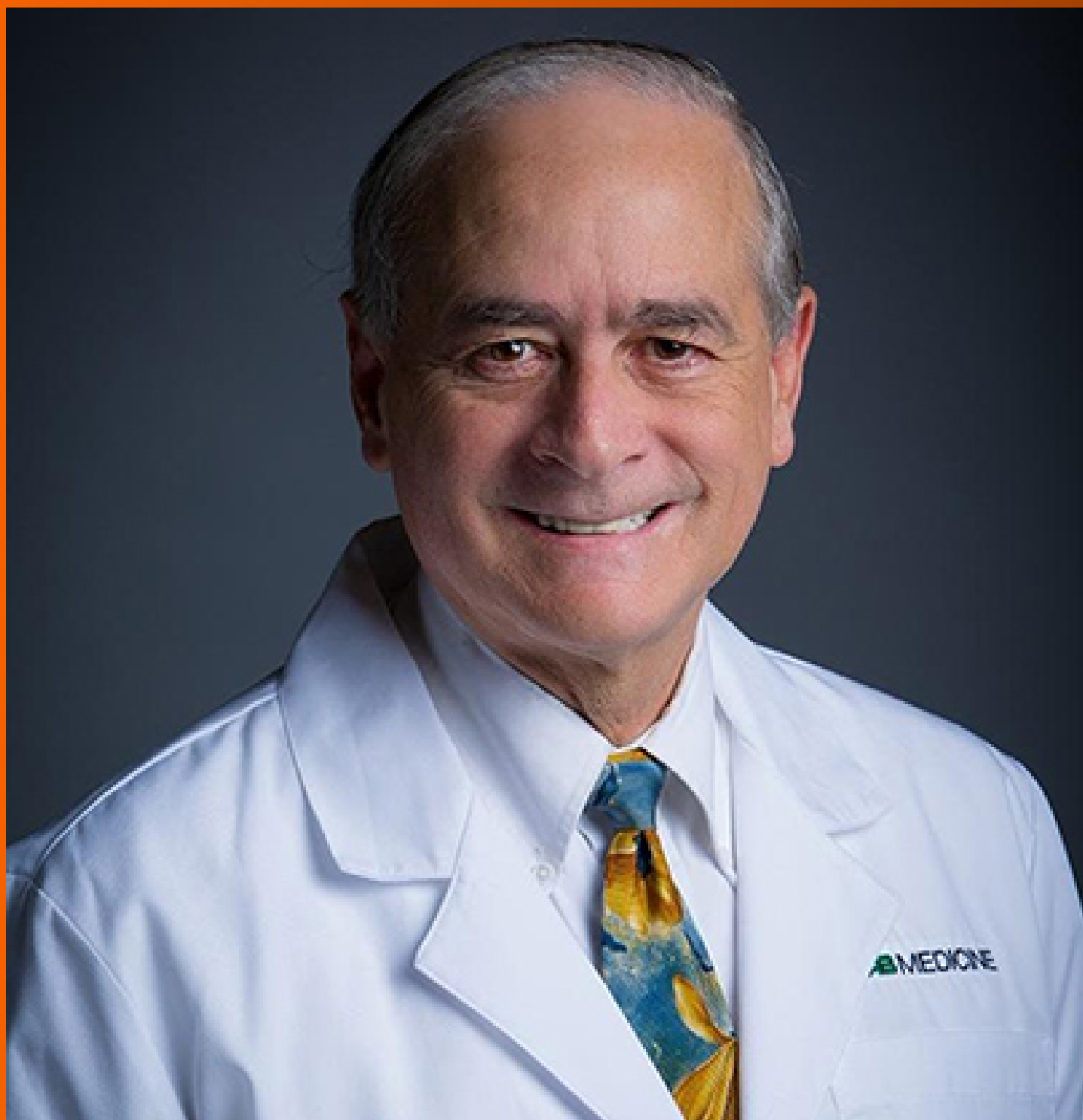


World Journal of *Obstetrics and Gynecology*

World J Obstet Gynecol 2023 May 11; 12(3): 17-32



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INDEXING/ABSTRACTING

The WJOG is now abstracted and indexed in Reference Citation Analysis, China Science and Technology Journal Database, China National Knowledge Infrastructure, and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Ying-Yi Yuan; **Production Department Director:** Xu Guo; **Editorial Office Director:** Yu-Jie Ma.

NAME OF JOURNAL

World Journal of Obstetrics and Gynecology

ISSN

ISSN 2218-6220 (online)

LAUNCH DATE

June 10, 2012

FREQUENCY

Continuous Publication

EDITORS-IN-CHIEF

Paolo Ivo Cavaletto

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2218-6220/editorialboard.htm>

PUBLICATION DATE

May 11, 2023

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INSTRUCTIONS TO AUTHORS

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<https://www.wjgnet.com/bpg/gerinfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/gerinfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Observational Study

Clinical implication of platelet to lymphocyte ratio in early onset preeclampsia: A single-center experience

Wisam Akram, Zina Abdullah Hussein, Mazin Hameed Humadi, Wassan Nori

Specialty type: Medicine, general and internal

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Imbeah EG, Ghana; Pahlavani HA, Iran

Received: January 26, 2023

Peer-review started: January 26, 2023

First decision: February 8, 2023

Revised: February 8, 2023

Accepted: April 4, 2023

Article in press: April 4, 2023

Published online: May 11, 2023



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Abstract

BACKGROUND

Preeclampsia (PE) is a pregnancy syndrome of undetermined etiology; inflammation was one of the proposed theories for its development.

AIM

To examine the platelet to lymphocyte ratio (PLR), an inflammatory biomarker, as a marker to predict poor maternal-neonatal outcomes in early-onset PE (EoPE).

METHODS

A cross-sectional study enrolled 60 pregnant women with EoPE (at 32-30 wk of gestation) at a university hospital. Demographic criteria and hematological indices were collected, including platelet counts and indices (mean platelet volume and platelet distribution width), PLR, and the Doppler study, which calculated estimated fetal weight (EFW), amniotic fluid index (AFI), resistance index (RI), and pulsatility index (PI). Participants were followed until delivery, where maternal outcomes were recorded, including; delivery mode and reason for cesarean section, and neonatal outcomes, including fetal growth restriction (FGR), meconium-stained liquid, the 5-min Apgar score, and admission to the intensive care unit.

RESULTS

There was a trend of insignificant increases in cesarean sections. Sixty-one-point two percent (37/60) fetuses were admitted to the neonatal care unit; 70.0% of admitted fetuses were meconium-stained liquor, and 56.7% of them had FGR. PLR was positively correlated with AFI and EFW as $r = 0.98, 0.97, P < 0.001$; PLR showed negative correlations with PI and RI as $r = -0.99, -0.98, P < 0.001$. The Apgar score and the number of days admitted to the intensive care unit had a positive and negative correlation (0.69, -0.98), $P < 0.0001$, respectively. Receiver

operating characteristic calculated a PLR cutoff value (7.49) that distinguished FGR at 100% sensitivity and 80% specificity.

CONCLUSION

Strong, meaningful relationships between PLR and FGR parameters and a poor neonatal outcome with a significant *P* value make it a recommendable biomarker for screening EoPE-related complications. Further studies are suggested to see the impact on maternal-neonatal health.

Key Words: Preeclampsia; Early onset; Maternal complication; Adverse perinatal outcome; Apgar score

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Core Tip: Women with preeclampsia (PE) suffer increased morbidity and mortality; their offspring endure higher risks in the early neonatal period and later life. Despite extensive research into PE, the only definitive treatment is to terminate the pregnancy. Many seek efficient prediction methods that may reduce expected risk. Platelet to lymphocyte ratio (PLR), an inflammatory biomarker, was studied in PE; however, little is known about its role in early-onset PE, a subtype with serious consequences for fetal and maternal health. Herein, we examine the role of PLR, which showed a strong, meaningful relationship between fetal growth restriction and poor neonatal outcome, making PLR a recommendable screening parameter.

Citation: Akram W, Abdullah Hussein Z, Hameed Humadi M, Nori W. Clinical implication of platelet to lymphocyte ratio in early onset preeclampsia: A single-center experience. *World J Obstet Gynecol* 2023; 12(3): 17-27

URL: <https://www.wjgnet.com/2218-6220/full/v12/i3/17.htm>

DOI: <https://dx.doi.org/10.5317/wjog.v12.i3.17>

INTRODUCTION

Preeclampsia (PE) is identified as new-onset hypertension in formerly normotensive pregnant women, combined with proteinuria, after the 20th wk of gestation; it affects 7% to 10% of all pregnancies. PE is primarily a placenta disease that can be early-onset or late-onset PE according to its onset below or above 32 wk of gestation[1,2]. Early-onset PE (EoPE) is a severe form of PE with a 0.35%-0.50% prevalence caused by inadequate recasting of the uterine spiral arteries and poor placental implantation. The hypoxic placenta produces excessive inflammatory mediators in maternal circulation as the pregnancy proceeds. As a result, vascular integrity is disrupted, and endothelial dysfunction occurs. The latter leads to hypertension, proteinuria, and other PE-related symptoms. The decreased perfusion to the fetus will reduce fetal growth rates; indeed, PE is a major cause of fetal growth restriction (FGR) [2-4].

FGR is linked to adverse obstetric effects, including higher cesarean sections (C-sections), poor neonatal outcomes; such as low Apgar scores, admission to the neonatal intensive care unit (NICU), and meconium-stained liquor, in addition to long-term health effects such as delayed neurodevelopmental milestones and adult cardiovascular disease[5-7].

Diagnosing FGR is made *via* serial ultrasound examination, which needs follow-up and patient compliance[3,8]. As a result, there was a necessity for prediction modules to assess current placental activity. Inflammation is a proposed cause of PE, and numerous inflammatory markers were examined to define PE severity and its related consequences[9-11]. Platelet turnover increases in the maternal circulation of PE women, which eventually reduces their numbers along with alterations in platelet size, and functionality; lymphocytes, on the other hand, will be increased in PE cases[12] owing to a maladaptive immune response and a hyper-inflammatory state in PE[13]. Therefore, the platelet to lymphocyte ratio (PLR) will decrease in severe PE cases as the numerator (platelets) decreases when divided by the increased denominator (lymphocyte). PLR has been studied for prognostic and predictive roles in various diseases, including PE and cancer prognosis. However, they presented inconsistent and sometimes contradicting results[11-13]. Moreover, PLR was not tested in EoPE.

We hypothesized that the reduction in PLR would predict poor obstetrical and neonatal outcomes in early-onset PE. We aimed to predict FGR through biological and ultrasonic markers for patients with EoPE as a primary goal. The secondary aim was to examine the correlation of PLR with predictors of maternal-fetal outcome.

MATERIALS AND METHODS

At the University Hospital in Baghdad, Iraq, a longitudinal study with a cross-sectional design recruited 60 eligible participants in June 2019 and ended in October 2020. The ethical committee of Mustansiriyah University approved the study (IRB 160, February 2019). The Declaration of Helsinki was followed in the study; all participants gave informed consent after we explained the study aims and methods prior to enrollment. The study participants were women with early-onset PE (less than 34 wk). Only women with severe PE were recruited (Figure 1).

Inclusion criteria

Pregnant between the ages of 18 and 40, with a gestational age of 30-32 wk, as determined by history and/or confirmed by an early ultrasound scan. They should not have started treatment. We aimed to have a narrow window in recruitment to make the study's demographics more uniform.

Exclusion criteria

Pregnant women with gestational age outside reference gestational age (> 32 wk and < 30 wk). Medical disorders like kidney and liver diseases, a personal or family history of thyroid, diabetes, or cardiovascular diseases, a personal history of chronic hypertension, blood dyscrasias, and anemia. Those with twin pregnancies and congenital fetal anomalies. Smoking mothers and those on aspirin or steroids were also excluded. Non-severe PE cases have been excluded.

Our hospital is a tertiary center that receives many cases of PE in addition to referred cases from the periphery of Baghdad. Admission, assessment of fetomaternal wellbeing, blood pressure control, accelerated lung maturity, and close follow-up for any deterioration of a pregnant mom or her unborn baby necessitating pregnancy termination are all part of the policy for managing severe EoPE.

Maternal assessment

A detailed history and general and obstetrical exams were conducted on the day of admission. In every case, maternal age, weeks of gestation, and systolic and diastolic blood pressure (SBP, DBP) were recorded while the patients were at rest. Lab tests were ordered, including blood biochemistry (serum creatinine, blood urea, alanine aminotransferase, and aspartate aminotransferase); a complete blood count to assess hematological indices hematocrit (10%), platelet distribution width, mean platelet volume, platelet counts, lymphocyte count, where the PLR was created; and a urine sample for evaluating total protein excreted.

Fetal assessment

On the same day of admission, an ultrasound scan was arranged to assess fetal wellbeing [gestational age, amniotic fluid index (AFI), estimated fetal weight (EFW), signs of fetal growth restriction (FGR)]. A color Doppler spectral study measured uterine artery pulsatility and resistance index (PI and RI).

Cases were followed until delivery, at which point the maternal outcomes, including; the mode of delivery and reason for a C-section, were recorded. In addition, the neonatal outcome included meconium-stained liquor, a 5-min Apgar score, and admission to the NICU. The information was saved on an Excel sheet so that it could be analyzed later.

Defining study parameters

PE was defined according to the ACOG technical bulletin No. 219 (American College of Obstetricians and Gynecologists), which includes patients with a systolic blood pressure of 140 mmHg or a diastolic blood pressure of 90 mmHg following 20 wk of gestation and albuminuria of > 300 mg or a sustained 1+ dipstick at 24 h. A gestational age of less than 32 wk defines EoPE[1].

Cases of severe PE had a systolic blood pressure of 160 mmHg or a diastolic blood pressure of 110 mmHg. In the absence of proteinuria, the diagnostic criteria for severe PE comprise hypertension plus thrombocytopenia, impaired liver function, pulmonary edema, new development of renal insufficiency, or new-onset cerebral or visual problems[2].

The early-onset FGR was defined as ultrasonic EFW or fetal abdomen circumference less than the 3rd percentile using a population chart, or EFW or fetal abdominal circumference less than the 10th percentile correlated with umbilical artery PI more than the 95th percentile, or cerebroplacental ratios less than the 5th percentile[3,8].

The sample size was calculated according to the following equation for a cross-sectional study with quantitative variables[14]: $Z_{1-\alpha/2}$ is a standard normal variate which is equal to 1.96; SD = standard deviation of a variable calculated by earlier published works; d = the precision level decided by the operator; sample size = $(1.96)^2 (0.35)^2 / (0.1)^2 = (3.84 \times 0.1225) / 0.01 = 43$ patients. So, the sample size is 43 patients; we recruited 60 cases.

Statistical analysis

The statistical analysis of the data was carried out through Microsoft Office Excel 2016 and the SPSS 26 program. The numerical data were expressed as mean, standard deviation. Categorical data were

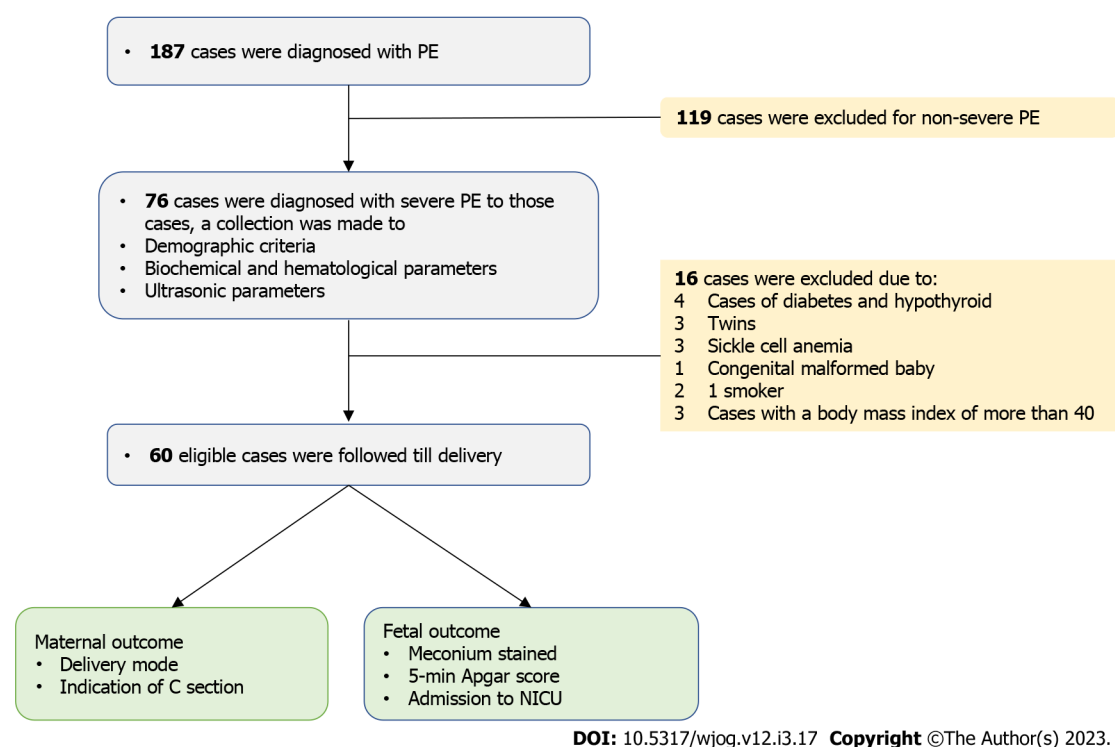


Figure 1 Study flow chart. PE: Preeclampsia; NICU: Neonatal intensive care unit.

presented as numbers and percentages. Linear regression assessed the correlation between PLR and the study parameters, including maternal and neonatal outcomes. The receiver operating characteristic (ROC) curve was constructed to calculate the PLR that correlates with FGR at the highest sensitivity and specificity. All tests were considered significant when the *P* value was 0.05.

RESULTS

This study examined 60 pregnant women diagnosed with severe PE at a gestational age of 32-30 wk. **Table 1** shows the primary criteria of the study. The mean maternal age was 27.0 ± 2.6 years, the PLR ratio was 7.86 ± 1.75 , the EFW was 1.30 ± 0.08 , the days of admission to the NICU were 7.09 ± 2.05 d, and the mean Apgar score was 6.54 ± 1.60 . **Table 2** describes the maternal outcome in terms of cesarean section (C-section), which showed a trend toward a higher percentage *vs* vaginal delivery with no statistical significance (65% *vs* 35%). **Table 3** describes the neonatal outcome of the delivered newborn. Of the total fetuses studied, 37/60 (61.2%) were admitted to the NICU. Seventy percent of admitted fetuses were meconium-stained liquor. The occurrence of meconium-stained liquor was significantly higher among admitted cases. The FGR was reported in 56.7% of the admitted fetuses, which is significantly higher in admitted fetuses. The lowest Apgar scores were found in the admitted cases to the NICU. A statistically significant difference was confirmed in the admission to the NICU between different Apgar scores. The percentage of dead fetuses is not statistically significant between admitted and unadmitted fetuses in **Table 4**. PLR, taken as an independent variable, was correlated with the FGR parameters (AFI, EFW, PI, and RI). All correlations were strongly significant, as the correlation coefficients (*r*) were (0.98, 0.97, -0.99, -0.98), respectively, with *P* < 0.001. As for newborn parameters, the Apgar score showed a positive correlation of 0.69, while admission days to the NICU showed a strong inverse correlation of -0.98; both had a *P* < 0.0001. The ROC curve calculated a PLR cutoff value < 7.49, an AUC of 0.8, and *P* < 0.001, which was correlated at 100% sensitivity and 80% specificity with FGR, as described in **Table 5**.

DISCUSSION

Analysis showed a strong, meaningful correlation of PLR to parameters that define FGR, which indicates PLR reliability in FGR prediction. The strong link between PLR and neonatal outcomes, such as Apgar score and number of days in the NICU, suggests that PLR is a good predictor of neonatal outcome.

Table 1 Primary characteristics of the studied group

Maternal demographic and biochemical parameter, n = 60	
Maternal age in yr	27.0 ± 2.6
Mean systolic BP in mL/Hg	160.2 ± 5.2
Mean diastolic BP in mL/Hg	105.2 ± 4.7
Urine for albumin in gm/dL	2.89 ± 0.09
Serum creatinine in mg/dL	0.86 ± 0.52
Blood urea in mg/dL	29.38 ± 14.04
Alanine aminotransferase in U/L	27.43 ± 5.32
Aspartate aminotransferase in U/L	21.80 ± 4.49
Maternal hematological indices, n = 60	
Hematocrit, 10%	36.58 ± 2.81
Platelet count as × 10 ⁹	182.40 ± 47.42
MPV in fL	10.52 ± 0.23
PDW in fL	16.68 ± 1.37
PLR ratio	7.86 ± 1.75
Fetal demographic criteria, n = 60	
Fetal AFI in cm	6.60 ± 1.19
Estimated fetal weight FW in kg	1.360 ± 0.08
PI UA Doppler	3.29 ± 0.59
RI UA Doppler	3.13 ± 0.55
Admission to NICU in d	7.09 ± 2.05
Mean Apgar score	6.54 ± 1.60

Data are mean ± SD. AFI: Amniotic fluid index; BP: Blood pressure; FW: Fetal weight; MPV: Mean platelet volume; NICU: Neonatal intensive care unit; PDW: Platelet distribution width; PI: Pulsatility index; PLR: Platelet to lymphocyte ratio; RI: Resistance index; UA: Uterine artery.

Table 2 Maternal outcome for the enrolled participants, n = 60

Parameter	Study participants presented	n (%)	P value
Mode of delivery	Vaginal delivery	21 (35)	< 0.407
	Cesarean delivery	39 (65)	
Indication for CS delivery	Previous scar	13 (22.5)	< 0.190
	Fetal distress	12 (20)	
	Failed induction	11 (17.5)	
	Malpresentation	3 (5)	

According to Mannaerts *et al*[15], PLR was low among the EoPE group compared to healthy controls. They confirmed that PLR tends to decrease after 20 wk of gestation in patients destined to have PE. Their results were in good agreement with the Yücel *et al*[16], which confirmed a lower PLR among severe PE cases compared to mild PE and healthy controls. Sisti *et al*[17] examined PLR in a case-control study involving cases of HELLP syndrome and healthy controls. Their analysis confirmed lower PLR among affected patients. They suggested that the ratio be included in the HELLP syndrome prediction mode.

Our results showed a strong positive link between PLR and AFI. Less blood flow to the placenta and ischemia cause less blood flow to the fetal kidneys, which lowers AFI[10].

The PLR showed a significant positive correlation with the EFW. Likewise, Can *et al*[18] investigated PLR and NLR in relation to birth weight in healthy and malnourished term babies. Both ratios were

Table 3 Neonatal outcome of the delivered newborn (*n* = 60) presented as numbers and percentage

Variable		Admitted, <i>n</i> = 37	Not admitted, <i>n</i> = 23	<i>P</i> value
Meconium	Meconium stain	26 (70%)	0 (0%)	0.000
	No meconium	11 (30%)	23 (100%)	
Occurrence of FGR	FGR	21 (56.7%)	0 (0%)	0.000
	No FGR	16 (43.3%)	23 (100%)	
Apgar score	> 7	0 (0%)	19 (51.3%)	0.000
	5-7	5 (21.7%)	18 (48.7%)	
	< 5	23 (78.3%)	0 (0%)	
Occurrence of dead fetus	Dead fetus	2 (5%)	0 (0%)	0.257
	Not dead fetus	35 (95%)	23 (100%)	

FGR: Fetal growth restriction.

Table 4 Correlation between the platelet to lymphocyte ratio and the studied variables

PLR vs variables	Correlation coefficient	<i>P</i> value
AFI	0.98	< 0.001
EFW	0.97	< 0.001
PI	-0.99	< 0.001
RI	-0.98	< 0.001
Apgar score	0.69	< 0.0001
Admission days to NICU	-0.98	< 0.0001

AFI: Amniotic fluid index; EFW: Estimated fetal weight; NICU: Neonatal intensive care unit; PI: Pressure index; PLR: Platelet to lymphocyte ratio; RI: Resistance index; UA: Uterine artery.

Table 5 Receiver operating characteristic curve defined the platelet to lymphocyte ratio cutoff value that discriminated fetal growth restriction with the utmost sensitivity and specificity

Parameter	Cutoff value	Sensitivity	Specificity	AUC	<i>P</i> value
PLR	< 7.49	100%	80%	0.9	< 0.001

AUC: Area under the curve; PLR: Platelet to lymphocyte ratio.

significantly high in the malnourished study division; they were recommended as reliable markers.

Akgun *et al*[19] investigated PLR with birth weight and gestational age. Their results show a significant correlation with birth weight. Furthermore, a significant correlation was found between infants' birth weight and gestational age. Kirmızı *et al*[20] examined PLR and NLR in late onset FGR in a case-control study. They did not recommend PLR as its levels were statistically insignificant compared to the NLR. Their study had a small sample size, which may explain the shortcomings of their results.

Both PI and RI were strongly correlated with PLR, which was consistent with previous research linking changes in PI and RI waveforms of uterine arteries to the development of PE and FGR[21]. A Cochrane review also showed that the use of a doppler can help reduce the number of C-sections, labor inductions, and perinatal deaths in FGR babies[22].

Platelet indices, along with PI and RI, were suggested by Abdel Razik *et al*[23] as a way to measure the severity of PE rather than predict its onset.

In terms of obstetric outcomes, 60.0% of cases were ended by C-section, 61.2% of fetuses were admitted to the neonatal care unit, 70.0% were meconium-stained, and 56.7% of the meconium-stained fetuses had FGR, which led to a lower Apgar score among admitted cases. Our results were in line with the study of Jha *et al*[24], where significant differences were seen in the PE groups they examined. In

addition to low Apgar scores at 1st and 5th min and on admission days to the NICU[24].

In the current study, the Apgar score showed a significant *P* value among newborns with a positive correlation to PLR. Okoye *et al*[25] discussed lower PLR in neonates of PE women, which correlates with hypertension severity. PLR has also been linked to poor birth outcomes, as evidenced by low Apgar scores. Their study examined PLR and other blood indices in the cord blood of neonates born to PE mothers. No meaningful association was seen between PLR and neonatal birth weight; it only correlated with 1st and 5-min Apgar scores in newborns.

Kim *et al*[26] discussed a considerably low PLR in women with severe PE. It was most strongly related to the time of admission to the delivery interval.

According to the Özdemirci *et al*[27], PLR in late-onset FGR cases did not show a significant increase. They suggested that an exaggerated inflammatory response was proposed to be a cause for FGR and to be absent in late-onset FGR cases, emphasizing our findings and forming the novelty of our study.

PE is a major risk factor for growth restriction; insufficient spiral artery penetration during early implantation has been blamed for early-onset FGR. To supply the fetus with nutrients, the diseased placenta will develop a mechanism to overcome increased resistance to blood flow and decreased placenta perfusion[5]. Since blood is a primary interface between the fetus and mother, any stressful event will cause blood parameters passing through the placenta to be altered. Therefore, many researchers addressed blood indices, searching for biomarkers that correlate with PE and consequent FGR[10,28].

Different pathophysiologic mechanisms underlie PE sub-types. EoPE is the result of impaired placenta development and improper innate immune system activation that trigger a systemic inflammatory response as early as the second trimester. The injured endothelial cells secrete many cytokines and inflammatory markers into the circulation that cause changes in the complete blood film parameters in PE cases[29,30].

Platelet numbers will be reduced due to consumption. Lymphocyte numbers, key players in systemic inflammation, will be increased. These changes are thought to be responsible for maternal and fetal complications[11]. Hence, PLR forecasts an impending or ongoing inflammatory pathology.

The current study result may have a clinical implication by preventing PE-related complications. Patients with known inflammatory biomarkers may benefit from prophylactic doses of low molecular weight heparin, which has immunomodulatory and anti-inflammatory properties. Low-molecular-weight heparin was recommended to prevent adverse obstetrical problems[31].

We have to acknowledge some of the inconsistencies in earlier studies regarding the value of PLR. Morisaki *et al*[32] technical report explained that different blood ratios were caused by different gestational ages, attributing these inconsistencies to different maternal criteria, gestational age, and inflammatory responses among pregnant women. Our findings clearly demonstrated that there was no statistical correlation between the PLR and the mode of delivery or the indication of the delivery, which was consistent with previous studies that criticized the insignificant role of blood ratios in predicting maternal outcomes[33,34]. Since delivery is the only treatment for PE progression, we must evaluate maternal risk against newborn problems. For that, early and accurate detection is necessary[35,36].

Study limitations

The cross-sectional nature of this study is one since the causal effect cannot be elucidated[37]. A case-control study may perform better in confirming the link between PLR and EoPE. We aimed to collect a higher sample size; however, the COVID-19 pandemic limited many work aspects. It is worth mentioning that risk analysis for the prevention of PE was not done; we think that the current analysis served our aim well. The fact that the current study was a single-center experience may limit the globalization of its results.

Study strengths

Although PLR was examined in late-onset PE, its role in EoPE was not addressed earlier. This paper emphasizes the significance of PLR in predicting early-onset PE associated with FGR[38-40]. PLR was intimately linked to FGR parameters; moreover, it correlated with important predictors of neonatal outcome; its significant correlation to FGR EoPE with high sensitivity and specificity (100%, 80%) and a significant AUC of 0.9, *P* < 0.001 makes it a valuable predictor. Since PLR was already validated for PE and its related co-morbidities, we needed no external validation. FGR is responsible for 50% of unexplained stillbirths. Its implications extend beyond postpartum, as it increases neonatal morbidity and the risk of cardiovascular diseases in the offspring[41]. PLR is simple, inexpensive, and can guide clinicians and assist with the timely referral of affected women to tertiary care centers to halt adverse fetal outcomes. Further studies are needed to explore the future implications of PLR on fetal and maternal health and their predictive value for early childhood and adult-onset diseases.

CONCLUSION

PLR is a reliable predictor of adverse fetal outcomes, including FGR parameters, a poor Apgar score,

and admission to the neonatal care unit among pregnant women with EoPE. PLR had high sensitivity and specificity with no added expanders, making it a recommendable marker in their prediction. In light of the promising role of anti-coagulant use in preventing obstetrical-related complications, PLR may be used in predicting, categorizing, and preventing early-onset PE-related complications.

ARTICLE HIGHLIGHTS

Research background

Preeclampsia (PE) is a pregnancy condition with an unknown origin that includes two subtypes based on 34 wk of gestation: Early and late onset PE; inflammation was postulated as an explanation. The platelet to lymphocyte ratio (PLR), an inflammatory biomarker, was investigated as a predictor of poor maternal-neonatal outcome in patients with early-onset PE (EoPE).

Research motivation

Much research has shown that inflammation may be an underlying pathology that triggers PE development. There is an increased need for new methods with enhanced predictive ability. Demonstrating changes in blood indices, PLR seems an appealing option given the promising results declared by earlier work.

Research objectives

To ascertain if PLR in cases with early-onset PE can be linked to essential predictors of fetomaternal wellbeing during the intrapartum period. The second goal is to analyze the reliability of PLR as a helpful marker for monitoring prenatal predictors in women with early-onset PE.

Research methods

Cross-sectional research at University Hospital involved 60 pregnant women with EoPE (at 32-30 wk of gestation). Platelet counts and indices (mean platelet volume and platelet distribution width), PLR, Doppler study, which produced estimated fetal weight (EFW), amniotic fluid index (AFI), resistance index (RI), and pulsatility index (PI) were all gathered. Participants were tracked until birth, when maternal outcomes such as delivery style and reason for cesarean section were documented, as well as newborn outcomes such as fetal growth restriction (FGR), meconium-stained fluids, five-minute Apgar score, and admission to the critical care unit.

Research results

A cesarean section trend has been noted. Sixty-one-point two percent (37/60) fetuses were hospitalized to the newborn care unit, 70% had meconium-stained liquid, and 56.7% had FGR. PLR was shown to be favorably connected with AFI and EFW ($r = 0.98, 0.97, P < 0.001$), and negatively correlated with PI and RI ($r = -0.99, -0.98, P < 0.001$). The Apgar score and the number of days admitted to the critical care unit had a positive and negative connection ($r = 0.69, -0.98, P < 0.001$), respectively. The PLR cutoff value derived by receiver operating characteristic (7.49) differentiated FGR with 100% sensitivity and 80% specificity.

Research conclusions

PLR had substantial P value associations with FGR measures and poor neonatal outcomes, making it a promising biomarker for screening EoPE-related problems. More research is needed to determine the influence on maternal-neonatal health.

Research perspectives

Defining reliable biomarkers that are antenatal clinics based with no added expense can be a promising option, especially for low-resource settings.

FOOTNOTES

Author contributions: Akram W contributed to conception and statistical analysis; Abdullah Hussein Z and Hameed Humadi M contributed to data collection and scientific editing; Nori W wrote, edited, and drafted the final version; all authors read and approved the final version.

Institutional review board statement: The study was reviewed and approved by the ethical committee of Mustansiriya University (No. 160).

Informed consent statement: All participants gave informed consent after we explained the study aims and methods

prior to enrollment.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest.

Data sharing statement: The data that support this study are available upon reasonable request to the corresponding author.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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S-Editor: Chen YL

L-Editor: Filipodia

P-Editor: Yuan YY

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