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Risk factors and pregnancy outcomes associated with retinopathy in patients presenting with severe preeclampsia

A retrospective cohort study

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Abstract

The visual system was reported to be affected in over half of patients with preeclampsia (PE), though fundus examination was performed only among patients complaining of visual symptoms. Delayed diagnosis and treatment of PE-related retinopathy may lead to permanent visual impairment. Therefore, we hypothesize that some clinical or laboratory parameters could predict severity of retinal damage.

The aim of the study was to explore the risk factors for retinopathy in severe preeclampsia (sPE) and investigate pregnancy outcomes with different degrees of retinopathy.

This retrospective cohort study included women with sPE who underwent ophthalmoscopy and delivered after admission to West China Second University Hospital, between June 2013 and December 2016. Clinical and laboratory characteristics were retrieved from medical records. Patients confirmed with retinopathy were followed up with telephones. Multiple logistic regression analysis was performed to identify risk factors of PE-related retinopathy.

Five hundred thirty-four patients were included, of which 17.6% having stage-1/2 retinopathy, 14.6% having stage-3/4 retinopathy, and 67.8% having normal retina. Compared with patients without retinopathy, patients with stage 3/4 retinopathy were more likely to have preterm-birth and low-birth-weight babies. Significant risk factors for stage 3/4 retinopathy in sPE included severe hypertension (odds ratio [OR] 2.24, 95% confidence interval [CI]: 1.10–4.56), elevated white blood cell (WBC) counts (OR 1.88, 95% CI: 1.05–3.35), decreased platelet counts (OR 2.12, 95% CI: 1.07–4.48), lactate dehydrogenase (LDH) concentration of >800 IU/L (OR 2.31, 95% CI: 1.05–5.06), low hemoglobin (HGB) concentrations of <110 g/L (OR 3.73, 95% CI: 1.21–11.47), 24-hour proteinuria of 2 to 5 g (OR 6.39, 95% CI: 2.84–14.39), and >5 g (OR 8.66, 95% CI: 3.67–20.44).

This study confirms the association between retinopathy and preterm-birth and low-birth weight in sPE. The risk factors for severe PE-related retinopathy, including severe hypertension, platelet and WBC count, HGB and LDH concentration, and proteinuria, are associated with the development of retinopathy. Routine and repeated fundus examination is recommended for maternal monitoring in sPE.

Abbreviations: ALB = albumin, ALT = alanine aminotransferase, ANOVA = analysis of variance, AST = aspartate aminotransferase, BP = blood pressure, BUN = blood urea nitrogen, CI = confidence interval, DBP = diastolic blood pressure, FGR = fetal growth restriction, HCT = hematocrit, HELLP syndrome = elevated liver transaminases, thrombopenia, and hemolysis, HGB = hemoglobin, ICP = intrahepatic cholestasis of pregnancy, ISSHP = International Society of Study of Hypertension in Pregnancy, IVF-ET = in-vitro fertilization and embryo transfer, LDH = lactate dehydrogenase, OR = odds ratio, PE = preeclampsia, PTC = platelet count, RBC = red blood cell, SBP = systolic blood pressure, sCr = serum creatinine, SGA = small for gestational age, sPE = severe preeclampsia, TB = total bile acid, WBC = white blood cell count.

Keywords: blood pressure, complications, fundus changes, retinopathy, severe preeclampsia

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1. Introduction

Preeclampsia (PE) is a common obstetrical complication occurring in nearly 3% to 5% of pregnancies[1] and is characterized by systemic vascular changes that could lead to new-onset hypertension and damage to at least 1 other organ or system after 20 weeks of gestation. Severe preeclampsia (sPE) is a progressive stage of PE complicating approximately 0.6% to 1.2% of pregnancies,[2] with features such as significantly elevated blood pressure (BP), or deteriorating systemic conditions in forms of proteinuria, oliguria, liver dysfunction, pulmonary edema, thrombocytopenia, or cerebral or visual abnormalities.[3] The visual system was reported to be affected in approximately 60% of patients with PE, comprising the visual cortex, optic nerve, retina, choroid, and conjunctiva.[4] In addition, the retina has always been implicated, manifesting mainly as a constriction of retinal arterioles, but also as retinal edema, exudates, cotton wool spots, hemorrhages, and even retinal detachment (Fig. 1). Subjective visual symptoms including decreased vision, visual field defects, diplopia, or photopsia were reported by approximately 40% of preeclamptic patients,[5] of which blindness just for fundus lesions was rare. Fundus changes and optic symptoms are usually reversible and respond well to magnesium sulfate, controlled BP, and delivery. However, in some sPE patients with retinal artery occlusion, visual impairment could be permanent.[6] Thus, the immediate identification of progressive retinopathy has great significance in the prognosis of vision in patients with PE.

Mounting case reports revealed that diverse pathogenic processes complicated retinopathy in PE, such as HELLP syndrome, severely elevated BP, and renal dysfunction.[7–9] In the PE cohort, leading laboratory markers of systemic injury such as overt proteinuria, elevated levels of lactate dehydrogenase (LDH) and uric acid, along with elevated systolic blood pressures (SBP) and/or diastolic blood pressures (DBP), were reported to increase the risks for retinopathy.[10–13] These laboratory and clinical markers have been proposed to predict the involvement of various systems in PE. We therefore hypothesize that the presence and progression of retinopathy in sPE are influenced by some PE-related complications, such as poor renal and liver functions and thrombocytopenia, as well as hypertension itself. The markers foretelling exaggerated systemic involvement in sPE, could also be indications for progressively retinal damage. To test our hypothesis on the association between ordinary clinical parameters and retinopathy in sPE, we investigated a clinically relevant cohort of patients confirmed with sPE. Meanwhile, we compared pregnancy outcomes among patients with different levels of retinopathy in sPE.

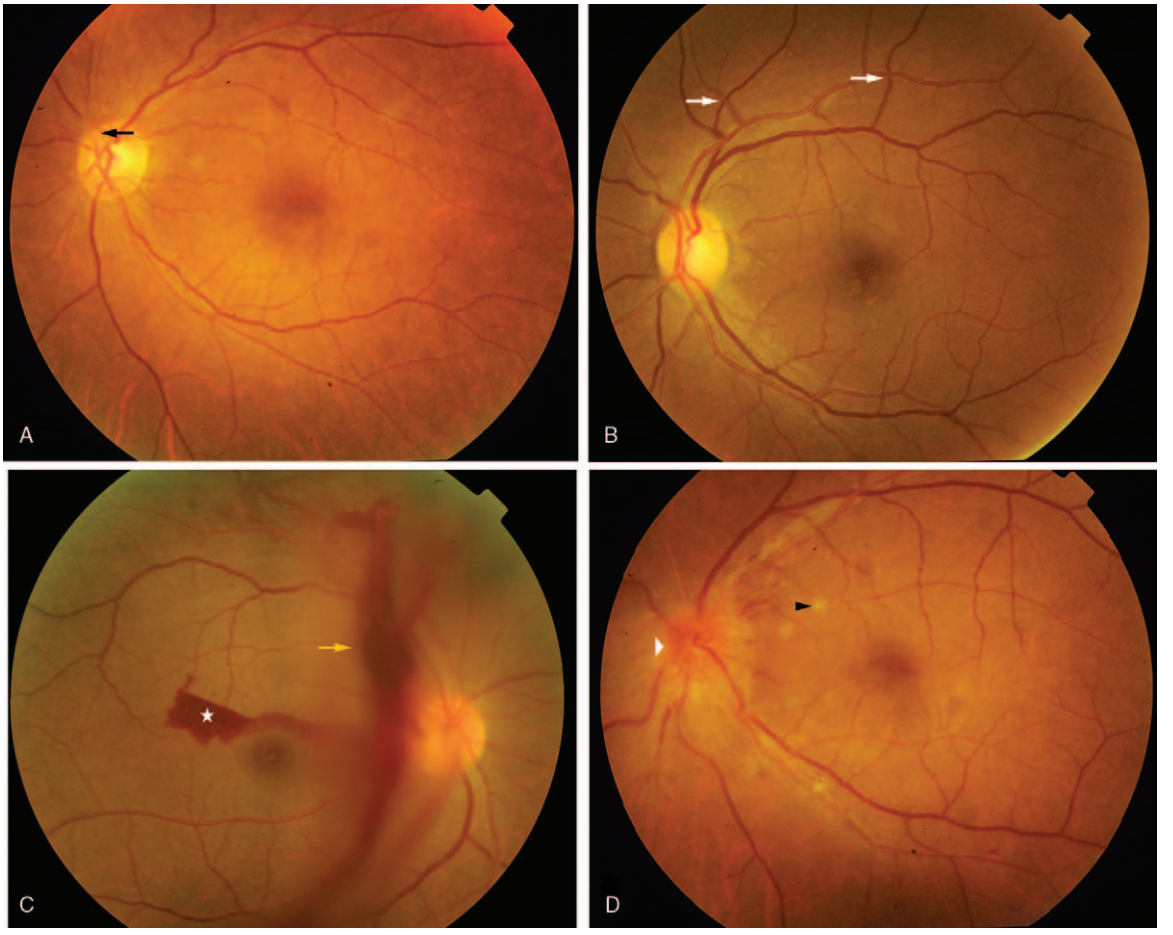

Figure 1. Fundus photograph revealing different fundus changes associated with preeclampsia. (A) Focal arteriolar narrowing (black arrows). (B) Arteriovenous nicking (white arrows) indicates progressing sclerosis of retinal arterioles. (C) Microaneurysms with active bleeding (yellow arrow), and boat-shaped hemorrhage (star). (D) Generalized arteriolar narrowing with optic disk swelling (white arrowhead) and cotton-wool spots (black arrowhead).

2. Methods

We retrospectively reviewed the medical records from a hospital-based cohort of pregnant women, who delivered at the West China Second University Hospital from June 2013 to December 2016. The ethics committee and the data inspectorate of West China Second University Hospital of Sichuan University approved this study. Medical records were independently reviewed by 2 observers. Patients with sPE who were admitted to the hospital were included in this study. Patients were excluded for the presence of retinopathy before pregnancy or unsuccessful assessment of the optic fundus.

The consensus statement from the International Society of Study of Hypertension in Pregnancy (ISSHP) was largely complied to establish the definition of PE in this study,[14,15] of which the criterion for abnormal creatinine level was adjusted to meet the attributes of Asian people, broadly as new-onset hypertension (SBP >140 mm Hg or DBP >90 mm Hg) after 20 weeks of gestation with at least 1 of the following features: proteinuria (creatinine ratio ≥30 mg/mmol or proteinuria ≥300 mg/day or persistent dipstick testing ≥2+), renal insufficiency (serum creatinine [sCr] >106 μmol/L without prior renal disease), at least twice-elevated alanine aminotransferase or aspartate aminotransferase (AST), neurological complications (severe headache, blurring vision, or convulsions), hematological complications (platelet count [PTC] $<150\times10^9$/L, hemolysis, clotting disorders), and fetal growth restriction (FGR). Given the wide discrepancy about the definition of sPE,[14] we arbitrarily defined sPE as a diagnosis of PE and coexistence with one or more of the following features: SBP ≥160 mm Hg or DBP ≥110 mm Hg, progressive renal insufficiency (proteinuria ≥2 g/day), new onset of headache or blurring vision, impaired liver function (marked serum transaminase elevation and/or severe right upper quadrant or epigastric abdominal pain), thrombocytopenia (PTC $<100\times10^9$/L), HELLP syndrome, pulmonary edema, and FGR.

A plotted form was used to document maternal characteristics, medical histories, retinopathy status, some maternal and perinatal outcomes, various laboratory parameters on the day of fundus examination, and SBP and DBP when diagnosed with PE, on the day of fundus examination and both before and after the delivery. The fundus changes were evaluated by experienced retinal specialists under ophthalmologic examination, and documented on medical records. Figure 1 shows some characteristic optic changes associated with PE. The Keith–Wagener–Barker grading[16] was used to classify fundus changes as follows: stage 1, minimal constriction of retinal arterioles; stage 2, stage 1 plus more severe narrowing of retinal arterioles with moderate to marked sclerosis of retinal arterioles, with or without arteriovenous nipping; stage 3, stage 2 plus retinal edema, hemorrhages, exudates; and stage 4, stage 3 plus optical disc edema.

Since it is difficult to distinguish the fundus manifestations of stage 1 and stage 2 under the ophthalmoscope, patients with these retinopathies were grouped into 1 group as stage 1/2. Meanwhile, in view of the low rates of severe retinopathy, we also grouped stage 3 and stage 4 as stage 3/4. Patients with normal retina were grouped into stage 0. Telephone follow-up interviews were used to determine the prognosis of patients with fundus lesions. All patients with fundus lesions were followed from the discharge of hospital until regain of normal sight or February 2018.

2.1. Statistics analysis

BP was analyzed using variance analysis of repeated measurements. Data were presented as the mean and standard deviation or as the number and incidence. Statistical comparisons were performed with the Chi-squared test for categorical variables, and one-way analysis of variance for continuous variables. We used multivariate logistic regression analysis to determine the odds of developing a specific degree of retinopathy associated with any clinical or laboratory parameter. In multivariable models, we adjusted for maternal age, in-vitro fertilization and embryo transfer, parity, multiple pregnancies, gestational diabetes, preexisting cardiovascular diseases, preexisting renal diseases, hematocrit, blood urea nitrogen, sCr, and total bile acid. These factors were considered potential confounders for their significant associations with PE in the univariate analysis. $P<.05$ for both sides was considered statistically significant. The statistical analyses were carried out using SPSS version 21.0 (SPSS, Inc, Chicago, IL).

3. Results

We identified 848 pregnant women diagnosed with PE, and collected data from the medical records of the 534 patients after eligibility. The process of selection is listed in Figure 2. A total of 172 patients were diagnosed with retinopathy after admission to the hospital, consisting of 94 patients (17.6%) with stage 1 or stage 2 fundus changes, 50 patients (9.4%) with stage 3 fundus changes, and 28 patients (5.2%) with stage 4 fundus changes. Eight patients had retinal detachment. Of all patients, 84 patients (15.7%) had self-reported eye symptoms, generally complaining of blurred vision and hypoplasia. Significantly more patients (43.6%) complaining of eye discomfort were found in stage 3/4 retinopathy than with stage 0 (7.2%) or stage 1/2 (25.5%) retinopathy ($P<.001$). Among the 8 patients reporting visual field defects, 7 patients were confirmed to have stage 3/4 retinopathy.

The maternal baseline characteristics and medical histories are described in Table 1. Since no patients reported a history of smoking, smoking status was not compared in our analyses. The maternal and perinatal outcomes among patients with various fundus changes are summarized in Table 2. Patients with stage 3/4 retinopathy delivered at a lower gestational age compared with patients with normal ocular fundus, and were more likely to had preterm delivery before 37 weeks of gestation or extremely preterm delivery before 34 weeks of gestation than patients with either stage 1/2 retinopathy or stage 0 retinopathy. Babies whose mother had stage 3/4 retinopathy had significantly lower birth weight than those whose mother had no retinopathy. No significant differences were observed among the 3 groups in terms of delivery mode and other maternal or perinatal outcomes.

3.1. Clinical and laboratory risk factors

The BP of patients with sPE was separately measured at 4 different time points, including at diagnoses, on the day of fundus examination, before delivery, and after delivery. In comparison with patients with stage 0 retinopathy, patients with either stage 1/2 or stage 3/4 retinopathy had significantly higher SBP and DBP at all time points (See Supplementary Table S1, http://links.lww.com/MD/D926 and Table S2 for a list of mutations, http://links.lww.com/MD/D927). The levels of both SBP and DBP showed no difference among patients with various levels of fundus lesions. SBP and DBP varied with the time points of measurement and fundus change (See Supplementary Fig. S1 for a list of mutations, http://links.lww.com/MD/D924). Among the 3 groups, BP

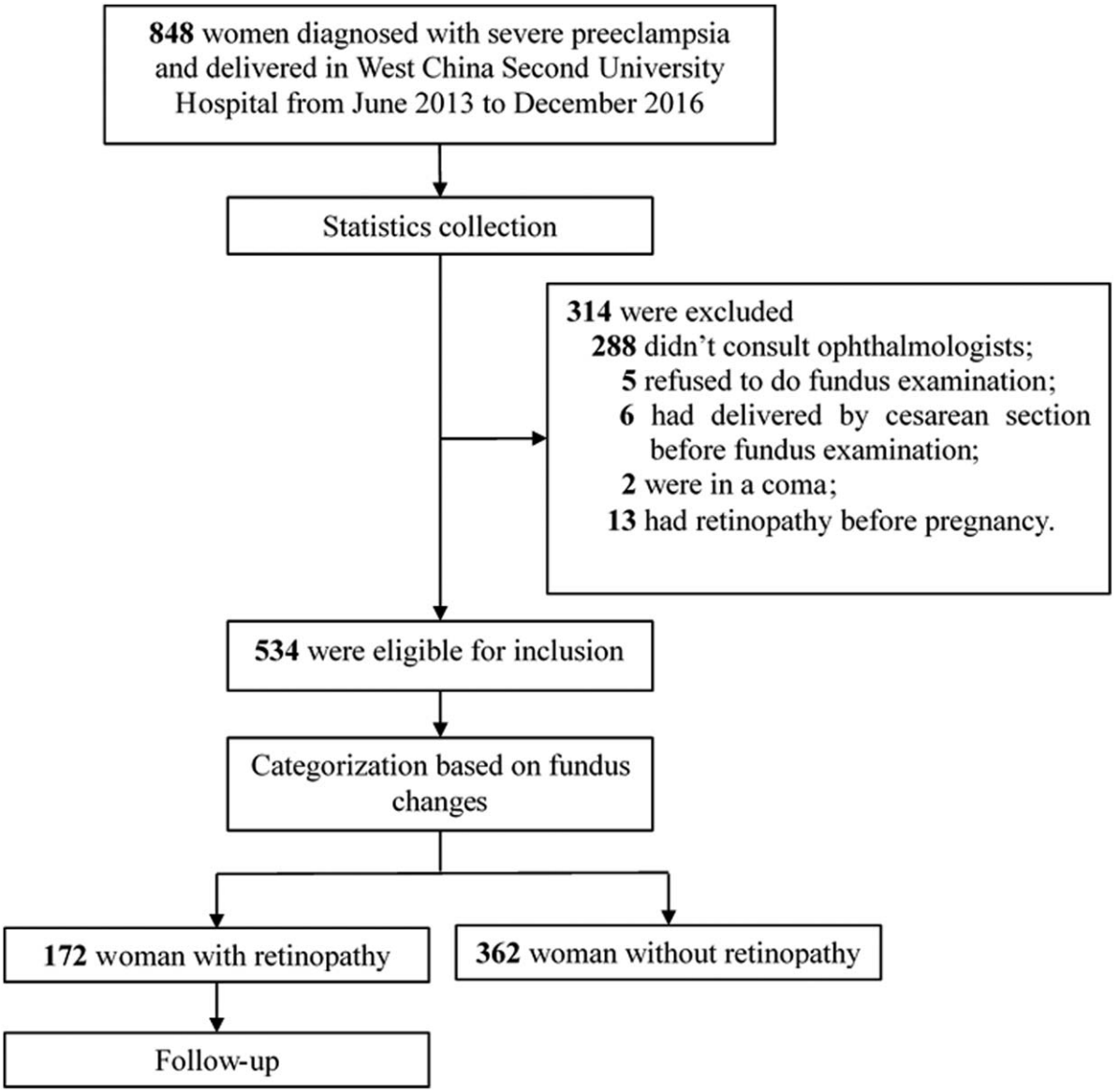

Figure 2. Flowchart of sample selection and statistics collection.

decreased after PE diagnosis as pregnancy progressed, and slightly increased after delivery.

The basic features of the clinical categorizations and laboratory parameters are summarized in Table 3. In univariate analyses, factors found to be associated with grading of retinopathy in sPE were type of PE ($P < .001$), severe hypertension ($P = .03$), elevated white blood cell (WBC) counts ($P = .02$), and abnormal hemoglobin (HGB) concentration ($P = .03$), lower PTCs ($P = .02$), higher LDH levels ($P = .03$), lower albumin ($P = .044$), higher 24-hour proteinuria ($P < .001$), and elevated AST ($P = .01$). Multivariate logistic regression analyses were performed to further analyze these potential risk factors (Table 4). After adjusting for potential confounders, none of the analyzed factors were significantly associated with the incidence of stage 1/2 retinopathy. Nonetheless, patients with severe hypertension, elevated WBC counts, decreased PTCs, abnormal HGB concentrations <110 g/L, LDH >800 IU/L, 24-hour proteinuria of 2 to 5 g and >5 g had increased risks for developing stage 3/4 retinopathy. Other factors, such as type of sPE, levels of aminotransferase, and albumin were not significantly associated with the incidence of stage 3/4 retinopathy.

3.2. Follow-up visits

One hundred seventy-two patients were confirmed with retinopathy and followed up with telephone interviews for detailed information on the maternal ophthalmic symptoms (See Supplementary Fig. S2 for a list of mutations, http://links.lww.com/MD/D925). All follow-ups were finished on February 2018. For patients with stage 1/2 retinopathy, optic symptoms fully disappeared within 3 months postpartum. Most patients with stage 3/4 retinopathy had optic symptoms relieved within 1 year postpartum, except 5 patients still reported occasional blurred vision after 1 year postpartum, but did not consult any ophthalmologist further. Of all followed patients, 23 patients still had elevated BP and were thus prescribed antihypertensive

Table 1

Maternal characteristics among patients with severe preeclampsia.

Characteristic	Categorizations by fundus changes			*P*
	Stage-0 group (n = 362)	Stage-1/2 group (n = 94)	Stage-3/4 group (n = 78)	
Age (yrs)[a]	30.93 ± 5.63	31.50 ± 5.55	31.26 ± 5.79	.66
Parity (%)				.22
Nulliparous	130 (35.9)	38 (40.4)	36 (46.2)	
Multiparous	232 (64.1)	56 (59.6)	42 (53.9)	
Gestational age[a,*] (wk)	33.09 ± 4.25	32.38 ± 4.18	31.76 ± 3.81[†]	.02
Multiple pregnancies (%)				.47
No	310 (85.6)	77 (81.9)	69 (88.5)	
Yes	52 (14.4)	17 (18.1)	9 (11.5)	
IVF-ET (%)				.76
No	316 (87.3)	84 (89.4)	70 (89.7)	
Yes	46 (12.7)	10 (10.6)	8 (10.3)	
HELLP syndrome (%)				.46
No	336 (92.8)	89 (94.7)	70 (89.7)	
Yes	26 (7.2)	5 (5.3)	8 (10.3)	
Gestational diabetes (%)				.38
No	269 (74.3)	74 (78.7)	63 (80.8)	
Yes	93 (25.7)	20 (21.3)	15 (19.2)	
Preexisting renal diseases (%)				.07
No	346 (95.6)	85 (90.4)	76 (97.4)	
Yes	16 (4.4)	9 (9.6)	2 (2.6)	
Chronic hypertension				.33
No	357 (98.6)	94 (100)	76 (98.7)	
Yes	5 (1.4)	0 (0)	2 (1.3)	
Cardiovascular diseases (%)[‡]				.52
No	335 (92.5)	84 (89.4)	73 (93.6)	
Yes	27 (7.46)	10 (10.64)	5 (6.41)	
Systemic lupus erythematosus (%)				.33
No	354 (97.8)	94 (100.0)	76 (97.4)	
Yes	8 (2.2)	0 (0)	2 (2.6)	
ICP (%)				.07
No	317 (87.6)	76 (80.9)	72 (92.3)	
Yes	45 (12.4)	18 (19.1)	6 (7.7)	
Thyroid dysfunction (%)				.53
No	318 (87.8)	83 (88.3)	77 (92.3)	
Yes	44 (12.2)	11 (11.7)	6 (7.7)	
Other diseases (%)				.48
No	205 (56.6)	49 (52.1)	39 (50.0)	
Yes	157 (43.4)	45 (47.9)	39 (50.0)	

Data are expressed as mean ± SD, or n (%).

Chi-squared test and [a]ANOVA (analysis of variance) comparing subjects with different stages of retinopathy.

HELLP syndrome = elevated liver transaminases, thrombopenia, and hemolysis, ICP = intrahepatic cholestasis of pregnancy, IVF-ET = in-vitro fertilization and embryo transfer, sPE = severe preeclampsia.

[*] Gestational age at the time of diagnosis.

[†] There is a significant difference comparing with stage-0, $P < .05$.

[‡] Chronic hypertension was not included in cardiovascular diseases.

medication, comprising 12 patients confirmed with stage 1/2 retinopathy and 11 patients with stage 3/4 retinopathy.

4. Discussion

4.1. Principal findings of the study

To emphasize the severe pathological fundus changes and poor optic prognosis in stage 3/4 retinopathy, we artificially defined stage 3/4 retinopathy as the "severe" retinopathy, and stage 1/2 retinopathy was the "mild" form. In this sPE cohort, we demonstrated that severe retinopathy was associated with a higher rate of preterm delivery and lower birth weight. In addition, the presence of severe retinopathy was associated with severe hypertension (SBP ≥160 mm Hg or DBP ≥110 mm Hg), elevated WBC counts, decreased PTCs, lowered HGB concentrations <110 g/L, LDH >800 IU/L, and 24-hour proteinuria of 2 to 5 g and >5 g.

Patients with sPE in this study exhibited a high prevalence of retinopathy. Our study confirms that some clinical characteristics were associated with stage 3/4 retinopathy, while not significantly associated with stage 1/2 retinopathy. However, patients with either stage 1/2 or stage 3/4 retinopathy had significantly higher SBP and DBP during pregnancy than patients without retinopathy. That is, reversible constriction of retinal arterioles which was caused by elevated BP, mainly accounts for the development of stage 1/2 retinopathy. Severe hypertension (BPs at or above 160/110 mm Hg) is universally endorsed as a detrimental condition for both mother and baby and requires urgent treatment.[4,16] In the Control of Hypertension in Pregnancy Study (CHIPS) study,

Table 2

Maternal and perinatal outcomes among patients with severe preeclampsia.

Outcome	Categorizations by fundus changes			*P*
	Stage-0 group (n = 362)	Stage-1/2 group (n = 94)	Stage-3/4 group (n = 78)	
Delivery gestational age (wk)				<.001
<28	28 (7.7)	8 (8.5)	6 (7.7)	
28–33	117 (32.3)	37 (39.4)	41 (52.6)	
34–36	112 (30.9)	35 (37.2)	21 (26.9)	
≥37	105 (29.0)	14 (14.9)	10 (12.8)*	
Placental abruption (%)				.053
Yes	17 (4.7)	1 (1.1)	7 (9.0)	
No	345 (95.3)	93 (98.9)	71 (91.0)	
Amniotic fluid volume disorder (%)				.56
Yes	26 (7.2)	6 (6.4)	3 (3.8)	
No	336 (92.8)	88 (93.6)	75 (96.2)	
Mode of delivery (%)				.82
Cesarean section	276 (76.2)	69 (73.4)	60 (76.9)	
Vaginal birth	86 (23.8)	25 (26.6)	18 (23.1)	
Postpartum hemorrhage (%)				.08
Yes	16 (4.4)	8 (8.5)	1 (1.3)	
No	346 (95.6)	86 (91.5)	77 (98.7)	
Stillbirth (%)	49 (13.5)	17 (18.1)	16 (20.5)	.22
Placenta inherence (%)				.33
Yes	47 (13.0)	12 (12.8)	15 (19.2)	
No	315 (87.0)	82 (87.2)	63 (80.8)	
Placenta accrete (%)				.21
Yes	10 (2.8)	4 (4.3)	0 (0.0)	
No	352 (97.2)	90 (95.7)	78 (100.0)	
Live birth	**Stage-0 group (n = 313)**	**Stage-1/2 group (n = 77)**	**Stage-0 group (n = 62)**	***P***
Preterm				
Yes	194 (62.0)	59 (76.6)*	50 (80.6)*	<.001
No	119 (38.0)	18 (23.4)	12 (19.4)	
Birth weight (g)[a]	2290.25 ± 775.19	2106.83 ± 717.20	1907.35 ± 639.76†	<.001
Birth length (cm)[a]	45.31 ± 4.58	44.06 ± 4.80	44.03 ± 4.79	.12
SGA				.14
Yes	49 (15.7)	7 (9.1)	13 (21.0)	
No	264 (84.3)	70 (90.9)	49 (79.0)	
Neonatal asphyxia				.28
Yes	12 (3.8)	5 (6.5)	5 (8.1)	
No	301 (96.2)	72 (93.5)	57 (91.9)	

Chi-squared test and [a]ANOVA (analysis of variance) comparing subjects with different stages of retinopathy.
Data are expressed as mean ± SD, or n (%).
SGA = small for gestational age.
* $P < .0167$, comparing with stage-0 by Chi-squared test.
† $P < .05$, comparing with stage-0 and stage-1/2 by ANOVA.

severe hypertension itself, other than complications of PE, was reported as a risk marker for stroke and significantly increased the risks for adverse pregnancy outcomes.[17] Thus, severe retinopathy as well as other perinatal morbidities may be all considered physiological disturbances partially resulting from progressive hypertension, known as the constriction of systemic arterioles. Notably, as pregnancy processes, both SBP and DBP levels fell after diagnoses of sPE in patients with different retinopathy. We ascribe this fall to the immediate antihypertensive therapy after diagnosis. Despite the instant management of BP in sPE, patients with either mild or severe retinopathy showed significantly higher BP compared with the normal group during pregnancy, warranting intensified BP control. In addition, BP slightly increased after delivery, which might have resulted from maternal pain after delivery.

In accord with prior studies,[16–18] this sPE cohort study found WBC counts, PTCs, HGB concentrations, LDH level, and 24-hour proteinuria were associated with severe retinopathy. The pathological features of stage 3/4 retinopathy manifested as severe narrowing and sclerosis of retinal arterioles complicating any following signs, like retinal edema, hemorrhages, exudates, and optical disc edema, which could be ascribed to endothelial damage, systemic inflammation, ischemia caused by hypoperfusion, or retinal edema caused by hyperfusion.[6] Both platelets and WBC are components of inflammatory processes in response to endothelial cell dysfunction, which has been considered a crucial player in PE.[19,20] Leukocyte activation participates in the development and progression of PE.[18,21,22] Activated platelets could promote leukocyte recruitment to the arterial wall and thus initiate and exacerbate intravascular inflammation, and then

Table 3

Basic features of subjects with various retinopathy.

Feature	Categorizations by fundus changes			P
	Stage-0 group (n = 362)	Stage-1/2 group (n = 94)	Stage-3/4 group (n = 78)	
Type of sPE (%)				
Early-onset	196 (54.10)	58 (61.70)	56 (71.80) *,†	<.001
Late-onset	166 (45.90)	36 (38.30)	22 (28.20)	
Severe hypertension‡ (%)				
No	111 (30.7)	23 (24.5)	13 (16.7)	.03
Yes	251 (69.3)	71 (75.5)	65 (83.3)*	
RBC (10^9/L)[a]	4.21 ± 1.81	4.17 ± 0.73	4.14 ± 0.66	.94
WBC (%)				
≤10.00 (10^9/L)	236 (65.2)	54 (57.4)	38 (48.7)	.02
>10.00 (10^9/L)	126 (34.8)	40 (42.6)	40 (51.3)*	
HCT (%)[a]	36.40 ± 5.35	36.75 ± 6.70	36.36 ± 5.45	.85
HGB (%)				
<110 g/L	19 (5.3)	12 (12.9)	8 (10.3)	.02
110–140 g/L	281 (77.8)	62 (66.7)	51 (65.4)	
>140 g/L	61 (16.9)	19 (20.4)	19 (24.4)*	
PTC (10^9/L)[a]	158.25 ± 65.78	156.35 ± 63.18	135.29 ± 58.00§	.02
ALT (%)				
Normal	271 (74.9)	61 (64.9)	59 (75.6)	.13
Elevated	91 (25.1)	33 (35.1)	19 (24.4)	
AST (%)				
Normal	190 (52.5)	36 (38.3)	31 (39.7)	.01
Elevated	172 (47.5)	58 (61.7)*	47 (60.3)	
TB (μmol/L)[a]	8.91 ± 8.19	9.34 ± 7.45	8.04 ± 4.78	.53
ALB (%)				
<30 g/L	158 (43.6)	52 (55.3)	43 (55.1)	.043
≥30 g/L	204 (56.4)	42 (44.7)	35 (44.9)	
LDH (IU/L)[a]	671.68 ± 609.46	728.15 ± 429.19	859.91 ± 521.79§	.03
BUN (mol/L)[a]	5.16 ± 2.56	5.81 ± 3.66	5.61 ± 2.53	.09
sCr (μmol/L)[a]	72.09 ± 39.51	82.71 ± 80.27	79.85 ± 30.16	.11
Proteinuria in 24 h (g)[a]	3.07 ± 2.83	3.68 ± 2.88	5.42 ± 3.69§	<.001

Chi-squared test and [a]ANOVA (analysis of variance) comparing subjects with different stages of retinopathy.

Data are expressed as mean ± SD, or n (%).

ALT = alanine aminotransferase, ALB = albumin, AST = glutamic oxaloacetic transaminase, BUN = blood urea nitrogen, DBP = diastolic blood pressure, HCT = hematocrit, HGB = hemoglobin, LDH = lactate dehydrogenase, PTC = platelet count, RBC = red blood cell, SBP = systolic blood pressure, sCr = serum creatinine, sPE = severe preeclampsia, TB = total bile acid, WBC = white blood cell.

* $P < .0167$, comparing with stage-0 by Chi-squared test.

† $P < .0167$, comparing with stage-1/2 by Chi-squared test.

‡ Severe hypertension is defined as SBP ≥160 mm Hg and/or DBP ≥110 mm Hg measured at diagnoses.

§ $P < .05$, comparing with stage-0 and stage-1/2 by ANOVA.

retinal vasculature suffers.[22] In this study, significantly higher WBC counts and lower PTCs were observed in patients with severe retinopathy than those without retinopathy and mild retinopathy.

We also found that LDH level of more than 800 IU/L were associated with an increased risk for having stage-3/4 retinopathy among patients with sPE, which was consistent with previous studies.[12,23] LDH is a product of glycolysis process, which serves as the major energy pathway in the placenta.[24] A higher level of LDH activity was found in placentas of PE than normal pregnancy, which was induced by hypoxia in trophoblasts and could reflect the severity of the cellular damage and dysfunction.[24,25] Proteinuria is known as one of the most effective indicators of renal function. Accruing evidence suggests that retinal microvascular abnormalities are associated with deteriorating renal function,[26,27] and that significant association between retinopathy and deteriorating renal function was independent of the effects of any associated hypertension or diabetes.[26] The plausible explanation for the retinopathy–kidney link might be common physiological mechanisms underlying diabetes, hypertension, and other processes, which are responsible for the development and progression of both retinopathy and deterioration of renal function. Our study is the first one reporting the association between HGB and PE-related retinopathy. Prior studies reported maternal anemia was a risk factor for preterm birth and low birth weight (LBW).[28,29] Considering the oxygen-carrier function of HGB, lowered HGB concentrations could result in organic hypoxia, such as placenta and retina, and thereby increase the risk for severe retinopathy in PE.[30]

Some evidence showed that retinal vascular changes were largely correlated with the severity of hypertension, and patients with severe retinopathy due to sPE were more likely to have poor perinatal outcomes,[15,17] which is consistent with our results. Since retinal hypoperfusion and placental hypoxia are both accepted as pathophysiological processes underlying the pathogenesis of PE, the severity of maternal fundus changes may indirectly indicate the status of the placental vasculature, and hence, placental insufficiency and FGR. In contrast to the routine fundus examination for women with PE, the indication for fundus examination is the presence of persistent visual disturbance according to the current guidelines for PE.[31,32] If we would agree on PE-associated retinopathy as a risk indicator of

Table 4

Potential risk factors for various stages of retinopathy among patients with severe preeclampsia.

Variable	Stage-1/2 retinopathy			Stage-3/4 retinopathy		
	Adjusted OR*	95% CI	*P*	Adjusted OR*	95% CI	*P*
Type of sPE						
Early-onset	1.10	(0.66, 1.83)	.71	1.45	(0.77, 2.71)	.25
Late-onset		Reference			Reference	
Severe hypertension†	1.45	(0.84, 2.52)	.18	2.24	(1.10, 4.56)	.03
Elevated WBC‡	1.14	(0.68, 1.89)	.63	1.88	(1.05, 3.35)	.03
HGB (g/L)						
<110	1.18	(0.51, 2.75)	.70	3.73	(1.21, 11.47)	.02
≥110		Reference			Reference	
Decreased PTC†	1.04	(0.55, 1.97)	.90	2.12	(1.07, 4.17)	.03
Elevated transaminase‡	1.59	(0.92, 2.74)	.10	0.99	(0.52, 1.89)	.99
Decreased ALB‡	1.35	(0.79, 2.31)	.28	0.76	(0.41, 1.39)	.37
LDH (IU/L)						
<600		Reference			Reference	
600–800	0.92	(0.49,1.71)	.79	1.44	(0.71, 2.95)	.32
>800	1.21	(0.62,2.38)	.58	2.31	(1.05, 5.06)	.04
24-h urinary protein						
<2 g		Reference			Reference	
2–5 g	1.36	(0.75, 2.46)	.31	5.70	(2.84,14.39)	<.001
>5 g	1.49	(0.77, 2.90)	.24	8.66	(3.67, 20.44)	<.001

ALB = albumin, CI = confidence interval, DBP = diastolic blood pressure, HGB = hemoglobin, LDH = lactate dehydrogenase, OR = odds ratio, PTC = platelet count, SBP = systolic blood pressure, sPE = severe preeclampsia, WBC = white blood cell.

* Adjusted for the following risk factors: maternal age, in-vitro fertilization and embryo transfer, parity, multiple pregnancies, gestational diabetes, preexisting cardiovascular diseases, preexisting renal diseases, abnormal hematocrit, blood urea nitrogen, serum creatinine, and total bile acid.

† Severe hypertension is defined as SBP ≥160 mm Hg and/or DBP ≥110 mm Hg measured at diagnoses.

‡ Normal group as reference.

maternal vasculature, then screening indication or follow-up for retinopathy would rise in a great number of patients, namely, 1 in every 6 (15.7%) patients with sPE complaining of visual symptoms and 1 in every 3 (32.2%) patients with sPE with retinopathy. Therefore, those patients with sPE should be screened and followed up for retinopathy, as these might warrant convulsion prophylaxis and intensified BP control.

It is widely acknowledged that PE-related retinopathy is a marker for PE, while less clear is the role of PE-related retinopathy in maternal monitoring in PE. ISSHP recommends BP monitoring, repeated assessments for serum HGB, PTC, liver transaminases, creatinine and uric acid, and proteinuria.[31] The predominant finding in this study is the association between the presence of severe retinopathy and some clinical characteristics, such as severe hypertension, proteinuria, serum PTC, and HGB, which gives a hint that these clinical characteristics might be related to the progression or regression of PE-related retinopathy. Due to the retrospective design of this study, most patients only had their fundus examined for once, while continuously monitoring on the fundus changes during the treatment of PE could demonstrate whether the regression or disappearance of PE-related retinopathy is associated with successful BP control and convulsion prophylaxis. In addition, the ophthalmoscopy could repeatedly evaluate the maternal circulation in PE, which may serve as a close surveillance for patients with sPE. Therefore repeated fundus examination could be repeated together with BP monitoring and laboratory tests after diagnosis of PE.

4.2. Strengths and limitations

The strengths of this study lie in investigating a rare complication in somewhat large population over 3 years, given small sample sizes from 40 to 300 in previous relevant studies. Although our study does not contribute to exploring the underlying role of multiple parameters in the development of retinopathy due to PE, our results demonstrate some important dominators for the risk calculation of severe retinopathy in sPE, which facilitates us to identify high-risk patients for severe retinopathy in sPE and take prompt measures. Retinal vessels are the only visible arterioles and venules of the human body. Retinal microvasculature is reputed to indicate systemic microcirculation status in humans.[26,27] Ophthalmoscope examination is a noninvasive operation, which could qualitatively depict ocular fundus changes in a short time. Consequently, based on the results of this study, ophthalmoscope could serve as an instrument for diagnosis and monitoring importance in preeclamptic patients. Our study had limitations. First, this study was conducted in a single tertiary hospital, which is one of the technique instruction centers for dubious and acute diseases in China; however, fundus examination is often not available at primary or even secondary level facilities. Second, patients with retinopathy were followed up for their symptoms, while no fundus examination was performed to evaluate fundus status after delivery. Furthermore, the status of the ocular fundus was assessed only by ophthalmologists using an ophthalmoscopy, which was largely affected by ophthalmologists' experiences. Finally, the potential confounders and the retrospective design itself may all result in the uncertainty of the results.

4.3. Research implications

Given the limitations discussed above, prospective randomized multicenter-based studies are needed to develop and validate a prediction model for PE-related retinopathy.

5. Conclusions

Fundus change could reflect the severity of PE and subsequent occurrence of adverse pregnancy outcomes. More than severe hypertension, elevated WBC counts, and LDH, decreased PTCs, abnormally lower HGB concentrations, and increased 24-hour proteinuria were associated with increased risks for severe retinopathy in sPE. To improve both maternal and perinatal outcomes, we recommend routine fundus examination for patients with sPE, and repeated fundus monitoring together with BP monitoring and laboratory tests after diagnosis of PE-related retinopathy.

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