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Risk factors of posterior reversible encephalopathy syndrome in patients with preeclampsia or eclampsia: A retrospective review

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Background and purpose – Posterior reversible encephalopathy syndrome (PRES) is characterized by vasogenic edema, usually reversible, with the prominent involvement of the parietal and occipital lobes. The exact etiopathogenesis leading to PRES is unknown. Because signs of eclampsia and preeclampsia in neuroimaging often overlap and manifest as PRES, we aimed to evaluate whether demographic, clinical, and laboratory parameters predict PRES in patients with preeclampsia or eclampsia.
Methods – 213 pre-eclampsia or eclampsia patients with cranial imaging were retrospectively examined. We recorded the patients' demographic information, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), hemogram, biochemical indicators, clinical symptoms, and imaging features.
Results – Of all patients, 69% (n = 147) had preeclampsia while 31% (n = 66) had eclampsia, and 24.4% (n = 53) were diagnosed with PRES. The mean age of patients who developed PRES was 25.81 ± 6.07 years and thus significantly less than that of patients who did not develop PRES (p = .000). Patients with PRES had significantly higher mean SBP (p = .015), DBP (p = .009), and MAP (p = .003) than patients without PRES, along with significantly higher aspartate aminotransferase (ASAT; p = .001), alanine aminotransferase (ALAT; p = .001) blood urea nitrogen (BUN;

A posterior reverzibilis encephalopathia szindróma kockázati tényezői praeeclampsiás vagy eclampsiás betegeknél: retrospektív áttekintés
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Háttér és cél – A posterior reverzibilis encephalopathia szindrómát (PRES) általában reverzibilis vasogen oedema jellemzi, ami leginkább a parietalis és occipitalis lebenyeket érinti. A PRES kialakulásához vezető pontos etiopatogenezis ismeretlen. Mivel az eclampsia és a praeeclampsia jelei az idegi képalkotó vizsgálatokon gyakran átfedik egymást, és PRES-ként manifesztálódnak, célunk annak értékelése volt, hogy a praeeclampsiás vagy eclampsiás betegeknél a demográfiai, klinikai és laboratóriumi paraméterek előre jelzik-e a PRES-t.
Módszerek – 213 olyan preeclampsiás vagy eclampsiás beteget vontunk be retrospektív módon, akiknél koponyaűri képalkotó vizsgálatot végeztek. Feljegyeztük a betegek demográfiai adatait, szisztolés vérnyomását (SBP), diasztolés vérnyomását (DBP), átlagos artériás nyomását (MAP), hemogramját, biokémiai mutatóit, klinikai tüneteit és képalkotó jellemzőit.
Eredmények – A betegek 69%-ánál (n = 147) praeeclampsiát, 31%-ánál (n = 66) eclampsiát, 24,4%-ánál (n = 53) pedig PRES-t diagnosztizáltak. Azok a betegek, akiknél PRES alakult ki, szignifikánsan alacsonyabb átlagéletkorral (25,81 ± 6,07 év) bírtak, mint azok, akiknél nem alakult ki PRES (p = 0,000). A PRES-ben szenvedő betegeknél szignifikánsan magasabb volt az átlagos SBP (p = 0,015), a DBP (p = 0,009) és a MAP (p = 0,003), mint a PRES nélküli betegeknél, valamint szignifikánsan

p = .001), white blood cell (WBC; *p* = .003), neutrophil (*p* = .001), and hemoglobin (Hb; *p* = .027) levels, but significantly lower albumin (*p* = .000) levels.

Conclusion – Age, high blood pressure, and BUN, neutrophil, and WBC levels were predictors of the development of PRES in patients with preeclampsia and eclampsia. Early neuroimaging considering those predictors should be performed to diagnose PRES in patients with preeclampsia and eclampsia.

Keywords: posterior reversible encephalopathy syndrome (PRES), preeclampsia, eclampsia, pregnancy, hypertension

magasabb volt a következők vérszintje: glutamát-oxálacetát-transzamináz (aszpartát-aminotranszferáz/ASAT; p = 0,001), glutamát-piruvát-transzamináz (alanin-aminotranszferáz/ALAT; p = 0,001), karbamid-nitrogén (BUN; p = 0,001), fehérvérsejtszám (WBC; p = 0,003), neutrophilsejt-szám (p = 0,001) és hemoglobin (Hb; p = 0,027), míg szignifikánsan alacsonyabb az albumin- (p = 0,000) szint.

Következtetés – Az életkor, a magas vérnyomás, valamint a BUN-, a neutrophilsejt- és a WBC-szintek a praeeclampsiás és eclampsiás betegeknél a PRES kialakulásának előrejelzői voltak. Ezeket a prediktív tényezőket figyelembe véve a praeeclampsiás és eclampsiás betegeknél a PRES diagnosztizálásának érdekében korán érdemes idegi képalkotó vizsgálatot végezni.

Kulcsszavak: posterior reverzibilis encephalopathia szindróma (PRES), praeeclampsia, eclampsia, terhesség, hypertonia

Posterior reversible encephalopathy syndrome (PRES), a finding in neuroimaging, is characterized by subcortical vasogenic edema, usually reversible, with the prominent involvement of the parietal and occipital lobes and is diagnosed by magnetic resonance imaging (MRI)[1, 2]. PRES is clinically characterized by headaches, visual disturbances, and sometimes seizures[2]. Although the exact etiopathogenesis leading to PRES is unknown, the hypotheses put forward include conditions such as endothelial damage, disruption of the blood–brain barrier, and vasogenic, neuropeptide, cytotoxic, and immunogenic conditions that eventually result in cerebral edema[3–6]. PRES can occur alongside hypertension, end-stage renal disease, active cancer, chemotherapy, allogeneic bone marrow transplantation, autoimmune disorders, sepsis, preeclampsia, or eclampsia[1, 2]. Although studies have shown PRES in a significant proportion (70%–98%) of women with eclampsia, their cohorts were small[6–8]. In a review, the prevalence of PRES in patients with eclampsia was 66.7%, while its prevalence in patients with severe preeclampsia was 24%[9]. In neuroimaging, signs of eclampsia and preeclampsia often overlap and manifest as PRES[2, 10]. Moreover, MRI scans to detect PRES can be difficult to obtain routinely. For those reasons, we aimed to evaluate whether standard demographic, clinical, and laboratory parameters predict PRES in patients with preeclampsia or eclampsia.

Methods

Our sample included patients who, between January 2015 and June 2023, were diagnosed with preeclampsia or eclampsia by obstetricians and referred to the neurology department for neurological evaluation; or who applied to the neurology outpatient clinic or emergency department and were diagnosed with PRES after experiencing preeclampsia or eclampsia. In total, 213 preeclampsia or eclampsia patients with cranial imaging were retrospectively examined. Preeclampsia was defined as complications with hypertension, proteinuria, and edema between the 20th week of pregnancy and the 6th week postpartum, whereas eclampsia was defined as seizures unrelated to other cerebral conditions in addition to preeclampsia[11, 12].

We recorded patients' demographic information, SBP, DBP, MAP (MAP; defined as 2/3 of DBP + 1/3 of SBP), biochemical indicators, clinical symptoms, and imaging features. Biochemical indicators examined included serum albumin, creatinine, blood urea nitrogen (BUN), ASAT, ALAT, total bilirubin, C-reactive protein, and Hb levels, along with WBC, neutrophil, and platelet counts.

Patients who developed eclampsia or preeclampsia were classified according to whether or not they had PRES. Patients without clinical or radiological findings of preeclampsia/eclampsia, patients with abnormal

Table 1. *Baseline demographics, clinical parameters and imaging features*

		with PRES (n=53)	without PRES (n=160)	*p*
Age (years)		25.81±6.07	31.54±6.67	0.743
MRI		86.8% (n=46)	90.6% (n=145)	
CT		13.2% (n=7)	9.4% (n=15)	
Week of Pregnancy at delivery		32.77±4.15	34.61±3.96	
Gravida		2.53±1.82	4.72±3.07	
Diagnosis with MRI	Yes	86.8% (n=46)	90% (n=144)	0.000
	No	13.2% (n=7)	10% (n=16)	
Seizure	Yes	77.4% (n=41)	15.6% (n=25)	0.000
	No	22.6% (n=12)	84.4% (n=135)	
Confusion	Yes	30.2% (n=16)	8.1% (n=13)	0.316
	No	69.8% (n=37)	91.9% (n=147)	
Headache	Yes	64.2% (n=34)	13.1% (n=21)	0.742
	No	35.8% (n=19)	86.9% (n=139)	
Syncope	Yes	5.7% (n=3)	1.2% (n=2)	0.068
	No	94.3% (n=50)	98.8% (n=158)	
Visual Disorders	Yes	15.1% (n=8)	8.1% (n=13)	0.039
	No	84.9% (n=45)	91.9% (n=147)	
Neurological Examination	Normal	1.9% (n=1)	64.4% (n=103)	0.072
	Pathological	98.1% (n=52)	35.6% (n=57)	

CT: computed tomography; MRI: magnetic resonance imaging; PRES: posterior reversible encephalopathy syndrome

neuroimaging features unrelated to PRES, patients with epilepsy unrelated to preeclampsia or eclampsia, patients with neurological diseases such as brain tumors or congenital brain malformations, patients with pre-gestational hypertension, and patients diagnosed with hypertension before the 20th week of pregnancy were excluded from the sample.

The study was approved by the local ethics committee (HRÜ/23.21.10) and conducted in accordance with the Declaration of Helsinki.

Statistical analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows version 20.0. After the patients' data were recorded, the distribution of the data was evaluated according to the Kolmogorov–Smirnov and Shapiro–Wilk normality tests. The Mann–Whitney U test was used for non-normally distributed variables, while an independent sample t-test was used to compare normally distributed variables. ROC analysis was performed to determine the diagnostic value of the variables, and a frequency analysis of variables was performed by cross-tabulation and frequency tests. A value of $p < .05$ was considered to indicate statistical significance in all tests.

Results

The sample included 213 patients diagnosed with preeclampsia (n = 147, 69%) or eclampsia (n = 66, 31%). The mean age of the sample was 30.12 ± 6.96 years (range: 17–54 years), while the average gestational age was 30.20 ± 6.99 weeks (range: 20–42). Of all patients, 53 were diagnosed with PRES: in 8.2% (n = 12) of patients with preeclampsia and 62.1% (n = 41) of patients with eclampsia. PRES was thus significantly more common in patients with eclampsia than ones with preeclampsia (p = .000). The average age of patients who developed PRES was 25.81 ± 6.07 years and was significantly younger than that of patients without PRES (p = .000). The most common symptoms in patients were seizure (33.3%), headache (25.8%), confusion (13.6%), and visual symptoms (9.9%), as shown in **Table 1**.

As **Table 2** shows, the mean SBP, DBP, and MAP of patients with PRES were significantly higher than those of patients without PRES (p = .015, p = .009, and p = .003, respectively). Although the SBP of patients who developed PRES during eclampsia was higher than that of other patients with eclampsia, the difference was non-significant (p = .078). However, the mean DBP and MAP were significantly higher of those patients than in patients with eclampsia who did not develop PRES (p = .041, p = .035, respectively), as shown in **Table 3**. In addition, SBP >142 mmHg and DBP >87.5 mmHg were found to predict PRES, though DBP's diagnostic accuracy was higher than SBP's **(Figure 1)**.

The average BUN, ASAT, and ALAT levels of patients diagnosed with PRES were significantly higher than those of patients without PRES (p = .001, p = .001, and p = .001, respectively), whereas their albumin levels were lower (p = .000). Mean WBC count, neutrophil count, and Hb level were significantly higher among patients diagnosed with PRES than other patients (p = .003, p = .001, and p = .027, respectively), as shown in **Table 2**. The laboratory parameters of patients who developed PRES during eclampsia or preeclampsia appear in **Table 3**.

Table 2. *Comparison of baseline characteristics of patients with preeclampsia/eclampsia with and without PRES*

	with PRES (n=53)	without PRES (n=160)	*p*
SBP (mmHg)	160.82±19.50	152.01±23.74	*0.015*
DBP (mmHg)	102.00±19.26	93.55±15.18	*0.009*
MAP (mmHg)	121.78±18.29	112.21±18.98	*0.003*
Urea (mg/dl)	29.26±10.70	23.30±9.11	*0.001*
ASAT (U/L)	297.04±538.75	77.58±251.53	*0.001*
ALAT (U/L)	139.04±227.58	48.66±110.83	*0.001*
Albumin (g/Dl)	2.76±0.62	3.21±0.61	*0.000*
WBC (10^9/L)	16.04±5.02	13.40±4.74	*0.003*
Neutrophil (10^9/L)	13.45±4.94	10.51±4.94	*0.001*
Hb (mg/dl)	12.86±2.12	12.04±2.04	*0.027*
CRP (mg/dl)	2.73±2.26	2.01±2.87	0.196
Bilirubin (total) (mg/dL)	1.17±1.42	0.80±1.32	0.097

SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP: mean arterial pressure, ASAT: aspartate aminotransferase, ALAT: alanine aminotransferase, WBC: white blood cell, Hb: hemoglobin, CRP: C-reactive protein.

Figure 2 illustrates the distribution of the areas of involvement in the cranial MRIs of patients with PRES. As shown, the most common was the bilateral occipito-parietal involvement (40%), followed by bilateral fronto-parieto-occipital involvement (31.1%).

Table 3. *The comparison of BP and laboratory parameters between preeclampsia (with PRES and without PRES) group and eclampsia (with PRES and without PRES) group*

	Eclampsia (n=66)		*p*	Preeclampsia (n=147)		*p*
	with PRES (n=41)	without PRES (n=25)		with PRES (n=12)	without PRES (n=135)	
SBP (mmHg)	164.49±19.56	151.67±28.43	0.078	148.00±13.37	152.07±22.59	0.404
DBP (mmHg)	105.71±18.68	94.48±19.61	*0.041*	89.00±15.95	93.38±14.31	0.421
MAP (mmHg)	125.53±17.80	112.20±24.13	*0.035*	108.63±13.84	112.02±18.63	0.485
Urea (mg/dl)	29.22±10.85	23.28±9.77	*0.040*	29.40±10.73	23.30±9.03	*0.046*
ASAT (U/L)	271.60±499.37	109.00±148.90	0.079	386.10±682.34	71.79±266.24	*0.002*
ALAT (U/L)	130.97±230.59	81.76±131.76	0.314	167.30±226.24	42.57±131.76	*0.003*
Albumin (g/Dl)	2.74±0.65	2.77±0.51	0.856	2.84±0.55	3.29±0.59	*0.030*
WBC (10^9/L)	16.28±5.28	17.30±6.30	0.539	16.28±5.28	12.68±4.46	*0.086*
Neutrophil (10^9/L)	13.66±5.19	14.25±4.94	0.669	12.75±4.08	9.82±4.39	*0.044*
Hb (mg/dl)	13.07±2.04	11.86±2.23	*0.032*	12.82±2.10	11.89±2.12	0.168
CRP (mg/dl)	2.49±2.18	1.61±1.80	0.086	3.57±2.43	2.09±3.03	0.078
Bilirubin (total) (mg/dL)	0.97±0.92	0.90±0.64	0.685	1.83±2.42	0.78±1.41	0.082

SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP: mean arterial pressure, ASAT: aspartate aminotransferase, ALAT: alanine aminotransferase, WBC: white blood cell, Hb: hemoglobin, CRP: C-reactive protein.

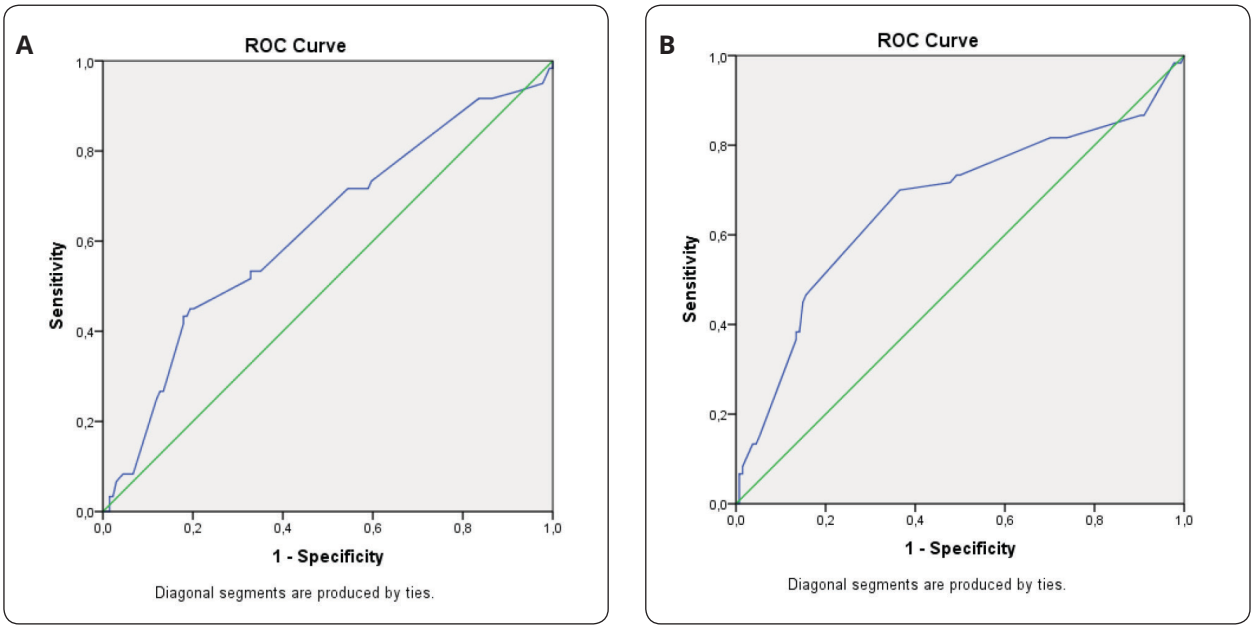

Figure 1. A *Cut-off value for SBP= 142 (AUC : 0.624, 95% CI: 0.537-0.711, sensitivity =73.3, specificity=62.7),* **B** *cut-off value for DBP= 87.50 (AUC: 0.669, 95% CI: 0.579-0.758, sensitivity =81.7%, specificity =70.1%)*

Discussion

Advances in imaging methods have led to increased diagnoses of PRES. In our study, PRES was frequently observed in patients with eclampsia, as consistent with the findings of a previous study[13]. Our results revealed that PRES is also present in patients without eclampsia. Moreover, regarding our aim to determine the predictive factors of PRES, we found that age, high blood pressure, BUN level, and neutrophil and WBC counts were effective predictors of PRES in patients with preeclampsia and eclampsia.

Despite arguments that PRES is an integral part of eclampsia[13], *Verma* et al.[6] found PRES in only 71.4% of patients with eclampsia in their prospective observational study. Furthermore, *Fisher* et al.[14] detected PRES in only 62.5% of patients with eclampsia and only in 10.5% of ones with preeclampsia. PRES had also been detected in the absence of eclampsia and thus not as one of its complications[15]. Consistent with the literature, in our study PRES was significantly more common in patients with eclampsia than in patients with preeclampsia.

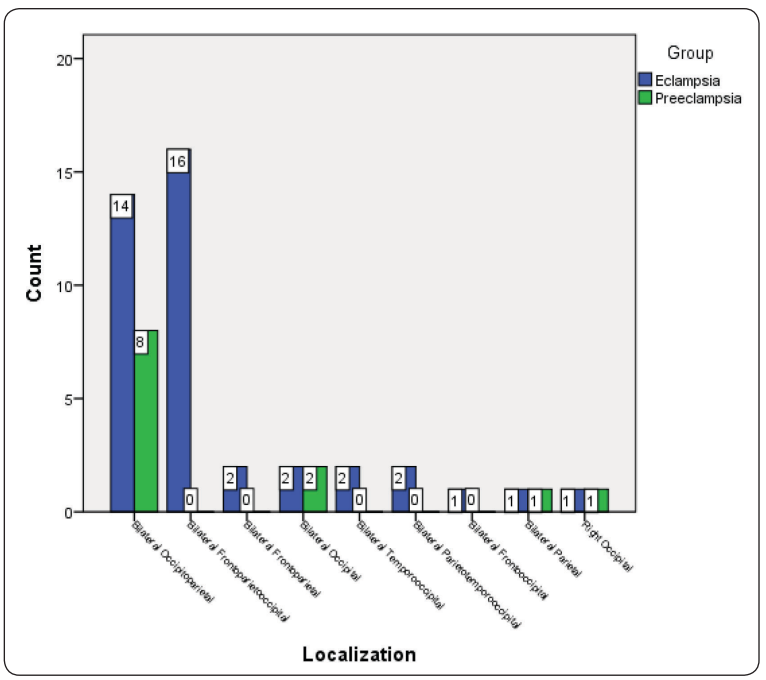

Figure 2. *Distribution of brain regions involved in PRES*

Although many studies have failed to find an association between PRES and age[7, 16], patients in our study who developed PRES were significantly younger than the ones who did not. Some studies have similarly shown that PRES is associated with younger age[14], while others have revealed that it may also be associated with low maternal age, primiparity, lack of education, and prenatal care[17–19]. Coupled with those findings, our results may reflect the socioeconomic profile of our patient population, most of

whom marry at a young age and have limited access to routine prenatal care. In a prospective study conducted to determine whether PRES occurs in hypertensive pregnant women without preeclampsia or features of eclampsia, one of the parameters that best predicted PRES was high SBP[20]. Although other studies have shown evidence supporting that result[13, 14], some have not indicated any relationship between blood pressure and PRES[6, 7, 16]. *Matsuda* et al. found that DBP was significantly higher among patients who developed PRES than among ones with normal cranial MRI results, but no significant difference in SBP emerged[21]. In our study, elevated mean SBP, DBP, and MAP among patients who developed PRES seemed to significantly contribute to the development of PRES. Among them, SBP in patients who developed PRES during eclampsia was higher than in other patients with eclampsia but not to a statistically significant extent, whereas DBP and MAP were significantly higher. We additionally observed that the SBP, DBP, and MAP of patients who developed PRES during preeclampsia were lower than in other patients with preeclampsia. Even so, SBP >142 mmHg and DBP >87.5 mmHg were found to predict PRES, though DBP's diagnostic accuracy was greater than SBP's. The differences in findings between studies may be due to differences in time when blood pressure was recorded owing to the retrospective nature of the studies.

Other research showing a high correlation between SBP or DBP and parameters of renal function (i.e., BUN, creatinine, and uric acid levels) has also revealed severe preeclampsia's positive correlation with renal function[22]. *Drakeley* et al.[23] and *Sibai* et al.[24] have also reported that preeclampsia is a cause of acute renal failure during pregnancy. In our study, the BUN levels of patients who developed PRES during eclampsia or preeclampsia were significantly higher than among ones who did not develop PRES. Those findings suggest that renal dysfunction in patients with eclampsia or preeclampsia predicts the development of PRES. Kidney and liver dysfunction are indeed common manifestations of end organ damage due to preeclampsia[25]. On that count, studies have shown increased ALAT level in patients with preeclampsia[26, 27]. A more recent study has also revealed a significant increase in ASAT and ALAT levels in pregnant women with preeclampsia compared with normotensive pregnant women[28]. In a similar study conducted by *Ekun* et al.[29], transaminases in patients with preeclampsia were increased as well. In research investigating the role of clinical and laboratory parameters in predicting PRES in hypertensive pregnant women, high liver markers (i.e., ASAT and ALAT levels) were found to predict PRES. In fact, ASAT level (>55 IU/L) was one of the parameters that best predicted PRES[20]. In our study, ASAT and ALAT levels were significantly higher in patients diagnosed with PRES. Although ASAT and ALT levels were higher in patients with preeclampsia and eclampsia who developed PRES than in patients who did not, the levels between the groups did not differ significantly. The increase in the former group may derive from a systemic inflammatory response following placental ischemia, which leads to endothelial dysfunction that can cause vasoconstriction and eventually liver and kidney dysfunction[28].

The excessive production of reactive oxygen species (ROS) can cause hypoalbuminemia along with endothelial dysfunction. Most likely because albumin is a vital plasma antioxidant that cleans and detoxifies ROS[30], serum albumin levels were found to be low in patients with PRES in a study investigating the laboratory and imaging characteristics of such patients in intensive care. A possible correlation between low albumin levels and PRES has also been discussed by *Ishikura* et al., who reported 7 pediatric patients with nephrotic syndrome and hypoalbuminemia who demonstrated significant clinical improvement following albumin replacement[31]. In our study, the mean albumin level of patients who developed PRES was significantly lower than that of patients who did not develop PRES. In patients who developed PRES during preeclampsia, the serum albumin level was significantly lower than in other patients with preeclampsia. Although the serum albumin level was also low in patients who developed PRES during eclampsia, the difference was non-significant. In light of those findings, hypoalbuminemia may cause low colloid osmotic pressure, fluid extravasation, the development of vasogenic edema, and PRES.

Studies have shown that leukocyte activation plays an important role in preeclampsia's disease process. Women with preeclampsia have shown significantly increased leukocyte activation as well as superoxide production in monocytes and neutrophils[32, 33]. Moreover, neutrophil activation is believed to be a major component of excessive inflammatory responses in the maternal vascular system during preeclampsia[33]. *Canzoneri* et al. have observed an increased number of leukocytes in patients with mild preeclampsia and a significantly increased number in patients with severe preeclampsia compared with normal pregnant controls. They also determined that the increased number of neutrophils was responsible for the increase in total leukocytes in patients with preeclampsia[34]. Authors including *Lurie* et al.[35] and *Liu* et al.[36] have also found an increased number of neutrophils in patients with severe preeclampsia. In our study, the mean WBC and neutrophil counts among patients who developed PRES were significantly higher than those among patients who did not develop PRES. Consistent with the literature, the mean neutrophil and WBC counts of patients who developed PRES due to preeclampsia were significantly higher than in other patients with preeclampsia.

Last, Hb levels were also significantly higher in PRES patients than in other patients in our study. Even so, no significant difference in Hb values arose between patients

with eclampsia and ones with preeclampsia. On that point, the literature shows conflicting findings. Whereas most studies did not reveal any relationship between PRES and Hb, in a study conducted to determine the serum levels of trace elements and macrominerals and their possible relationships with preeclampsia, patients with preeclampsia had lower Hb levels than normotensive pregnant women[37]. In another study evaluating predictive factors of PRES, low Hb levels (i.e., <8.7 g/dl) indeed predicted PRES[20]. Contrarily, in our study, high Hb levels emerged as a predictor of the development of PRES. *Mayama* et al.[3] have also found higher hematocrit levels in women with PRES. Increased blood viscosity with high hematocrit levels exacerbates endothelial dysfunction, which leads to dysfunction in the blood–brain barrier and results in vasogenic edema and vasoconstriction despite normal systemic blood pressure[38, 39].

Conclusion

We found that age, high blood pressure, BUN levels, and neutrophil and WBC counts were predictors of the development of PRES in patients with preeclampsia and eclampsia. Because the neurological disorder can be overcome with early diagnosis and appropriate treatment, we propose that those predictors can be used to determine the risk of PRES in pregnant women and thus optimize the time of treatment and treatment outcomes. Along those lines, future studies should evaluate the role of biomarkers and their long-term neurological effects in pregnant women diagnosed with PRES. Our study was limited in being a single-center retrospective study and having a relatively small sample. Prospective multicenter studies are required for more comprehensive data collection and analysis.

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