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ABOUT COVER

Editorial Board Member of *World Journal of Clinical Cases*, Dr. Quach is an Associate Professor of Gastroenterology at the University of Medicine and Pharmacy at Hochiminh City, Viet Nam, where he received his MD in 1997 and his PhD in 2011. Dr. Quach has published more than 100 reviews and original papers in local and international journals. He has received several awards, including Outstanding Presentation at the Biannual Scientific Congress of Vietnamese Nationwide Medical Schools, Medal of Creativeness from the Vietnamese Central Youth League, etc. Currently, he serves as a Vice President of the Vietnam Association of Gastroenterology and Secretary General of the Vietnam Federation for Digestive Endoscopy. (L-Editor: Filipodia)

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Case Control Study

New indicators in evaluation of hemolysis, elevated liver enzymes, and low platelet syndrome: A case-control study

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Abstract

BACKGROUND

Indices such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), mean platelet volume (MPV), platelet distribution width (PDW), and red cell distribution width (RDW) are considered new markers of the systemic inflammatory response (SIR), and have been widely implemented for the diagnosis of patients with inflammatory diseases. These new indicators have also been widely investigated in preeclampsia (PE) but less analyzed in hemolysis, elevated liver enzymes, and low platelet (HELLP) syndrome.

AIM

To compare SIR markers among HELLP patients, PE only patients, and healthy gravidae.

METHODS

This retrospective case-control study enrolled 630 cases, including 210 patients with HELLP syndrome (HELLP group), 210 patients with only PE (PE group) and 210 healthy gravidae (control group). The three groups were matched by age, parity, status of assisted reproduction, and multiple pregnancies. Birthweight, gestational age at complete blood count collection, gestational age at delivery, mode of delivery, etc. were recorded. The main indices as NLR, PLR, MPV, PDW, and RDW among the groups were compared, as well as some secondary outcomes including neutrophil, platelets, and hemoglobin.

RESULTS

The NLR (6.4 vs 4.3 vs 3.5), MPV (11.9 vs 11.2 vs 10.7), PDW (16.4 vs 13.3 vs 14.2), leukocyte ($12.4 \times 10^9/L$ vs $9.7 \times 10^9/L$ vs $8.7 \times 10^9/L$) and neutrophil count ($9.9 \times$

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$10^9/L$ vs $7.3 \times 10^9/L$ vs $6.1 \times 10^9/L$) were highest in the HELLP group, lower in the PE group, and lowest in the control group. Both the overall comparisons between the three groups (all $^bP < 0.01$) and pairwise comparisons between every two groups elicited statistically significant differences (all $^dP < 0.01$, except control vs PE: $^cP < 0.05$ in PDW). The average lymphocyte counts were $1.4 (1.1, 2.0) \times 10^9/L$ in the HELLP group, $1.6 (1.3, 2.0) \times 10^9/L$ in the PE group and $1.7 (1.4, 2.0) \times 10^9/L$ in the control group. The overall comparison of lymphocyte count within the three groups had statistically significant differences ($P = 0.000$). The pairwise comparisons between every two groups demonstrated that the HELLP group had a lower lymphocyte count than both the PE ($P = 0.019$) and control groups ($P = 0.000$), but the difference between the PE and control groups was not statistically significant ($P = 0.432$). The overall comparisons on platelet counts and the PLR among these three groups also showed statistically significant differences (both $P = 0.000$), from low to high being those in the HELLP group ($43.4 \times 10^9/L$, 64.0), control group ($180.5 \times 10^9/L$, 103.6) and PE group ($181.5 \times 10^9/L$, 112.8). Pairwise comparisons of neither index displayed statistically significant differences between the PE and control groups (both $P > 0.05$), while the differences in the two indices between the HELLP group and the two other groups were still statistically significant (all $P = 0.000$). RDW values were highest in the HELLP group (14.5% [13.6, 15.3]), lower in the control group (14.1% [13.5, 14.8]) and lowest in the PE group (13.9% [13.4, 14.9]). The difference between the PE and control group did not show statistical significance ($P = 1.000$), while RDW values in the HELLP group were higher than those in the other two groups ($^cP < 0.05$ vs control, $^dP < 0.01$ vs PE).

CONCLUSION

SIR markers such as NLR, RDW, MPV, and PDW were increased and PLR was decreased in HELLP. These SIR markers may become new indicators in the evaluation of HELLP syndrome.

Key Words: Hemolysis, elevated liver enzymes, and low platelet syndrome; Neutrophil-to-lymphocyte ratio; Platelet-to-lymphocyte ratio; Mean platelet volume; Platelet distribution width; Red cell distribution width

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Core Tip: Systemic inflammatory response (SIR) markers including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), mean platelet volume (MPV), platelet distribution width (PDW) and red cell distribution width (RDW) have been widely investigated in preeclampsia (PE) and less analyzed in hemolysis, elevated liver enzymes, and low platelet (HELLP) syndrome. In this retrospective case-control study, SIR markers were compared among HELLP/PE patients and healthy gravidae. NLR, RDW, MPV and PDW were increased and PLR was decreased in HELLP syndrome. These parameters may become predictive and prognostic indicators and useful additions to the current diagnostic standard of HELLP syndrome, if confirmed by further more studies.

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INTRODUCTION

Hemolysis, elevated liver enzymes, and low platelet (HELLP) syndrome is a severe complication in the third trimester of pregnancy. First described by Weinstein in 1982, HELLP syndrome is mainly characterized by intravascular hemolysis, elevated liver

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enzymes, and low platelet counts^[1]. The prevalence of HELLP syndrome is reportedly 0.17%-0.85% of all pregnancies. Associated with adverse pregnancy outcomes, the maternal and perinatal mortality rates of HELLP syndrome may reach up to 23.1% and 56.9% respectively, which is life threatening to both the gravida and the fetus^[2].

Although researchers have studied the pathogenesis of HELLP syndrome from several aspects including genetics, immunology, and the inflammatory response^[3], its exact etiology remains unknown. To date, the only clear hypothesis regarding the pathogenesis of HELLP syndrome is the involvement of diffuse endothelial cell injury and vascular stenosis, particularly in the liver, leading to hemolysis and erythroclasis. Moreover, the activated platelets adhere to the injured vascular endothelial cells, causing excessive platelet consumption and consequently thrombocytopenia^[4].

Since HELLP syndrome often co-exists with preeclampsia (PE), it is sometimes considered a severe complication of PE. However, up to 15% of patients with HELLP syndrome do not have elevated blood pressure^[5]. Whether HELLP syndrome should be regarded as a severe stage of PE or a separate pathological entity remains a subject of debate^[6].

Although HELLP syndrome and PE share some similar pathophysiological changes, their laboratory results and clinical features are not identical. The inflammatory reaction present in HELLP is stronger and has a preferentially damages on the liver and coagulation system^[4].

Recently, systemic immune inflammatory indices derived from peripheral blood cells have attracted the attention of researchers, mainly due to the fact that these markers can be measured quite easily. Indices such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), mean platelet volume (MPV), platelet distribution width (PDW) and red cell distribution width (RDW) have been considered new markers of systemic inflammatory response (SIR). The NLR and PLR have been widely implemented for the diagnosis of patients with inflammatory diseases such as septic shock and axial spine arthritis^[7,8]. The RDW, MPV, and PDW are related to occurrence of the systemic inflammatory response syndrome (SIRS)^[9,10].

Abnormal changes in immune-mediated inflammation contribute to the pathogenesis of PE. Over the past few years, there have been an increasing number of studies on inflammatory indices in PE. While different studies have shown inconsistent results, the majority of previous studies have reported that patients with PE have increased leukocyte counts (mainly neutrophils) and decreased lymphocytes^[11]. In addition, higher NLRs and lower PLRs have been found in patients with PE compared to healthy pregnancies^[12-14].

The inflammatory reaction in HELLP syndrome is more severe than that of PE, but studies on the levels of inflammatory indices (*e.g.*, NLR, PLR, MPV, PDW, RDW) in HELLP patients have rarely been reported. Sisti *et al.*^[15,16] found that the NLR was higher and the PLR was lower in patients with HELLP syndrome in the third trimester, but these indices in the first trimester did not predict the occurrence of HELLP in the third trimester. Only a relatively small number of cases were included in previous studies on this topic and no simultaneous comparison of normal pregnancies, HELLP, and PE was found.

We hereby conducted a retrospective case-control study to investigate the changes in inflammatory indices in HELLP syndrome patients. To this end, we observed the components of complete blood counts (CBCs) in healthy gravidae and patients with HELLP syndrome and PE in the third trimester. The NLR, PLR, RDW, MPV, and PDW were compared amongst the three groups.

MATERIALS AND METHODS

This case-control study was conducted at the Department of Obstetrics, Suzhou Affiliated Hospital of Nanjing Medical University (Suzhou Municipal Hospital, Suzhou, China). We enrolled 210 HELLP syndrome patients and 210 PE patients who were admitted to our hospital from April 2013 to October 2019, and 210 healthy pregnant women who delivered at our hospital during the same period were included as the control group. The three groups were matched by age, parity, status of assisted reproduction and multiple pregnancies.

The diagnostic criteria of HELLP syndrome were in accordance with the Mississippi Diagnostic and Classification Criteria (platelets < 150 × 10⁹/L, coupled with an elevated lactate dehydrogenase > 600 IU/L; aspartate aminotransferase and/or alanine aminotransferase ≥ 70 U/L). Among the 210 HELLP syndrome cases, there were 52, 142, and 18 cases of grade I, grade II, and grade III, respectively^[17]. In the PE

group, only PE patients without a concurrent diagnosis of HELLP syndrome were included. The diagnosis of PE was made according to 2019 guidelines of the American College of Obstetricians and Gynecologists^[18].

The exclusion criteria were as follows: Patients with other complications induced by hepatic dysfunction; patients with other thrombocytopenia-induced complications; and patients with any history of membrane rupture or any infection that could cause alterations in the maternal SIR markers.

The venous serum samples for CBCs were collected from non-fasting patients at the time of admission, before the initiation of any medical treatment such as magnesium sulphate or antenatal corticosteroids. Then, 2 mL of venous blood samples were drawn into ethylenediaminetetraacetic acid tubes and processed within 2 h after the venipuncture using an automatic blood cell counter (MINDRAY BC2000).

Demographic characteristics and clinical information including (but not limited to) the participants' age, parity, status of assisted reproduction and multiple pregnancies, birthweight, gestational age at CBC collection, gestational age at delivery, and mode of delivery were recorded. Gestational age was noted as the number of weeks, and days were converted to weeks by calculation and presented in decimal form.

The NLR, PLR, MPV, PDW and RDW were compared among the three groups, as well as the platelet counts, leukocytes, neutrophils, lymphocytes, hemoglobin levels, and erythrocyte counts.

Data analyses were performed using SPSS software for Windows, Version 22.0 (Chicago, IL, United States). The Kolmogorov-Smirnov test was used to analyze the normal distribution of the continuous variables. Variables that did not follow the normal distribution were expressed as the median (25th-75th percentile). The non-parametric Kruskal-Wallis test was used to compare the measurement data among the three groups, while the count data were analyzed using the chi-square test of the $R \times C$ contingency table. Comparisons between any two groups were performed *via* the Bonferroni test. $P < 0.05$ were considered statistically significant.

RESULTS

The comparisons based on demographic characteristics among the three groups are shown in Table 1. A total of 630 pregnant women were enrolled in this study, with 210 in each group. There were no statistically significant differences among the three groups in terms of median age, parity, or status of assisted reproduction (all $P > 0.05$). Therefore, patients in the three groups had equal baseline characteristics.

However, the three groups had statistically significant differences in terms of the gestational age at delivery ($P = 0.000$), which from low to high was that in the HELLP group (33.6 [31, 36.3]), PE group (36.4 [33.8, 38.2]) and control group (39.3 [38.9, 39.7]). Birthweight also delineated significant differences among the three groups ($P = 0.000$), with the highest in the control group (3350 [3100, 3650]), lower in the PE group (2500 [1889, 3050]), and the lowest in the HELLP group (1800 [1200, 2350]). The pairwise comparisons in gestational age at delivery and birthweight between every two groups also showed statistically significant differences (all $P = 0.000$) (Table 1).

The NLR (6.4 *vs* 4.3 *vs* 3.5), MPV (11.9 *vs* 11.2 *vs* 10.7), PDW (16.4 *vs* 13.3 *vs* 14.2), leukocyte ($12.4 \times 10^9/L$ *vs* $9.7 \times 10^9/L$ *vs* $8.7 \times 10^9/L$) and neutrophil count ($9.9 \times 10^9/L$ *vs* $7.3 \times 10^9/L$ *vs* $6.1 \times 10^9/L$) were highest in the HELLP group, lower in the PE group, and lowest in the control group. Both the overall comparisons among the three groups (all $^bP < 0.01$) and pairwise comparisons between every two groups elicited statistically significant differences (all $^dP < 0.01$, except control *vs* PE: $^cP < 0.05$ in PDW) (Table 2).

The average lymphocyte counts were $1.4 (1.1, 2.0) \times 10^9/L$ in the HELLP group, $1.6 (1.3, 2.0) \times 10^9/L$ in the PE group and $1.7 (1.4, 2.0) \times 10^9/L$ in the control group. The overall comparison among these three groups produced statistically significant difference ($P = 0.000$). The pairwise comparisons between every two groups demonstrated that the HELLP group had a lower lymphocyte count than both the PE ($P = 0.019$) and control groups ($P = 0.000$), but the difference between the PE and control groups was not statistically significant ($P = 0.432$) (Table 2).

The overall comparisons with respect to platelet counts and the PLR among these three groups also showed statistically significant differences (both $P = 0.000$), from low to high being those in the HELLP group ($43.4 \times 10^9/L$, 64.0), control group ($180.5 \times 10^9/L$, 103.6) and PE group ($181.5 \times 10^9/L$, 112.8). Pairwise comparisons of neither index displayed statistically significant differences between the PE and control groups (both $P > 0.05$), while the differences in the two indices between the HELLP group and the two other groups were still statistically significant (all $P = 0.000$) (Table 2).

Table 1 Comparisons of demographic and clinical features among the three groups

	HELLP ①	Controls ②	PE ③	H/z/ χ^2	P value
Age in yr	30 (27, 34)	29 (27, 33)	30 (27, 33)	1.378 ¹	0.502
Parity > 1	90/210	94/210	88/210	0.362 ³	0.834
Assisted reproduction	43/210	33/210	48/210	3.514 ³	0.173
Multiple pregnancies	29/210	15/210	23/210	4.944 ³	0.084
GA at delivery in wk	33.6 (31, 36.3)	39.3 (38.9, 39.7)	36.4 (33.8, 38.2)	313.102 ¹	0.000 ^b
				①:②-305.843 ²	0.000 ^d
				①:③-90.494 ²	0.000 ^d
				②:③215.379 ²	0.000 ^d
Neonatal birthweight in g	1800 (1200, 2350)	3350 (3100, 3650)	2500 (1889, 3050)	291.917 ¹	0.000 ^b
				①:③-297.086 ²	0.000 ^d
				①:③95.086 ²	0.000 ^d
				②:③202.000 ²	0.000 ^d

¹Indicates Kruskal-Wallis test with ^a $P < 0.05$, ^b $P < 0.01$.

²Indicates Bonferroni test with ^c $P < 0.05$, ^d $P < 0.01$.

³Indicates Chi-square test of R \times C contingency table with ^e $P < 0.05$, ^f $P < 0.01$.

GA: Gestational age (noted as the number of weeks, and days were converted to weeks by calculation and showed in decimal form); HELLP: Hemolysis, elevated liver enzymes, and low platelet syndrome; PE: Preeclampsia.

RDW values were highest in the HELLP group (14.5% [13.6, 15.3]), lower in the control group (14.1% [13.5, 14.8]) and lowest in the PE group (13.9% [13.4, 14.9]). The overall comparison demonstrated statistically significant difference ($P = 0.000$). Nevertheless, the difference between the PE and control groups did not show statistical significance by pairwise comparisons ($P = 1.000$), while RDW values in the HELLP group were higher than those in the other two groups (^c $P < 0.05$ *vs* control, ^d $P < 0.01$ *vs* PE) (Table 2).

DISCUSSION

HELLP syndrome is a serious complication in the gestational period, which leads to harmful maternal and fetal outcomes such as placental abruption, disseminated intravascular coagulation, fetal growth restriction and premature birth. In severe cases, HELLP syndrome may ultimately lead to maternal and perinatal deaths^[9].

Many researchers believe that HELLP syndrome is a complication of PE since both entities often co-exist and have some striking similarities, while others argue that HELLP is a separate disease^[6]. However, whether or not it is a separate disease, HELLP syndrome remains a multisystem disorder with an unclear etiology so far, just like PE. Therefore, in addition to symptomatic treatment and timely termination of pregnancy, there is no therapeutic intervention targeting its pathogenesis at present, and predicting the disease before its onset is highly challenging. Thus, effective and simple indicators are urgently needed to predict and assess the prognosis of HELLP syndrome.

Previous studies have found that heredity, immunity, inflammation, metabolism, and blood coagulation are all related to the onset of HELLP syndrome. Many factors are intertwined and interact with each other in its pathogenesis, including activated inflammatory processes and immune responses in which neutrophils, lymphocytes, and platelets take part by releasing inflammatory mediators (cytokines)^[3].

Recent studies have shown that some indices obtained from peripheral hematological parameters such as the NLR, PLR, MPV, PDW and RDW, which are known as SIR markers, have predictive and prognostic values in various diseases including inflammatory diseases, PE and malignant tumors^[9,10,12,20,21].

Alterations in the NLR and PLR, as well as the MPV, PDW and RDW have been widely investigated in PE^[12,14,22]. However, little attention has been paid to the effects of

Table 2 Indicators comparison among the complete blood count of three groups

	HELLP①	Controls②	PE③	H/z/ χ^2	P value
GA at CBC collection in wk	33.3 (30.3, 35.9)	39.1 (38.7, 39.7)	36.0 (33.0, 37.6)	310.493 ¹	0.000 ^b
				①:②-310.140 ²	0.000 ^d
				①:③-76.881 ²	0.000 ^d
				②:③224.260 ²	0.000 ^d
NLR	6.4 (4.4, 9.8)	3.5 (2.8, 5.1)	4.3 (3.1, 6.4)	95.279 ¹	0.000 ^b
				①:②171.681 ²	0.000 ^d
				①:③106.648 ²	0.000 ^d
				②:③-65.033 ²	0.001 ^d
PLR	43.4 (28.1, 61.9)	103.6 (85.7, 129.7)	112.8 (83.3, 147.4)	312.217 ¹	0.000 ^b
				①:②-262.669 ²	0.000 ^d
				①:③-280.102 ²	0.000 ^d
				②:③-17.433 ²	0.979
Leukocyte count as 10 ⁹ /L	12.4 (9.2, 15.7)	8.7 (7.1, 11.4)	9.7 (7.9, 12.4)	73.342 ¹	0.000 ^b
				①:②150.395 ²	0.000 ^d
				①:③94.955 ²	0.000 ^d
				②:③-55.440 ²	0.000 ^d
Neutrophil count as 10 ⁹ /L	9.9 (7.1, 13.3)	6.1 (4.8, 8.7)	7.3 (5.6, 9.8)	81.810 ¹	0.000 ^b
				①:②163.433 ²	0.000 ^d
				①:③104.267 ²	0.000 ^d
				②:③-59.167 ²	0.003 ^d
Lymphocyte count as 10 ⁹ /L	1.4 (1.1, 2.0)	1.7 (1.4, 2.0)	1.6 (1.3, 2.0)	18.153 ¹	0.000 ^b
				①:②-74.538 ²	0.000 ^d
				①:③-48.590 ²	0.019 ^c
				②:③25.948 ²	0.432
Platelet as 10 ⁹ /L	64.0 (49.0, 80.0)	180.5 (152.8, 211.3)	181.5 (146.0, 227.3)	401.059 ¹	0.000 ^b
				①:②-305.821 ²	0.000 ^d
				①:③-310.236 ²	0.000 ^d
				②:③-4.414 ²	1.000
Hemoglobin in g/L	104.0 (89.0, 118.0)	115.0 (107.0, 122.0)	116.5 (107.0, 125.0)	54.286 ¹	0.000 ^b
				①:②-104.145 ²	0.000 ^d
				①:③-120.662 ²	0.000 ^d
				②:③-16.517 ²	1.000
Erythrocyte count	3.5 (3.0, 3.9)	3.8 (3.6, 4.0)	3.9 (3.7, 4.2)	67.793 ¹	0.000 ^b
				①:②-100.467 ²	0.000 ^d
				①:③-142.198 ²	0.000 ^d
				②:③-41.731 ²	0.056
RDW as %	14.5 (13.6, 15.3)	14.1 (13.5, 14.8)	13.9 (13.4, 14.9)	11.003 ¹	0.000 ^b

				①:②45.767 ²	0.029 ^c
				①:③54.899 ²	0.006 ^d
				②:③9.133 ²	1.000
MPV in fL	11.9 (11.2, 12.9)	10.7 (10.2, 11.5)	11.2 (10.4, 12.1)	84.146 ¹	0.000 ^b
				①:②160.798 ²	0.000 ^d
				①:③102.867 ²	0.000 ^d
				②:③-57.931 ²	0.003 ^d
PDW in fL	16.4 (14.3, 18.8)	13.3 (11.9, 15.4)	14.2 (12.4, 16.2)	98.052 ¹	0.000 ^b
				①:②170.395 ²	0.000 ^d
				①:③122.919 ²	0.000 ^d
				②:③-47.476	0.023 ^c

¹Indicates Kruskal-Wallis test with ^a $P < 0.05$, ^b $P < 0.01$.

²Indicates Bonferroni test with ^c $P < 0.05$, ^d $P < 0.01$.

CBC: Complete blood count; GA: Gestational age; HELLP: Hemolysis, elevated liver enzymes, and low platelet; MPV: Mean platelet volume; NLR: Neutrophil-to-lymphocyte ratio; PDW: Platelet distribution width; PE: Preeclampsia; PLR: Platelet-to-lymphocyte ratio; RDW: Red cell distribution width.

inflammation on neutrophilic activation and endothelial injury in HELLP syndrome. The Sisti *et al*^[15,16] reports were two of the very few related articles available in 2019. They observed the NLR/PLR and other CBC components in HELLP syndrome by establishing comparisons between patients and controls, but the number of cases studied was relatively small and patients with concurrent PE which was more clinically prevalent were excluded^[15,16].

In our study, a total of 630 women in their third trimester of pregnancy were studied. We performed comparisons with respect to indices such as the NLR, PLR, MPV, PDW, RDW and other CBC components between patients with HELLP syndrome and normal gravidae, as well as comparisons between patients with HELLP syndrome and those with only PE. Cases of HELLP syndrome coexisting with PE were more clinically common, and thus they were also included in the study.

Previous studies reported conflicting results on the association between the NLR and PE. Canzoneri *et al*^[11] discovered that the leukocyte and neutrophil counts were significantly increased in patients with PE compared with normal pregnant women. Serin *et al*^[12] compared 30 healthy pregnant females and 77 females with PE (37 mild cases and 40 severe cases) in their third trimester, and the results indicated that maternal NLR was significantly higher in pregnant women with PE than in healthy ones. There was also a significant and positive correlation between the NLR and systolic/diastolic arterial pressure. However, Yücel *et al*^[14] failed to find any significant difference regarding the NLR between PE patients and normal gravidae in a retrospective cohort study of 109 PE patients and 110 controls. Sisti's study on 14 women with HELLP syndrome and 14 healthy pregnant women in their third trimester revealed that both the NLR (5.8 *vs* 3.6, $P = 0.002$) and neutrophil count were higher in the HELLP group. Besides, HELLP patients had lower lymphocyte counts than healthy gravidae, but the difference delineated no statistical significance^[16]. Our results also found increased NLRs and neutrophil counts in HELLP syndrome patients, which was in accordance with Sisti's study, but lymphocyte counts were found to be lower in HELLP syndrome patients compared to healthy gravidae, which were contradictory to findings reported in Sisti's study. Additionally, we also found out that the NLR, leukocyte and neutrophil counts were all higher in PE patients than in normal gravidae, just as suggested in some previous studies. Maternal circulating leukocytes including neutrophils, lymphocytes, and monocytes are activated in pregnant women, especially in those with PE. PE is believed to be induced by a defect of implantation, causing abnormal immune activation and inflammation at the maternal-fetal interface. Subsequently, leukocytes activated by lipids secreted by the placenta circulate through the intervillous space and re-enter the maternal circulation, possibly resulting in the vascular dysfunction associated with PE. Neutrophils are usually considered as the first line of defense against infection, and recent studies have also confirmed that they are capable of infiltrating systemic blood vessels and initiate

the inflammatory response in PE patients^[23,24]. In HELLP syndrome, we speculate that even stronger inflammatory and pathological immune responses are initiated, which might explain the higher NLR, leukocyte and neutrophil counts in HELLP patients compared to PE patients and normal gravidae.

Previous studies on the relationship between the PLR and PE reached different conclusions. Gezer *et al*^[25] found an elevated first-trimester PLR in the PE group compared to the controls, indicating that a high first-trimester PLR is an indicator for the early diagnosis of PE. Notwithstanding, Yücel *et al*^[14] revealed a lower PLR in patients with severe PE than in the control group, and the difference was statistically significant. Gogoi *et al*^[26], however, noticed that PE patients had a significantly higher PLR and lower platelets than normal gravidae. In Yavuzcan's study^[27], the PLR did not show any statistically significant difference between PE patients and normal pregnant women. The PLR and platelet counts were both reported to be decreased in women with HELLP syndrome in Sisti's study on third-trimester cases^[15]. They also investigated the concentration of these indices in the first trimester but failed to identify statistically significant differences both in terms of the PLR and platelet counts between the HELLP syndrome and control groups, pointing out that the PLR could not be used as a predictor of HELLP syndrome in early pregnancy^[16]. In our study, patients with HELLP syndrome were found to have significantly decreased PLRs and platelet counts compared with both PE patients and healthy gravidae, which is in accordance with Sisti's results in third trimester cases. Nevertheless, we did not find significant differences in terms of these two parameters between PE patients and normal pregnant women, similar to the findings observed in Yavuzcan's study. Even though the inconsistency of the results obtained from previous studies on the PLR in PE patients cannot be fully explained at present, we still tried to elaborate the reason for lower PLRs in patients with HELLP syndrome. Similar to the NLR, the PLR also plays a role in the cytokine-dependent immune response and inflammatory changes. PE is related to placental hypoxia, increased oxidative stress, and decreased levels of antioxidants^[23]. However, in patients with HELLP syndrome, much more severe inflammatory and immune responses are stimulated, attacking the coagulation system and liver to a greater extent. A large quantity of inflammatory mediators and cytokines are released in the body of patients with HELLP syndrome, which is followed by the activation of the intrinsic and extrinsic coagulation pathways. The formation of extensive microvascular thrombosis and large consumption of coagulation factors lead to thrombocytopenia^[10]. The characteristic low platelet counts in HELLP patients might be responsible for the lower PLR compared to PE patients and healthy gravidae.

Many reports have demonstrated that the MPV is elevated in PE patients. Yücel *et al*^[14] found significantly higher MPV in the PE group than in normal gravidae, so they inferred that elevated MPV is associated with the presence of PE. By comparing the MPV between severe and mild PE patients, they also demonstrated that the MPV could be used as a marker to identify severe PE from mild PE^[14]. In Kashanian's study^[28], the MPV in the first and third trimesters of PE patients was significantly higher than that of normal pregnant women, but it had low value in the prediction of PE. Sisti's case-control studies on a small sample size did not find any significant difference regarding the MPV in first and third trimesters between patients with HELLP syndrome and healthy gravidae^[15,16]. Our study discovered that the MPV was highest in HELLP syndrome patients, lower in PE patients, and the lowest in healthy pregnant women, which is consistent with the results of some previous studies on the correlation between the MPV and PE. The MPV, which represents the size of circulating platelets, is considered as a marker of platelet activation, reflecting megakaryocyte proliferation, metabolism and thrombogenesis in the bone marrow. Related research showed that the quantity, size, and activity of platelets are heavily involved in the pathogenesis of a variety of inflammatory diseases and also varied with the severity of the inflammatory response. The MPV was found to be elevated in many chronic diseases and decreased in acute ones^[29]. We speculated since HELLP patients elicit a stronger inflammatory response, a large quantity of inflammatory mediators activates the coagulation pathways, leading to microvascular thrombosis and consumption of coagulation factors. Platelet activation is also enhanced and accompanied by a stimulated proliferation of megakaryocytes in the bone marrow, resulting in an elevated MPV in the peripheral circulation of patients with HELLP syndrome.

The PDW is a parameter that reflects the variation of platelet volume in blood, representing the heterogeneity in platelet morphology and being clinically related to platelet activation. Moreover, the PDW is thought to be a more significant marker of platelet activation than the MPV in some studies^[30,31]. Some reports suggest an

increased PDW in PE patients, and report that the PDW is related to both the presence and severity of PE^[22]. However, Gogoi *et al*^[26], did not find any statistically significant difference in the PDW between PE patients and controls. The PDW in HELLP patients has been rarely studied in the past. Our results indicate that HELLP patients have a higher PDW than both PE patients and healthy gravidae. On the other hand, we also found that the PDW was higher in PE gravidae than in normal ones, which was identical to the results in Karateke's study^[22]. We presume that this is due to the fact that the stronger inflammatory response in patients with HELLP syndrome activates the coagulation pathways, causing clotting factors and platelets to be consumed heavily. As a result, megakaryocytes in the bone marrow were stimulated to proliferate and more immature platelets were released into the circulation, contributing to the increased PDW in the blood.

The RDW is a hematologic index measuring the heterogeneity in size of circulating red blood cells, which was initially used in the classification of anemia. It is found to be associated with severe infection, sepsis, and cardiac emergencies. Although the pathophysiological mechanism is not clear, a high RDW is thought reflect an underlying inflammatory response. The RDW is also believed to be related to PE in several studies^[32]. Kurt's study indicated that the average RDW was significantly higher in PE patients than in healthy gravidae, and pairwise comparison also revealed that the RDW in patients with severe PE was significantly higher than that in both mild PE patients and controls, suggesting that the RDW level was related to PE and its severity^[33]. Yücel *et al*^[14] found that the RDW was significantly higher in severe PE patients than in the controls, but it could not be used to predict the severity of PE. There were also some opposite results. Abdullahi's study^[34], for instance, indicated that the RDW was not related to either the presence or severity of PE. Sisti's study^[15] did not illustrate any statistically significant difference in the RDW between patients with HELLP syndrome and normal pregnant women in their third trimester. Furthermore, their study on the RDW in the first trimester revealed that the RDW was higher in patients with HELLP syndrome than in controls, but the difference was not statistically significant, indicating that first trimester RDW values are not predictive of later HELLP syndrome onset^[16]. Our study revealed that the RDW in patients with HELLP syndrome was higher than that in both PE patients and normal pregnant women, which was inconsistent with the reports of previous studies. Besides, we did not find any significant difference in terms of the RDW between PE patients and healthy pregnant women, which was similar to Abdullahi's results. The most possible underlying mechanism of increased RDW in patients with HELLP syndrome might also be explained by the severe ongoing inflammation in these patients. Inflammation and oxidative stress might lead to deformation of red blood cells *via* disruption of iron metabolism and impaired response to erythropoietin, while the entry of immature red blood cells (erythroblasts) in the maternal circulation due to impaired erythrocyte maturation leads to an increase in the RDW^[9]. Compared with PE patients, HELLP patients experience a stronger inflammatory response, which possibly leads to the destruction of more red blood cells through interaction free radicals and proteolytic enzymes. Given the even stronger state of oxidative stress in patients with HELLP syndrome, the repair ability of red blood cells is very poor and more erythrocytes are destroyed, so immature ones enter the blood, leading to a rise in the RDW.

In summary, our study found that HELLP syndrome patients had increased NLR, MPV, PDW, RDW, leukocyte and neutrophil counts compared to patients diagnosed with only PE and normal pregnant women. At the same time, the PLR, platelet and lymphocyte counts in HELLP syndrome patients were all lower than those in both PE patients and healthy gravidae.

Our study's main limitation was that it was a single-center study, and the laboratory indices were only compared in the third trimester. Hence, the predictive values of these indices in HELLP syndrome were not investigated. Moreover, we did not exclude cases of HELLP syndrome with coexisting PE, which probably weakened some unique characteristics of HELLP syndrome. However, considering that the majority patients with HELLP syndrome had concurrent PE, this research model should have a more practical clinical value.

CONCLUSION

Our study discovered that inflammatory markers such as the NLR, MPV, PDW and RDW were increased in patients with HELLP syndrome, meanwhile the PLR was decreased in these patients. Being easily obtainable, these parameters may become

ideal predictive and prognostic indicators, and even useful additions to the current diagnostic standard of HELLP syndrome, if these findings are confirmed by further investigations. Further, multicenter prospective studies are warranted to better reveal the correlation between inflammatory indices from CBC and HELLP syndrome.

ARTICLE HIGHLIGHTS

Research background

Hemolysis, elevated liver enzymes, and low platelet (HELLP) syndrome is a severe complication in the third trimester of pregnancy. It often co-exists and shares some similar pathophysiological changes with preeclampsia (PE), however, the inflammatory reaction of HELLP is stronger. Since HELLP syndrome is life-threatening to both the gravida and the fetus, there is an urgent need for available predictive and prognostic indicators of HELLP.

Research motivation

Recently, new available systemic inflammatory response (SIR) markers from complete blood cell count (CBC), such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), mean platelet volume (MPV), platelet distribution width (PDW) and red cell distribution width (RDW), have been widely implemented in the diagnosis of patients with inflammatory diseases. These indicators have been widely investigated in PE but less analyzed in HELLP syndrome.

Research objectives

To analyze SIR markers in HELLP syndrome patients.

Research methods

A case-control study enrolled 630 cases (210 patients with HELLP syndrome, 210 patients with merely PE, and 210 healthy gravidae [control group]) was conducted. SIR markers such as NLR, RDW, MPV, PDW and PLR were compared among three groups.

Research results

The NLR, MPV, PDW, leukocyte and neutrophil count were highest in the HELLP group, lower in the PE group, and lowest in the control group. The HELLP group had a lower lymphocyte count than both the PE and control groups. The platelet counts and the PLR in the HELLP group were lower than those in the two other groups. RDW values in the HELLP group were higher than both the PE and control groups.

Research conclusions

SIR markers such as NLR, RDW, MPV and PDW were increased in patients with HELLP syndrome, meanwhile the PLR was decreased in these patients.

Research perspectives

Being easily available, these SIR markers from CBC may become predictive and prognostic indicators and even useful additions to the current diagnostic standard of HELLP syndrome if they are confirmed by further more studies.

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