	< 0.001[b]
Birth weight (g)	2813 ± 482	2731 ± 921	2492 ± 859	0.011[a]
Bleeding 2 h after parturition (mL)	237 ± 132	392 ± 435	481 ± 288	< 0.001[a]
Gestational age at delivery	36.05 ± 2.69	36.99 ± 3.06	36.14 ± 3.01	0.580[b]
SBP(mmHg)	121.23 ± 7.60	141.10 ± 5.18	153.13 ± 13.67	< 0.001[a]
DBP(mmHg)	74.23 ± 6.59	88.50 ± 7.69	97.05 ± 10.53	< 0.001[a]
Gender of baby	n	n	n	
Female	48	49	51	0.936[c]
Male	52	51	49	
Delivery mode				
Vaginal	60 (60%)	19 (19%)	13 (13%)	< 0.001[c]
Abdominal	40 (40%)	81 (81%)	87 (87%)	

PE, pre-eclamsia; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.
[a] One-way ANOVA test.
[b] Kruskall–Wallis test.
[c] Pearson chi-squared test.

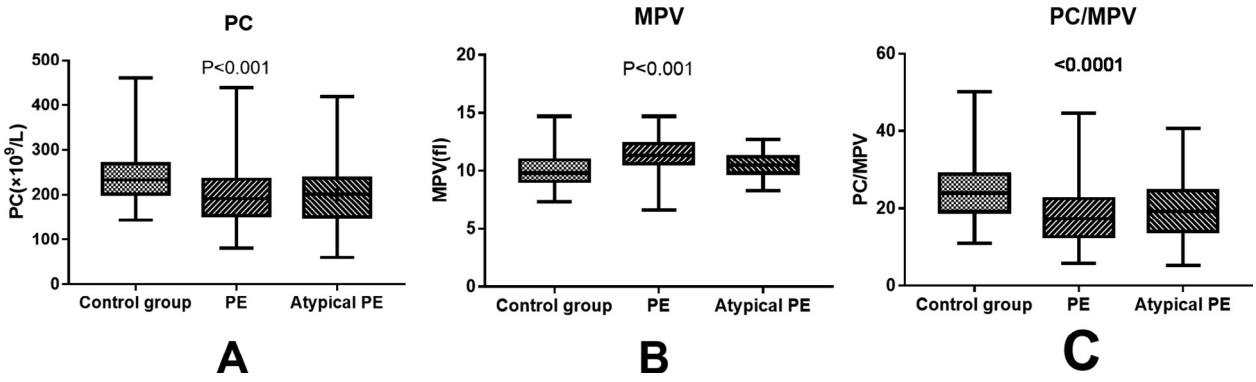

Fig. 1. Independent sample Kruskall-Wallis test. (A-C) Quantitative data showing the Kruskall-Wallis test in platelet count (PC; A), mean platelet volume (MPV; B), and ratio of PC to MPV (PC/MPV; C) for control (ctrl), atypical pre-eclampsia (atypical PE), and pre-eclampsia (PE). Box plots show the range of data (25%–75%), and data represent the mean ± SD with $n = 100$.

Table 2
PC, MPV, and PC/MPV in the Atypical PE, PE, and control groups.

Variables	Mean ± SD			χ^2/F	P-value
	Control	Atypical PE	PE		
PC(×10^9/L)	239.40 ± 54.53	199.87 ± 71.88[c]	198.54 ± 64.54[c]	27.732	< 0.001[b]
MPV(fl)	10.17 ± 1.42	10.51 ± 0.99[c]	11.38 ± 1.39[c,d]	50.760	< 0.001[b]
PC/MPV	24.59 ± 7.88	19.46 ± 7.82[c]	18.11 ± 7.51[c]	37.694	< 0.001[b]
WBC(×10^9/L)	10.04 ± 2.72	11.53 ± 4.71[c]	10.90 ± 2.65[c]	6.841	0.033[b]
N%(%)	71.99 ± 9.37	75.45 ± 10.77	75.80 ± 7.27	10.802	0.005[b]
HB(g/L)	117.12 ± 20.27	116.73 ± 17.06	117.68 ± 17.19	0.069	0.943 [a]

PC, platelet count; MPV, mean platelet volume; WBC, white blood cell; N%, percentage of neutrophils; HB, hemoglobin.
[a] One-way ANOVA test.
[b] Kruskall–Wallis test.
[c] Compared with the control group P < 0.05.
[d] Compared with the Atypical PE group P < 0.05.

not homogeneous through the homogeneity of variance test ($p < 0.05$). Therefore, the Kruskal-Wallis test was used to compare the differences in PC (Fig. 1A), MPV (Fig. 1B), and PC/MPV (Fig. 1C) among the three groups. We found that the mean values of PC and PC/MPV in the atypical PE and PE groups were less than that in the control group (Table 2), while the mean value of MPV in the atypical PE and PE groups was larger than that in the control group (Table 2). We further performed a pairwise comparison to analyze the statistical significance, and observed that the differences in the PC, MPV, and PC/MPV among the three groups were statistically significant. Overall, these results suggest that the platelet parameters (PC, MPV, and PC/MPV) are indeed altered in atypical PE patients.

While the one-way ANOVA showed no statistically significant differences between the groups for serum hemoglobin (HB) levels, statistical differences were present in the white blood cell (WBC) counts among the three groups of patients. The WBC counts in the PE and

Table 3
Predictive models of Atypical PE and PE.

Co-variable	Regression coefficient	Standard error	P-value	Odds ration	95% CI of OR	
					Low Limit	Upper limit
Intercept 1	1.640	1.197	0.171	/		
Intercept 2	3.211	1.209	0.008	/		
BMI	0.068	0.029	0.018	1.071	1.015	1.130
N%	0.028	0.012	0.018	1.028	1.006	1.052
PC/MPV	−0.078	0.015	< 0.001	0.925	0.899	0.951

Intercept 1: Control VS Atypical PE + PE.
Intercept 2: Control + Atypical PE VS PE.
Test of Parallel lines: Chi-square = 0.250, df = 3, p-value = 0.969.
Goodness-of-fit test of Pearson: Chi-square = 590.437, df = 595, p-value = 0.545, Pseudo R2 = 0.162, AIC = 622.573.

atypical PE groups were higher than that in the control group (P = 0.013 and 0.048).

4.1. The ordinal logistic regression model of atypical PE and PE

Having identified the changes in the PC, MPV, and PC/MPV in atypical PE patients, we continued to adjust for potential confounding variables. The ordinal logistic regression model was used to evaluate the predictive efficacy of the platelet parameters. If variables were collinear, the variable with the strongest correlation with the outcome was included in the multivariable analysis. After adjusting for gestational weeks, age, BMI, WBC count, N%(percentage of neutrophils), and HB level, PC/MPV demonstrated a statistically significant correlation with the diagnosis of PE and atypical PE after a few days (Table 3). On the basis of these models, we proposed an intuitive model for the prediction of PE and atypical PE by nomogram (Fig. 2).

In multivariate analysis, PC/MPV decline, BMI and N% increase act as independent risk factors for the onset of PE. In the ordinal logistic regression model, the Test of Parallel lines was not significant (Chi-square = 0.250, p-value = 0.969). This shows that the model meets the proportional odds assumption. Both Deviance and Pearson goodness of fit test show that the model fits well ($\chi2$ = 612.573, P = 0.595 and $\chi2$ = 590.437, P = 0.545). The risk reduced with the increase of PC/MPV. The OR value is 0.925 (95%CI 0.899–0.951), indicating that it could act as a marker to identify patients at risk of developing atypical PE and PE (Table 3). In addition, for each additional unit of BMI and N%, the OR value of disease occurrence is 1.071 and 1.028 times, respectively. (95% CI: 1.015–1.130 and 1.106–1.153). To facilitate clinical evaluation and application, we used the lrm and nomogram functions of R to draw the nomogram of the ordinal logistic regression model (Fig. 2). The nomogram provides a practical tool to identify the risks of developing PE in pregnant woman who are about to give birth.

Additionally, we investigated the combined effects of PC/MPV on the prognostic and predictive significance of PE and atypical PE. The model was evaluated using Harrell's concordance index (c-index). The C-index = 0.684, this suggests that the model has moderate accuracy.

5. Discussion

Among the 100 patients who were diagnosed with atypical PE in our study, 37 patients had no significant increase in blood pressure at the time of onset, and 50 patients had negative proteinuria. Lack of typical symptoms leads to missed diagnosis. Therefore, we sought to find a simple composite indicator for the early diagnosis of atypical PE.

There are still major limitations in the treatment of pre-eclampsia. Preeclampsia can give rise to severe complications if not diagnosed and managed properly. Traditional indicators such as blood pressure and proteinuria are still the main basis for the diagnosis of preeclampsia in clinical practice [12].

At present, many studies have confirmed that the blood routine indices change with the increase in the gestational weeks. With increase of gestational age, the WBC count increases and the HB value and platelet count gradually decrease in late pregnancy [13]. Therefore, to reduce the influence of gestational age, we chose normal pregnant women matched for gestational weeks and without pregnancy complications to constitute the control group. There were no significant differences in the HB levels among the three groups of patients. In a subsequent model, we adjusted for potential confounders to ensure that the three sets of data were comparable. Conforming to the findings by Neiger et al. that the PC in PE patients was significantly lower than that in normal pregnant women and the MPV in severe PE was markedly higher than that in normal pregnant women [14], a growing number of

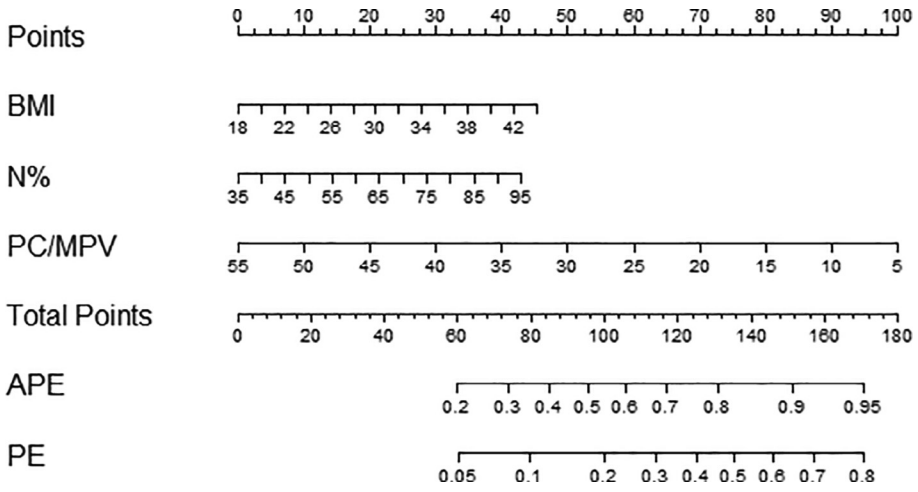

Fig. 2. A nomogram for Predictive models of Atypical PE and PE.

researches have reported that the platelet indices, including MPV and PC/MPV, can be used as an index of PE [15–17]. However, some studies have shown that PE platelet parameters were not different from that in the control group [18]. This may be related to the sample size as well as the presence of confounding factors; the test time after blood sampling was also found to affect the experimental results. The latest meta-analysis combined with these studies suggests that platelet parameters in PE patients do undergo substantial changes [19]. In this study, we also found that PC, MPV, and PC/MPV can be a good predictive index for PE, which is similar to the results published in previous studies.

Interestingly, when compared to that in the control group, PC, MPV, and PC/MPV were significantly changed in atypical PE as well, with a decrease in the PC and PC/MPV and an increase in the MPV, demonstrating that platelet parameters undergo a change in atypical PE patients also. Our data also support the predictive value of PC/MPV in predicting the risk and the prognosis of PE, which is consistent with the results of previous research [11]. Importantly, we also found that the predictive value of PC/MPV in the atypical PE and PE groups was comparable since the ROCs of both the single parameter test and the combined parameter test between the atypical PE and PE groups were similar. These observations suggest that PC, MPV, and PC/MPV could also become excellent candidates for predicting atypical PE.

In this work, we have demonstrated that the platelet parameters, including PC, MPV, and PC/MPV, were significantly changed in atypical PE patients even when the parturients did not have any symptoms of hypertension or a hypertensive disorder complicating pregnancy (HDCP), suggesting that the platelet index may act as a good predictor in helping diagnose atypical PE.

In the past, it was easy to miss the diagnosis during clinical work-up in patients with atypical PE because the patients did not have hypertension or proteinuria. In recent years, although the number of atypical PE cases has increased and various diagnostic methods for atypical PE have been studied [20], clinicians still only use a conglomeration of nonspecific tools to diagnose atypical presentations of PE. The commonly used methods are ambulatory blood pressure measurement, laboratory monitoring, and the assessment of fetal and maternal health [21]. In our hospital, we also diagnosed a large number of atypical PE patients and reviewed their clinical characteristics and platelet index. We found that the PC, MPV, and PC/MPV showed clinical significance in their ability to predict the development of atypical PE, since the area under the ROCs of both predicted by combined platelet parameters in atypical PE were close to that in the PE group, suggesting that the prediction effect of these platelet parameters in atypical PE is similar to that in PE. This may be due to the similar pathophysiological mechanisms of the two diseases (atypical PE and PE). It is known that abnormal coagulation activity is involved in the pathogenesis of PE. Accordingly, platelet activation occurs before symptoms of PE occur [22]. Abnormal activation leads to a reduction in the PC and the increase in both the platelet-leukocyte and platelet-platelet aggregates leads to an increase in the MPV [23]. As the pathophysiological mechanisms of atypical PE and PE are similar, it is possible that the changes in the platelet index in patients with atypical PE could help in predicting the condition.

In conclusion, our findings suggest that PC, MPV, and PC/MPV have a clinical significance in the diagnosis of atypical PE. Considering the fact that blood routine examination has the advantages of being non-invasive and easy to repeat with a low cost, it is worth promoting and applying blood routine evaluation in diagnosing atypical PE at the grassroots level. Careful attention to detect derangement in these three indices can help diagnose atypical PE in time. However, this work also has some drawbacks: 1) the small sample size; 2) performance at a single center and retrospective design. Further multicenter studies with large numbers of patients are needed to confirm these findings.

Declarations

Ethics approval and consent to participate

This study was ratified by the Fujian Provincial Maternity and Children's Hospital of China Ethics Committee who deemed that written informed consent was not required (Ethical approval number: 17-20).

Consent for publication

Not applicable.

Availability of data and materials

Full data will not be made available in order to protect participants' identity. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Funding

This work is supported by funds from the Fujian Science and Technology Leading Project (2018Y0005). Fujian Provincial Maternity and Children's Hospital Research Fund Project (17-20).

Authors' contributions

H. Z. and Y. Z. designed this work. H. Z. performed the data analysis. Z. W. helped analyze and explain the results. H. Z., J. Y., and Y. Z. drafted the manuscript. All authors discussed the design, critically revised the manuscript, and agreed on the final version. All authors had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses. All authors have read and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We thank Mr. Feng Lin (Department of Mechanics, Peking University) for his help in revising the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preghy.2019.08.003.

References

[1] L. Alkema, D. Chou, D. Hogan, S. Zhang, A.-B. Moller, A. Gemmill, D.M. Fat, T. Boerma, M. Temmerman, C. Mathers, et al., Global, regional, and national levels and trends in maternal mortality between 1990 and 2015, with scenario-based projections to 2030: a systematic analysis by the UN Maternal Mortality Estimation Inter-Agency Group, Lancet 387 (10017) (2016) 462–474.

[2] U.V. Ukah, D.A. De Silva, B. Payne, L.A. Magee, J.A. Hutcheon, H. Brown, J.M. Ansermino, T. Lee, P. von Dadelszen, Prediction of adverse maternal outcomes from pre-eclampsia and other hypertensive disorders of pregnancy: A systematic review, Pregnancy Hypertens. 11 (2018) 115–123.

[3] M. Albayrak, I. Ozdemir, Y. Demiraran, S. Dikici, Atypical preeclampsia and eclampsia: report of four cases and review of the literature, J. Turk. Ger. Gynecol. Assoc. 11 (2) (2010) 115–117.

[4] S. Niroomanesh, F. Mirzaie, Atypical postpartum eclampsia: status epilepticus without preeclamptic prodromi, Women Birth 21 (4) (2008) 171–173.

[5] B.M. Sibai, C.L. Stella, Diagnosis and management of atypical preeclampsia-eclampsia, Am. J. Obstet. Gynecol. 200 (5) (2009) 481 e481-487.

[6] J.L. Rojas-Arias, L.D. Ortiz-Lopez, W.J. Orduna-Aparicio, C.A. Quintero-Loaiza, E. Acuna-Osorio, A. Franco-Hernandez, M. Parra-Saavedra, S. Molina-Giraldo, F. Figueras, Characterization of atypical preeclampsia, Fetal Diagn. Ther. 38 (2) (2015) 119–125.
[7] A. Konijnenberg, E.W. Stokkers, J.A. van der Post, M.C. Schaap, K. Boer, O.P. Bleker, A. Sturk, Extensive platelet activation in preeclampsia compared with normal pregnancy: Enhanced expression of cell adhesion molecules, Am. J. Obstet. Gynecol. 176 (2) (1997) 461–469.
[8] S. Kohli, S. Ranjan, J. Hoffmann, M. Kashif, E.A. Daniel, M.M. Al-Dabet, F. Bock, S. Nazir, H. Huebner, P.R. Mertens, et al., Maternal extracellular vesicles and platelets promote preeclampsia via inflammasome activation in trophoblasts, Blood 128 (17) (2016) 2153–2164.
[9] A.M. Nooh, H.M. Abdeldayem, Changes in platelet indices during pregnancy as potential markers for prediction of preeclampsia development, Open J. Obstetrics Gynecol. 05 (12) (2015) 703–712.
[10] M. Rezk, W. Gaber, A. Shaheen, A. Nofal, M. Emara, A. Gamal, H. Badr, First versus second trimester mean platelet volume and uric acid for prediction of preeclampsia in women at moderate and low risk, Hypertens. Pregnancy 37 (3) (2018) 111–117.
[11] K. Dogan, H. Guraslan, M.B. Senturk, C. Helvacioglu, S. Idil, M. Ekin, Can platelet count and platelet indices predict the risk and the prognosis of preeclampsia? Hypertens. Pregnancy 34 (4) (2015) 434–442.
[12] M. James, M. Roberts, Phyllis A. August, George Bakris, John R. Barton, Ira M. Bernstein, Maurice Druzin, Hypertension in pregnancy report of the American college of obstetricians and gynecologists' task force on hypertension in pregnancy, Obstetrics Gynecol. (2013) 1122–1131.
[13] A. Klajnbard, P.B. Szecsi, N.P. Colov, M.R. Andersen, M. Jorgensen, B. Bjorngaard, A. Barfoed, K. Haahr, S. Stender, Laboratory reference intervals during pregnancy, delivery and the early postpartum period, Clin. Chem. Lab. Med. 48 (2) (2010) 237–248.
[14] M.D. Ran Neiger, Stephen A. Contag, Donald R. Coustan, Preeclampsia effect on platelet count, Am. J. Perinatol. 9 (1992) 378–380.
[15] G. Vilchez, M. Lagos, K. Kumar, P. Argoti, Is mean platelet volume a better biomarker in pre-eclampsia? J. Obstet. Gynaecol. Res. 43 (6) (2017) 982–990.
[16] E.K.A. Kurtoglu, H. Celik, et al., Validity of platelet indices in predicting the risk of developing preeclampsia, J. Experiment. Clin. Med. 33 (2) (2016) 57–61.
[17] L. Han, X. Liu, H. Li, J. Zou, Z. Yang, J. Han, W. Huang, L. Yu, Y. Zheng, L. Li, Blood coagulation parameters and platelet indices: changes in normal and preeclamptic pregnancies and predictive values for preeclampsia, PLoS One 9 (12) (2014) e114488.
[18] T. Ceyhan, C. Beyan, I. Baser, K. Kaptan, S. Gungor, A. Ifran, The effect of preeclampsia on complete blood count, platelet count and mean platelet volume, Ann. Hematol. 85 (5) (2006) 320–322.
[19] I. Bellos, G. Fitrou, V. Pergialiotis, N. Papantoniou, G. Daskalakis, Mean platelet volume values in preeclampsia: A systematic review and meta-analysis, Pregnancy Hypertens. 13 (2018) 174–180.
[20] N. Kumar, R. Singh, N. Sharma, A. Jain, Atypical presentation of posterior reversible encephalopathy syndrome: two cases, J. Anaesthesiol. Clin. Pharmacol. 34 (1) (2018) 120–122.
[21] B.C. Young, S.A. Karumanchi, Toward a better diagnosis for preeclampsia, Clin. Chem. 62 (7) (2016) 913–915.
[22] M. Alice Konijnenberg, Els W. Stokkers, Joris A.M. van der Post, Marianne C.L. Schaap, Kees Boer, Otto P. Bleker, Augueste Sturk, Extensive platelet activation in preeclampsia compared with normal pregnancy: Enhanced expression of cell adhesion molecules, Am. J. Obstet. Gynecol. 176 (2) (1999) 461–469.
[23] M.E. Stavroula Tsiara, I. Anita Jagroop, Dimitri P. Mikhailidis, Platelets as predictors of vascular risk: is there a practical index of platelet activity? Clin. Appl. Thromb. Hemost. 9 (3) (2003) 177–190.