

Prediction of posterior reversible encephalopathy syndrome (PRES) due to obstetric causes

Nizamettin Bozbay¹ , Özlem Polat Bozbay¹ , Elif Ağaçayak¹ , Süleyman Cemil Oğlak² ,
Fazıl Avcı³ , Abdullah Acar⁴ 

¹Dicle University, Faculty of Medicine, Department of Obstetrics and Gynecology, Diyarbakır, Türkiye

²Health Sciences University, Gazi Yaşargil Training and Research Hospital, Department of Obstetrics and Gynecology, Diyarbakır, Türkiye

³Selçuk University, Faculty of Medicine, Department of Gynecologic Oncology, Konya, Türkiye

⁴Dicle University, Faculty of Medicine, Department of Neurology, Diyarbakır, Türkiye

Abstract

Objective: This study aimed to identify the demographic, laboratory, and clinical parameters that would help us identify patients at risk of posterior reversible encephalopathy syndrome (PRES) due to obstetric causes. Also, we analyzed the variables that might predict the development of obstetric-related PRES.

Methods: This retrospective study examined a total of 274 hypertensive pregnant women diagnosed with preeclampsia (PE) and eclampsia from January 2010 to December 2017 at Dicle University Faculty of Medicine. Of these, 85 cases who underwent cranial imaging by magnetic resonance imaging (MRI) or computed tomography (CT) were included in the study.

Results: According to the cranial imaging results, 48 patients (56.47%) were reported as PRES (Group 1) and 37 patients (43.53%) were normal (Group 2). The incidence of patients diagnosed with PRES was found to be 17.51% when all PE and eclampsia patients were included. International Normalized Ratio (INR), and prothrombin time (PTT) values were significantly higher, and maternal age, gravida, parity, platelet (PLT), and albumin values were significantly lower in the PRES group compared to the cases in group 2 ($p<0.05$). As a predictor of PRES, INR values higher than 0.94 (sensitivity=75.0%, specificity=67.6%) and PTT values higher than 11.7 (sensitivity=75.0%, specificity=54.1%) were found to be significant factors.

Conclusion: We consider that high INR, PTT, low PLT, low albumin, young age, early gestational week, low gravida, and parity parameters can help clinicians to predict and diagnose earlier PRES cases due to obstetric causes.

Keywords: Eclampsia, hypertension, preeclampsia, PRES

Introduction

Posterior reversible encephalopathy syndrome (PRES) is a clinico-radiological syndrome characterized by a headache, seizures, altered mental status, and visual loss and characterized by white matter vasogenic edema affecting the posterior occipital and parietal lobes of the brain predominantly using imaging modalities such as magnetic resonance imaging (MRI) or computerized tomography (CT). The condition was first defined by Hinchey et al. in 1996,^[1] yet its exact incidence still remains unknown. The presumed pathophysiology of PRES is believed to appear with the development of brain edema as a result of inadequate cerebral autoregulation in response to increased systemic blood pressure. Four theories have so far been coined to explain cerebral vascular insufficiency,^[2]

which are: “Vasogenic”,^[1] “Cytotoxic”,^[3] “Immunogenic”,^[4] and “Neuropeptide” theory.^[5]

The etiology of PRES includes hypertension encephalopathy, sepsis, immunosuppressive therapy, renal and autoimmune diseases, HIV syndrome, acute intermittent porphyria, organ transplantation, preeclampsia (PE), eclampsia, and HELLP syndrome.^[6] This condition is also characterized by symptoms such as seizure, headache, vomiting, neurosis, hemianopsia, coma, aphasia, confusion, dysarthria, ataxia, dizziness, hemiparesis, and other various focal neurological symptoms and signs.^[7,8] In clinical practice, the most common symptom is a seizure. A study reported a seizure prevalence of 90% for the cases followed by a diagnosis of PRES.^[9] While diagnosing PRES, one does not need the particular symptoms

Correspondence: Süleyman Cemil Oğlak, Health Sciences University, Gazi Yaşargil Training and Research Hospital, Department of Obstetrics and Gynecology, Diyarbakır, Türkiye, **e-mail:** sampson_21@hotmail.com, **Received:** April 17, 2023, **Accepted:** August 07, 2023

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ORCID ID: N Bozbay 0000-0001-9632-5093; ÖP Bozbay 0000-0003-1975-6687; E Ağaçayak 0000-0002-4215-1371; SC Oğlak 0000-0001-7634-3008; F Avcı 0000-0002-9244-9168; A Acar 0000-0001-5792-4712

mentioned here. The symptoms often improve within 3-8 days.^[10] However, delay in diagnosis and appropriate treatment can end up with irreversible neurological deficits and mortality due to the development of conditions such as brain hemorrhage, and ischemia.^[11]

The condition is categorized into two groups: severe and non-severe PE. In a patient with a possible developing PE, a systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 110 mmHg; the presence of cerebral or visual complaints, more than 2-fold increase in liver function tests, platelet count less than 100000 platelets/microL, and creatinine level above 1.1 mg/dL indicate severe PE.^[12]

PE is considered an important cause of PRES in which non-reversible complications can also occur.^[13,14] Therefore, early diagnosis and treatment are important.^[15] Changes in the brain can cause seizures when in the motor cortex and can lead to PRES when in the occipital cortex.^[16] Should an antepartum or postpartum case have complaints of seizures, visual disturbance, and headache, one should always question the probability of PRES.^[17] Brain MRI is the most appropriate diagnostic tool.^[18] CT, electroencephalography, and other diagnostic tests can be used to exclude other disorders.^[19] The prognosis remains good if PRES is diagnosed and treated early and 75-90% of patients recover without any sequelae.^[20]

In this study, we aimed to identify the demographic, laboratory, and clinical parameters that would help us identify patients at risk of developing PRES patients developing the condition due to obstetric causes. Also, we analyzed the variables that might predict the development of obstetric-related PRES.

Methods

This retrospective study was carried out at the Obstetric Department of Dicle University Faculty of Medicine between January 2010 and December 2017. Patient information was obtained through file archives and an electronic file environment. The study was planned in accordance with the principles of the Helsinki Declaration and the ethical committee approval was obtained from the Local Ethics Committee of Dicle University (Ethics Committee number: 2018/119) before starting the study.

The cases presenting with the complaints for the first time in the current pregnancy, without a known previous disease and cranial pathology were included in the study. PE is defined as new-onset hypertension (systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, taken at least over 2 measurements at 4-hour intervals) and/or presence of organ dysfunction (thrombocytopenia, renal dysfunction, liver dysfunction, pulmo-

nary edema and cyanosis, headaches, visual disturbances) in a previously normotensive woman, usually after the 20th week of gestation.^[21] In this study, the pregnant patients with hypertension and new-onset symptoms such as cerebral, visual, epigastric, and right upper quadrant pain were considered as presenting severe PE traits. Imaging procedures were performed on patients with new-onset symptoms during their current pregnancy, the patients who had new onset severe headaches, treatment-resistant hypertension, eclamptic seizures, and symptoms of vision loss. Imaging methods were not used for patients whose symptoms improved with treatment undergoing screening in this study. All the patients included were examined using one of the imaging methods such as CT (Toshiba Japan), 1.5 Tesla MRI (Philips Netherlands), and 3 Tesla MRI (Philips Netherlands). However, MRI imaging takes longer than CT imaging in emergencies and is more difficult to access. CT imaging should also be considered as an option for PRES patients as they may be unstable and CT imaging may be more easily accessible. When evaluated by experienced specialists, PRES diagnosis can also be made through CT.

The most important factors while terminating these pregnancies were MRI-confirmed PRES diagnosis, the presence of treatment-resistant hypertension, eclamptic seizure, persistent severe headache, and symptoms of visual loss. Sixteen patients diagnosed as PRES with antenatal MRI were delivered by cesarean section. CT imaging method was not applied due to antenatal fetal radiation for these patients, therefore all CT imaging modalities were applied postnatally. Patients without cranial imaging, the ones whose information was not accessible, those with a previously known disease, and those with screening reports presenting another condition other than PRES were also excluded from the study.

Maternal age, presence of convulsions, obstetric anamnesis (gravidity, parity, weeks of gestation, and delivery mode), laboratory parameters (Htc, Hb, PLT, AST, ALT, LDH, urea, Cr, Glucose, INR, PTT, proteinuria), hospitalization time and intensive care unit stay of the cases were examined. While evaluating the laboratory parameters of the patients, the values prior to the application of the imaging method were taken into account. All information about the study was obtained from file archives and electronic file media.

In cases of severe PE, prophylaxis with magnesium sulfate is recommended to prevent eclampsia. In our study, all cases received magnesium sulfate treatment for seizure prophylaxis. 4 grams of magnesium sulfate was given IV over 5-10 minutes for loading and then switched to 1

gram IV per hour for maintenance treatment. Treatment was completed by giving it for 24 hours after birth.^[22]

In patients with systolic blood pressure above 160 mm Hg and diastolic blood pressure above 110 mm Hg, emergency antihypertensive treatment was started immediately to prevent maternal organ damage, the aim of which is to gradually control blood pressure. On the other hand, the resistant hypertension cases were provided intravenous antihypertensive perlinganite (Melusin). In cases of mild hypertension, oral antihypertensive drugs such as methyldopa (Ibrahim Etem Ulugay), Norvasc (Pfizer), and Adalat Crono (Bayer) were used. Also, antiepileptic levetiracetam (Keppra) loading and maintenance treatment was started in cases of eclampsia seizures. In the study, Group 1 patients were started on anti-edema mannitol (Ibrahim Etem Ulugay) treatment. Routine antiepileptic treatment was not started in PRES cases. This treatment was only started for cases of eclampsia seizures.

Statistical Analysis

All statistical calculations were done using SPSS version 21 (IBM SPSS Statistics, IBM Corporation, Armonk, NY, USA). Measurement variables with normal distribution were presented as mean \pm standard deviation (SD) and non-homogeneous variables were presented as median. Categorical variables were presented as numbers and percentages (%). The Kolmogorov-Smirnov test was used to determine whether the data had a normal distribution. Student's t-test was used for parametric data, and the Mann-Whitney U test was used for non-parametric data. Comparisons of categorical parameters were analyzed with the help of Pearson Chi-Square and Fisher's Exact Test. Logistic regression analysis was performed on the data to calculate 95% CI and odd ratios. ROC analysis was done to determine the cut-off, sensitivity, and specificity of the data. A p-value <0.05 was considered statistically significant.

Results

In our retrospective study, we examined a total of 274 hypertensive pregnant women diagnosed with PE and eclampsia during the study period. Of these, 85 cases who underwent cranial imaging by magnetic resonance imaging (MRI) or computed tomography (CT) were included in the study, while those who had vascular edema in the parietal and occipital regions on CT and MRI imaging were considered as PRES (Figure 1).

According to the cranial imaging results, 48 patients (56.47%) were reported as PRES (Group 1) and 37 patients (43.53%) were non-PRES (normal cranial imaging, Group 2). The incidence of patients diagnosed with PRES was found to be 17.51% when all PE and eclampsia

patients were included.

In this study, 5 pregnant women with the presence of convulsion had cranial imaging results consistent with sinus venous thrombosis (SVT). It was determined that 2 cases had intracranial hemorrhage (ICH), reported as accompanying PRES in cranial imaging, who were excluded from the study as the cause of the ICH could not be explained. Whether ICH developed based on PRES or secondary to hypertension based on a vascular pathology in these 2 cases could not be explained. The treatment of these 2 patients was performed by neurosurgeons through medical approaches, not requiring any surgery. Also, 2 cases had imaging results reported as ICH who were found to have developed disseminated intravascular coagulation (DIC) during their clinical follow-up and passed away, and 9 cases in total were excluded from the study (Figure 2).

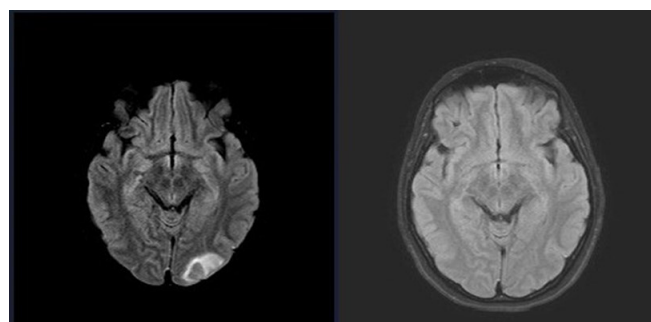


Fig 1. Antenatal MRI and postnatal 40th day control MRI image of a 35w pregnant patient (Left MRI: area of hyperintense vasogenic edema in cortical and subcortical T2W-FLAIR image in the left occipital lobe; Right MRI: T2W-FLAIR hyperintense edema area disappeared in the control MRI of the same patient.)

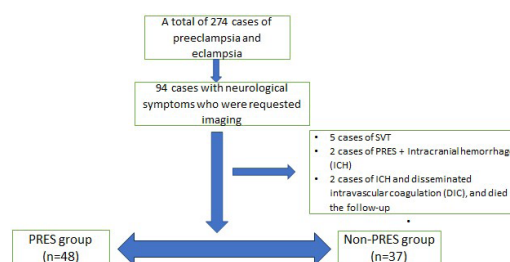


Fig 2. Flow chart of the study groups

While 21 patients underwent antenatal MRI, 6 patients underwent only postnatal MRI, and 52 patients underwent postnatal CT for cranial imaging in the study. Of the 6 patients who underwent postnatal MRI only, 4 were

diagnosed with PRES and 2 were excluded from PRES diagnosis. On the other hand, of the 52 patients who underwent postnatal CT, 23 were diagnosed with PRES on CT, and 5 patients underwent MRI imaging because vascular pathologies could not be clearly distinguished after postnatal CT. PRES diagnosis was also made for these 5 patients. However, the diagnosis was ruled out in 24 patients. Out of 21 patients undergoing antenatal MRI screening, the results of 16 patients were interpreted as PRES, of whom 5 had results consistent with normal cranial structures. After the diagnosis of severe PE in these 21 patients, their pregnancies were terminated. In our study, 16 patients were diagnosed with antenatal and 32 patients with postnatal PRES (Figure 3)

When the cases were compared in terms of age, the mean age for Group 1 and Group 2 was respectively found to be 27.4 ± 5.7 and 32.3 ± 8.0 years, which was statistically significant ($p=0.001$, Table 1). There was a statistically significant difference between the groups in terms of gravida ($p=0.002$), parity ($p=0.007$), and gestational week ($p=0.01$), whereas no significant difference was found

between the groups in terms of the need for intensive care ($p=0.23$), length of hospital stay ($p=0.07$), presence of eclampsia seizures ($p=0.1$), and mode of delivery ($p=0.14$).

When Group 1 cases were compared with Group 2, the difference between PLT, Albumin, INR, and PTZ values was statistically significant ($p=0.027$, $p=0.007$, $p=0.001$, and $p=0.001$, respectively, Table 2).

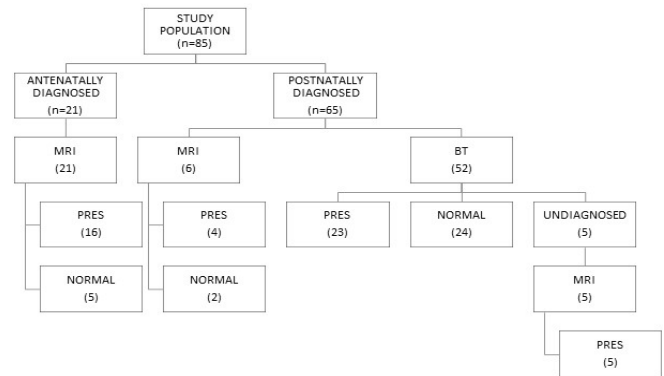


Fig 3. Flow chart of the imaging

Table 1. Comparison of clinical data of groups

	PRES group n=48	%	Non-PRES group n=37	%	p-value
Age, year	27.4 ± 5.7		32.27 ± 8.0		0.001
Gravida	1.73 ± 1.3		3.14 ± 2.7		0.002
Parity	0.56 ± 1.2		1.86 ± 2.6		0.007
Gestational week	32.3 ± 4.2		34.6 ± 4.0		0.010
Delivery type					0.140
Cesarean	39	81.3	25	67.6	
Vaginal	9	18.8	12	32.4	
Length of hospitalization	8.4 ± 5.7 (2-25)		6.5 ± 4.0 (2-20)		0.07
ICU					0.23
Yes	32	66.7	20	54.1	
No	16	33.3	17	45.9	
Total	48	100	37	100	
Convulsion					0.10
Yes	42	87.5	36	2.7	
No	6	12.5	1	97.3	
Total	48	100	37	100	

Table 2. Comparison of laboratory parameters

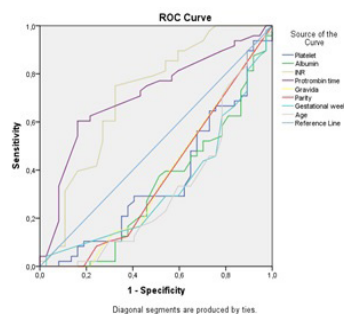
	PRES group n=48	Non-PRES group n=37	p-value
Hematocrit (%)	34.86 ± 5.454 (21.45-45.44)	36.16 ± 5.536 (20.40-45.36)	0.223
Hemoglobin (g/dL)	11.44 ± 1.916 (7.45-15.59)	11.989 ± 2.132 (6.71-16.30)	0.223
Platelet (K/uL)	144335 ± 97715 (242x10 ³ -385x10 ³)	202721 ± 124637 (286x10 ³ -466x10 ³)	0.027
Albumin	1.85 ± 0.27 (1.24-2.49)	2.12 ± 0.49 (1.37-4.00)	0.007
AST	269.25 ± 429.08 (14-1892)	181.73 ± 473.42 (15-2432)	0.134
ALT	178.82 ± 332.62 (6-1788)	95.24 ± 186.26 (6-871)	0.056
LDH	178.82 ± 332.62 (6-1788)	732.30 ± 526.00 (210-1995)	0.283
Urea	34.48 ± 28.36 (2-178)	28.12 ± 17.74 (12-120)	0.417
Creatinine	1.11 ± 1.17 (0.39-6.93)	0.82 ± 0.70 (0.48-4.86)	0.121
Glucose	134.13 ± 66.76 (63-424)	166.59 ± 120.349 (58-689)	0.680
INR	1.01 ± 0.14 (0.84-1.76)	0.92 ± 0.15 (0.67-1.40)	0.001
PTZ	12.95 ± 2.50 (10.00-25.00)	11.66 ± 2.50 (9.00-15.00)	0.001
Proteinuria	2.50 ± 1.22 (0-4)	2.73 ± 1.36 (0-4)	0.234

In the ROC analysis performed with the parameters in our study, only the INR and PTT levels remained above the AUC curve and were found to be statistically significant

in predicting PRES (AUC=0.712 and AUC=0.711, respectively, Table 3, Figure 4).

Table 3. ROC analysis results in data found to be significant between groups.

Variables	AUC	p-value	95 % CI		Cut off	Sensitivity (%)	Spesifity (%)
			Lower bound	Upper bound			
Platelet	0.360	0.027	0.239	0.480	84.500	64.6	27
Albumin	0.330	0.007	0.213	0.447	1.75	58.3	21.6
INR	0.712	0.001	0.597	0.827	0.94	75.0	67.6
Prothrombin Time	0.711	0.001	0.599	0.823	11.7	75.0	54.1
Gravida	0.370	0.041	0.247	0.493	1.5	33.3	48.6
Parity	0.370	0.040	0.247	0.492	0.5	25.0	54.1
Gestational week	0.331	0.008	0.214	0.448	31.5	62.5	21.6
Maternal age	0.318	0.004	0.199	0.437	24.5	70.8	21.6

**Fig 4.** ROC analysis of the variables in predicting PRES

In the logistic regression analysis of variables, low albumin was determined as the most important risk factor for developing PRES (OR= 5.258, 95% CI= 1.031-26.828, p=0.046) (Table 4).

Table 4. Logistic regression analysis of the data

	%95 CI		Odds ratio	p-value
	Lower	Upper		
Platelet	0.998	1.009	1.004	0.197
Albumin	1.031	26.828	5.258	0.046
INR	0.000	1.749	0.022	0.088
Prothrombin time	0.458	1.150	0.726	0.173
Gravida	0.293	2.699	0.890	0.836
Parity	0.423	4.557	1.388	0.589
Gestational week	0.966	1.328	1.133	0.126
Maternal age	0.978	1.207	1.086	0.122

Discussion

The study aims to identify findings that can help predict PRES. These findings can help prevent the development of hypertension-related PRES as well as the complications that may occur after onset, which will let us guide the clinical-pathological data and prevent maternal morbidity and mortality in the following periods. In our study, the risk PRES was higher in cases with small maternal age, small gravida, small parity, and pregnancy-related hypertension at early gestational weeks. In addition to this, it was found that high PT, INR values, low PLT, and albumin values entail a higher risk in terms of PRES.

Brewer et al. diagnosed PRES in a retrospective cohort study of 47 cases with eclampsia in which 23 cases were reported as antepartum eclampsia and 24 cases as postpartum eclampsia. There were no differences between antepartum and postpartum cases in terms of race, age, and number of gravida, but the gestational weeks were smaller in antepartum cases, and the cesarean delivery rate was 74% in antepartum cases and the vaginal delivery rate was 67% in postpartum cases, which were significantly higher.^[23] Our study also differs from this study in that ours included both PRES and non-PRES cases. In this study, all cases were eclampsia cases and no hypertensive cases were included. In our study, we aimed to evaluate the risk factors for the development of PRES in hypertensive cases.

75 cases, the incidence of PRES was examined in eclampsia, symptomatic, and asymptomatic PE cases. 86.7% of eclampsia patients having a seizure, and 20% and 26.6% of symptomatic and asymptomatic PE cases were present with PRES, respectively.^[24] In another study, a total of 151 eclampsia cases were examined of which 16.7% of cases developed PRES.^[25] In our study, 85 cases were examined and 76 of the cases were seen to have eclampsia seizures. It was found that 55.3% of the eclampsia patients who had seizures developed PRES. When comparing the prevalence rates of PRES in the literature, there are differences. When the studies in the literature are compared, the prevalence rates of PRES are seen to be differing. One of the reasons for this is that not all patients with PE and eclampsia have CT or MRI imaging, while another reason is the selection of the patient for cranial imaging and the experience of the physician evaluating the imaging. Therefore, the true prevalence of PRES is unknown. Large-scale studies are needed to determine the true prevalence.

In a total of 30 hypertensive pregnant women, Singh et al. detected PRES in 8 cases, 5 of whom were eclampsia and 3 were PE and age, PLT, ALT, AST, Hb levels, and the presence of convulsions were found to be the most

specific predictive values for PRES. The best predictive value with AUC>70 was found to be age, AST, and Hb levels in this study. In women with PE, younger age, high AST, and low Hb levels were found to be predictors of PRES.^[26] An et al. compared 33 PRES and 45 non-PRES cases out of 78 pregnant women diagnosed with severe PE and eclampsia. As a result, age, gestational week, primiparity, convulsion, Hb, APTT, AST, urea, and Cr levels were not found to be significant, while PLT, ALT, and serum albumin levels were significant. In regression analysis, LDH and Albumin levels were not significant between the groups, while PLT and ALT levels were found to be significant, and also, PLT and ALT levels were found to be important risk factors for PRES.^[27]

In our study, the cases were investigated in two groups as PRES and non-PRES. As a result, small gestational weeks, maternal age, gravida, parity, low PLT, and albumin levels, and high INR and PTZ levels were found to increase the risk of PRES. Additionally, INR and PTZ with AUC above in ROC analysis of PRES cases were identified as the best predictive values. In regression analysis, only albumin level was found to be statistically significant.

There is limited information in the literature regarding risk factors for PRES in hypertensive pregnant women. The prevalence of PRES in hypertensive pregnant women is still unknown as imaging methods are not ordered for all cases. Ekawa et al. suggested that not only clinically suspected pregnant women with PRES but also asymptomatic pregnant women with a diagnosis of severe preeclampsia should undergo MRI, and if cerebral edema is detected, they suggest an emergency delivery before the onset of the eclamptic crisis and neurological symptoms.^[28] In a study from Turkey, Demirtaş et al. identified PRES in 18 of 39 eclamptic pregnant women in 2005.^[29] In our study, we think that stronger predictive values for PRES were obtained in our study by comparing groups with more variables, involving severe preeclamptic cases in addition to just cases with seizures.

In our study, there are more cases of PRES. One reason for this is that we are the only tertiary center in the area and high-risk pregnant women are referred to our clinic. Another is that our center is composed of an experienced multidisciplinary team, enabling us not to overlook these cases. In this study, additional imaging methods were applied to the patients with accompanying clinical findings (severe headache, visual symptoms, and convulsions) in addition to hypertension. Imaging methods were not applied to all hypertensive cases, considering unnecessary radiation exposure and a possible increase in costs. Because not all patients were subjected to additional imaging tests, the data remains insufficient to give the inci-

dence of PRES alone.

The first step in treating PRES cases is to bring hypertension to normal levels and prevent seizures. Once these conditions are met, the clinical picture improves quickly. This is why it is called reversible.^[30] In cases of PE, PRES should be considered when there are unusual neurological symptoms, as early diagnosis and treatment can prevent the development of sequelae. Imaging is important in the diagnosis. Given all this information, as soon as such high-risk pregnancies are detected, a multidisciplinary approach and transfer to a tertiary center with the necessary conditions must be immediately ensured. A multidisciplinary approach is important and lifesaving in PRES cases, therefore, the cases must be followed and treated in a tertiary center until a full recovery is ensured.

This study makes a significant contribution to the literature in terms of prognosis and approach to treatment methods for PRES cases by investigating the factors to be effective in the prediction of PRES developing in obstetric cases. There are some limitations in this study. This study is limited by its retrospective nature and low sample size. Also, this study was conducted at a tertiary care referral hospital, limiting its generalizability. We did not perform a multivariable logistic regression analysis to adjust for potential confounders. We only included pregnant women who developed hypertension due to obstetric reasons in our study. Excluding other cases of PRES caused by other reasons limits us from providing information on the true incidence of PRES. Therefore, larger multi-center studies are needed to confirm our findings.

Conclusion

We consider that high INR, PTT, low PLT, low albumin, young age, early gestational week, low gravida, and parity parameters can help clinicians to predict and diagnose earlier PRES cases due to obstetric causes. The outcomes yielded from this study will enable us to recognize PRES cases due to obstetric reasons earlier, thus letting us perform the early intervention and affecting the prognosis of PRES positively. In addition, we think that it will guide the physician and reduce maternal morbidity and mortality.

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