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Clinical significance of S100B protein in pregnant woman with early-onset severe preeclampsia

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ABSTRACT

Objectives: Preeclampsia is one of the most feared complications of pregnancy, which can progress rapidly to serious complications such as death of both mother and fetus. To present, the leading cause of preeclampsia is still debated. The purpose of this article was to explore the clinical significance of S100B protein, a kind of Ca^{2+} — sensor protein, in the early-onset severe preeclampsia.

Material and methods: Nine pregnant women with early-onset severe preeclampsia (the study group) and 13 healthy pregnant women (the control group) were included in this study. The level of S100B in the amniotic fluid, maternal blood, and umbilical cord blood were detected by enzyme-linked immunosorbent assay (ELISA) and surface plasmon resonance imaging (SPRi) methods. Diagnostic values of S100B for early-onset severe preeclampsia were assessed by receiver operating characteristic(ROC) curve analysis.

Results: The levels of S100B in maternal blood and amniotic fluid in the study group were higher than those in the control group ($p < 0.05$). ROC curve analysis showed that S100B detected by SPRi method (SPRi-S100B) showed a cut-off level of 181 ng/mL with sensitivity of 100%, a specificity of 84.6%, and a Youden index of 0.846 in the maternal blood, which had better clinical significance and diagnostic value (at than that detected by ELISA (ELISA-S100B).

Conclusions: The levels of S100B detected by SPRi in maternal blood can indicate early-onset severe preeclampsia and perinatal brain injury.

Keywords: S100B; early-onset severe preeclampsia; enzyme-linked immunosorbent assay; surface plasmon resonance imaging

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INTRODUCTION

Preeclampsia is a severe condition with high blood pressure and increased protein in the urine in pregnant women. It commonly occurs after gestational week 20 and can be divided into early-onset (< 34 weeks) and late-onset (> 34 weeks) preeclampsia. It is believed that early-onset and late-onset preeclampsia have different aetiologies and pathogenesis, although both can cause high morbidity and mortality for pregnant women and fetuses [1, 2]. Prompt recognition and diagnosis of preeclampsia and perinatal brain injury (PBI) are essential to save lives and improve outcomes [3]. However, most clinical studies have focused on late-onset preeclampsia, and relatively few studies investigated early-onset preeclampsia.

Researchers have searched for various markers of brain injury to diagnose preeclampsia and PBI early, as preeclampsia can cause PBI in the fetus. Perinatal brain injury (PBI) is the main cause of perinatal death and long-term disability. It is reported that 8% of full-term infants suffer from cerebral palsy due to asphyxia at birth, and 40% of preterm infants die of perinatal death due to neurological defects [4]. Pierrat et al. [5], (2005) found that prenatal-perinatal asphyxia accounts for 10% and postpartum asphyxia accounts for 2% in newborn encephalopathy. At present, scholars lack a unified understanding of the diagnosis of this condition. Current understanding of PBI by obstetricians is that preventive measures must be taken in a timely manner; however, this remains controversial. Therefore,

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measures must be taken to diagnose PBI in a timely and accurate manner.

Several studies have reported that the S100B protein expression is elevated in pregnant women with preeclampsia, indicating the involvement of S100B protein in preeclampsia [6]. The S100B protein synthesized and secreted by brain neuroglia and Schwann cells is a member of the S100 protein family (calcium-regulation protein) [7]. It acts as both an intracellular regulator and a secreted signaling molecule and plays important roles in many cellular processes such as cell proliferation, differentiation, migration, and apoptosis [8]. Alterations in the level of expression of S100B can lead to four different categories of diseases including the heart disease, central nervous system disease, inflammatory disorders and cancer [9]. It was found that the effects and physiological functions of S100B are concentration dependent. A low concentration (nanomolar level) of S100B can nourish and support the neuroglia and neurons, which facilitates nerve growth and injury repair. A high concentration (micromolar level) of S100B can have toxic effects on nerves to induce neuron degeneration apoptosis and death [10]. S100B is sensitive enough to detect and evaluate different types of intracranial trauma, such as traumatic subarachnoid hemorrhages and epidural hematomas, depending on the receptor for advanced glycation end-products (RAGE) which is up-regulated by S100B levels and may lead to pro-inflammatory gene activation [11]. Some researchers have described S100B as "the C-reactive protein (CRP) of the brain." [12] and suggested its use in monitoring fetal distress and other high-risk fetuses [13]. In 2012, Cai et al. [14], reported that the S100B expression in women with early-onset preeclampsia was significantly higher than that in the control group and in late-onset preeclampsia group, indicating that S100B may be a risk factor in early-onset preeclampsia. Serum S100B levels may also be suitable markers of severe preeclampsia given the severity of hypoperfusion both in the placenta and brain [15]. In another previous study, S100B levels were found to be much higher in women with preeclampsia than that in control subjects, and high S100B is significantly associated with visual impairment in the preeclampsia group [6] S100B protein may help obstetrician screen for PBI, monitor the progression of the disease, identify the timing of the injury, and predict the time of birth [16]. The level of S100B may be an ideal indicator for the diagnosis in preeclampsia and PBI, however, it is difficult to detect S100B at the mRNA level in clinical laboratories.

In our study, we examined the S100B expression levels in the maternal blood, amniotic fluid, and umbilical cord blood in pregnant women with preeclampsia using ELISA and SPRi and evaluated specificity and sensitivity of two methods to detect S100B for identification of early-onset severe preeclampsia and PBI.

MATERIALS AND METHODS

Study design and ethical approval

This retrospective study protocol was approved by the Ethics Committee of the Maternal and Child Health Hospital of Hunan Province (No. 2013-P2-006-01) and complied with the Declaration of Helsinki. Informed consents were obtained from all participants.

Patients

Between January 2017 and December 2018, nine pregnant women with early-onset severe preeclampsia, showing fetal distress and causing hypoxic-ischemic encephalopathy (HIE) after delivery, and 13 pregnant women without early-onset severe preeclampsia and having prenatal diagnosis when they were 32–34 weeks pregnant at the Maternal and Child Health Hospital of Hunan Province, were assessed for eligibility based on inclusion and exclusion criteria. Their nationality, age, parity, fetal number, weeks pregnant, inflammation status, tumor status, and family history of hypertension were recorded.

Inclusion criteria: 1. They were diagnosed fetal distress by non-stress test and ultrasound and caused hypoxic-ischemic encephalopathy after delivery; 2. Han nationality; 3. 35 years old; 4. Primiparous; 5. Singleton pregnancies; 6. 32–34 weeks pregnant; 7. No inflammation; 8. No tumors, and 9. No family history of hypertension. Pregnant women included in the control group: 1. Perinatal and they delivered baby in full-term smoothly; 2. Han people; 3. 35 years old; 4. Primiparity; 5. Singleton pregnancy; 6. 32–34 weeks pregnant; 7. No inflammation; 8. No tumors and 9. No family history of hypertension.

Sample collection

In the control group, we obtained 3 mL of blood from the pregnant women's antecubital veins at 8:00 a.m. and 5 mL amniotic fluid from the amniotic sac of the uterus at 4:00 p.m. In the study group, in addition to the peripheral veins and amniotic fluid, we also collected 3 mL of blood from the umbilical vein in the operating room in cases of fetuses with diagnosed fetal distress in utero by non-stress test (NST) and ultrasound. All samples were centrifuged at 3,500 rpm at 4°C for 15 min. Supernatants were deposited at –80°C. The S100B protein expression was detected using enzyme-linked immunosorbent assay (ELISA) and surface plasmon resonance imaging (SPRi) in the hospital laboratory according to the instruction manual [17, 18].

Statistical analysis

The data were analyzed with Statistical Product and Service Solutions (SPSS) version 25.0 software (IBM, Chicago, IL, USA). S100B concentrations were presented as the mean ± standard deviation (SD), and compared by Wilcox-

con rank sum test. The correlation of S100B levels among maternal blood, cord blood, and amniotic fluid in the study and control groups were evaluated using Spearman's correlation test. Receiver operating characteristic (ROC) curve analysis was assessed for early-onset severe preeclampsia and PBI diagnostic values of the ELISA and the SPRi in maternal blood, cord blood and amniotic fluid. $P < 0.05$ was considered a statistical significance.

RESULTS

Characteristics of study participants

The baseline characteristics of maternal and fetus status in the control and study groups were listed in Table 1. It was suggested that there were no significances in pregnant week and body mass index (BMI) for pregnant women in both groups. Blood pressure was 160–190/100–120 mmHg in the study group and lower than 140/90 mmHg in the control group. 2+ to 4+ proteinuria was found in the study group, while — proteinuria was observed in the control group. Results of fetal status suggested that non-stress test was abnormal for the study group and normal for the control group. Ultrasound score was 4–6 for the study group and 8 for the control group. Fetus weight was normal in the control group while fetal growth was restricted in the study group.

Concentrations of S100B protein in the study and control groups

As shown in Table 2, there were no statistical differences in the concentration of S100B protein in the amniotic fluid tested by ELISA between the study group and the control group ($p > 0.05$). Following SPRi measurement, a significant difference in the concentration of S100B protein in the amniotic fluid was found between two groups ($p < 0.05$). Furthermore, there was a significant difference in the concentration of S100B protein in maternal blood between the study group and the control group tested by ELISA and SPRi methods (both $p < 0.05$).

Correlation of concentrations of S100B between maternal blood and amniotic fluid in the control and study groups

As shown in Table 3, for the study group, the concentration of ELISA-S100B protein in maternal blood was positively correlated with the concentration of SPRi-S100B protein in maternal blood (0.883, $p < 0.05$). The concentration of ELISA-S100B in amniotic fluid was positively correlated with the concentration of SPRi-S100B in amniotic fluid (0.720, $p < 0.05$). However, there were no positive correlations between ELISA-S100B protein in the maternal blood and ELISA-S100B and or SPRi-S100B in amniotic fluid, between

Table 1. Baseline characteristics of maternal and fetus status in both study and control groups

Items	Study group	Control group
Maternal status		
Pregnant week	32–34	32–34
BMI	18–25	18–25
Blood pressure [mmHg]	160–190/100–120	< 140/90
Proteinuria	++ to ++++	–
Fetal status		
Non-stress test	Abnormal	Normal
Ultrasound scores	4–6	8
Weight	Fetal growth restriction	Normal

BMI — body mass index

Table 2. Comparison of the ELISA-S100B and SPRi-S100B in study and control groups

Variables	Control group (n = 13)	Study group (n = 9)	Z	p value
Maternal blood (ELISA-S100B)	111.63 ± 42.64	198.91 ± 51.02	2.709	0.007
Maternal blood (SPRi-S100B)	115.18 ± 51.02	209.01 ± 27.54	3.976	0.000
Amniotic fluid (ELISA-S100B)	168.49 ± 37.33	144.93 ± 42.74	1.637	0.102
Amniotic fluid (SPRi-S100B)	82.88 ± 45.12	142.88 ± 22.93	3.103	0.002

Table 3. Correlations of S100B protein concentrations in the control group between maternal blood and amniotic fluid

	Maternal blood (ELISA-S100B)	Amniotic fluid (ELISA-S100B)	Maternal blood (SPRi-S100B)	Amniotic fluid (SPRi-S100B)
Maternal blood (ELISA-S100B)	1.000			
Amniotic fluid (ELISA-S100B)	–0.055	1.000		
Maternal blood (SPRi-S100B)	0.883**	0.016	1.000	
Amniotic fluid (SPRi-S100B)	0.055	0.720**	0.121	1.000

**indicated $p < 0.05$

Table 4. Correlations of S100B protein concentrations in the study group

	Maternal blood (ELISA-S100B)	Umbilical cord blood (ELISA-S100B)	Amniotic fluid (ELISA-S100B)	Maternal blood (SPRi-S100B)	Umbilical cord blood (SPRi-S100B)	Amniotic fluid (SPRi-S100B)
Maternal blood (ELISA-S100B)	1.000					
Umbilical cord blood (ELISA-S100B)	0.741*	1.000				
Amniotic fluid (ELISA-S100B)	0.213	0.650	1.000			
Maternal blood (SPRi-S100B)	0.850**	0.706*	0.176	1.000		
Umbilical cord blood (SPRi-S100B)	0.562	0.517	0.233	0.620*	1.000	
Amniotic fluid (SPRi-S100B)	0.443	0.333	0.533	0.579*	0.313	1.000

*indicated $p < 0.05$; **indicated $p < 0.01$

SPRi-S100B in maternal blood and ELISA-S100B and or SPRi-S100B in amniotic fluid ($p > 0.05$).

Correlation of ELISA-S100B and SPRi-S100B concentrations in study group

For the study group, Table 4 showed that there was a positive correlation between ELISA-S100B expression level and SPRi-S100B expression level in maternal blood (0.850, $p < 0.05$) and ELISA-S100B in umbilical cord blood (0.741, $p < 0.05$) between SPRi-S100B in maternal blood and ELISA-S100B in umbilical cord blood (0.706, $p < 0.05$), and or SPRi-S100B in umbilical cord blood (0.620, $p < 0.05$) and in amniotic fluid (0.579, $p < 0.05$). By contrast, there were no positive correlations between the ELISA-S100B in the maternal blood and ELISA-S100B and or SPRi-S100B in the amniotic fluid and SPRi-S100B in the umbilical cord blood ($p > 0.05$). There were no positive correlations for ELISA-S100B in umbilical cord blood and ELISA-S100B and SPRi-S100B in the amniotic fluid, and the SPRi-S100B in the umbilical cord blood ($p > 0.05$). The ELISA-S100B expression level in amniotic fluid was not positively correlated with the SPRi-S100B in maternal blood, in umbilical cord blood and in amniotic fluid ($p > 0.05$). There were no statistical differences in SPRi-S100B between the amniotic fluid and the umbilical cord blood ($p > 0.05$).

ROC analysis for ELISA-S100B and SPRi-S100B

Table 5 and Figure 1 showed ELISA-S100B and SPRi-S100B in maternal blood and in amniotic fluid. ROC analysis proved that the area under ROC curve (AUC) of SPRi-S100B in maternal blood was 0.959 ($p < 0.001$), which was greater than that of ELISA-S100B in maternal blood of 0.846 ($p = 0.07$). The AUC of SPRi-S100B in amniotic fluid was 0.858 ($p = 0.002$), which was greater than that of ELISA-S100B in amniotic fluid of 0.709 ($p = 0.102$). There were no statistical differences in the AUC for ELISA-S100B in amniotic fluid ($p > 0.05$). Additionally, the sensitivity and specificity of ELISA and SPRi were provided in Table 6. The cut-off level for detecting ELISA-S100B and SPRi-S100B in maternal blood was 178 ng/mL and 181 ng/mL, the sensitivity was 66.7% and 100%, and the specificity was 44.4% and 84.6%, respectively. The cut-off level for detecting ELISA-S100B and SPRi-S100B in amniotic fluid was 126 ng/mL and 99 ng/mL, the sensitivity was 0% and 100%, and the specificity was 0% and 69.2%, respectively.

Table 5. Receiver Operating Characteristic analysis of the S100B protein concentration

	AUC	p value	95% CI
Maternal blood (ELISA-S100B)	0.846	0.007	0.672–1.000
Maternal blood (SPRi-S100B)	0.959	0.000	0.888–1.000
Amniotic fluid (ELISA-S100B)	0.709	0.102	0.463–0.956
Amniotic fluid (SPRi-S100B)	0.858	0.002	0.705–1.000

AUC — the area under ROC curve; CI — confidence interval

Above findings indicated that SPRi-S100B is superior to the ELISA-S100B for the diagnosis of early-onset severe preeclampsia in pregnant women.

DISCUSSION

In pregnant women with early-onset and severe preeclampsia, arteriolar convulsions can cause fetal distress through poor placental perfusion, which can lead to PBI and neonatal hypoxic ischemic encephalopathy. Despite these potential issues, screening high-risk fetuses for brain injury early and accurately remains challenging [2]. In this study, the concentrations of S100B protein in samples of pregnant women with and without preeclampsia were detected by ELISA and SPRi methods, and ithe feasibility, safety and accuracy of ELISA and SPRi were evaluated, providing the evidence that SPRi-S100B protein level can accurately and reliably provide clinical benefits to identify early-onset severe preeclampsia.

S100B is a calcium-binding protein concentrated in nervous glial cells, which is essential to oligodendrocyte (OL) differentiation and maturation. Elevated S100B is suggested to disrupt astrocyte proliferation and inflammation

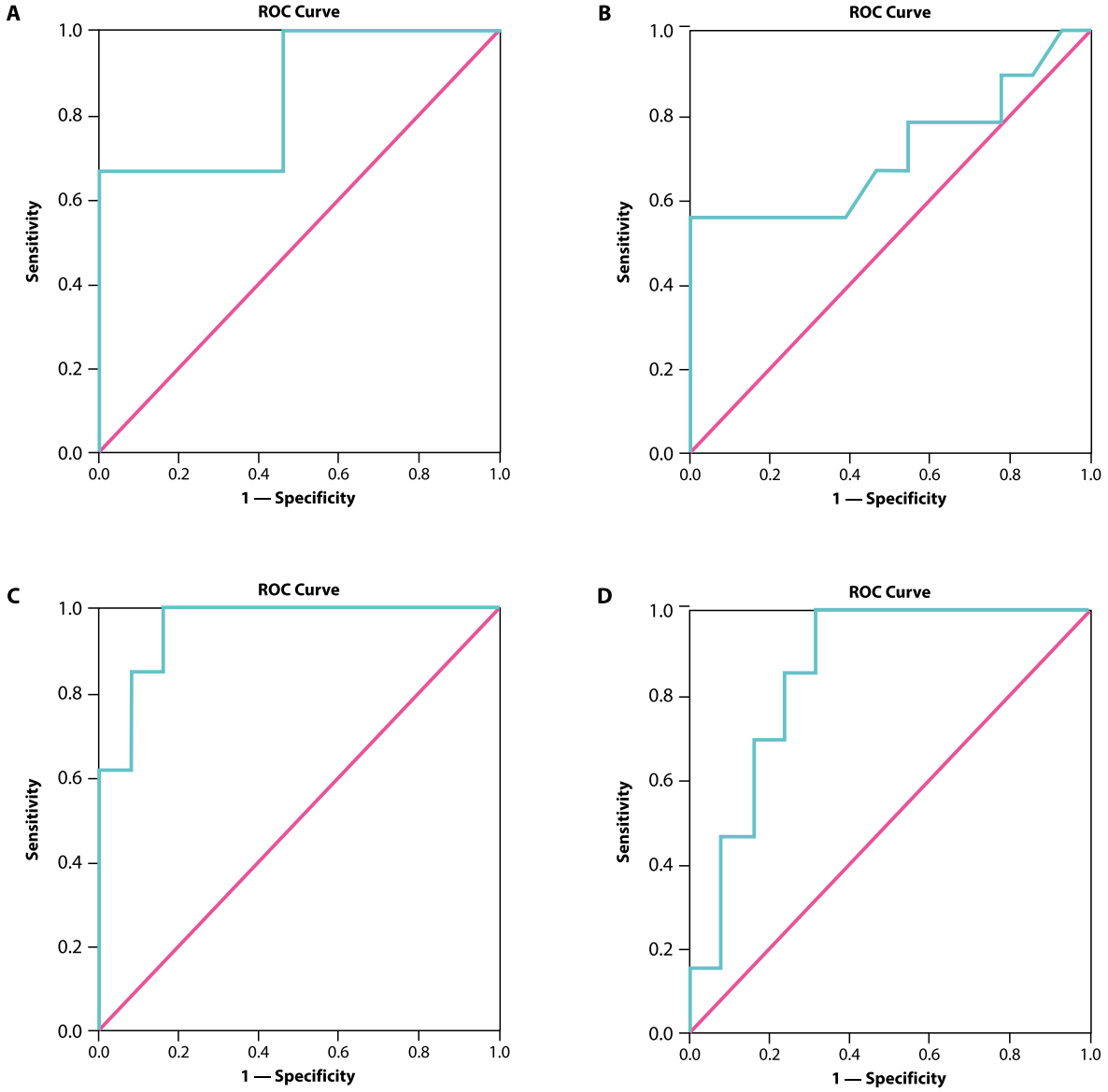

Figure 1. Receiver Operating Characteristic (ROC) curve of S100B protein in blood and amniotic fluid of pregnant women with preeclampsia detected by ELISA and SPRi; **A.** ROC of ELISA-S100B in maternal blood; **B.** ROC of ELISA-S100B in amniotic fluid; **C.** ROC of SPRi-S100B in maternal blood; **D.** ROC of SPRi-S100B in amniotic fluid

Table 6. Clinical significance of S100B protein detected by SPRi and ELISA in maternal blood and amniotic fluid

	Sensitivity	Specificity	Youden Index
Maternal blood (ELISA-S100B)	0.667	1.000	0.667
Maternal blood (SPRi-S100B)	1.000	0.846	0.846
Amniotic fluid (ELISA-S100B)	0.444	0.000	–0.556
Amniotic fluid (SPRi-S100B)	1.000	0.692	0.692

while destroy neuronal and synaptic integrity, reduce the morphological maturation of differentiated OL [11]. The high S100B levels in biological fluids are thus considered biomarkers of pathological conditions in many brain disorders [12]. Serum S100B levels can be used not only as a biomarker for hypoxic-ischemic encephalopathy, but also as a useful marker of perinatal acute brain injury, especially for fetal distress [2, 10, 19, 20, 21]. Also, it has been used to monitor brain damage and evaluate neuroprotective effects in high-risk newborns [22, 23]. S100B concentration was also found to be associated with umbilical artery pH,

amplitude integral electroencephalogram (EEG), hypoxic ischemic encephalopathy (HIE) stage and death/sequelae up to age 6 [24]. S100B was positively correlated with the severity of the disease and the risk of neurodevelopmental sequelae and death [25]. The elevation of plasma S100B in patients with preeclampsia may be secondary to cerebral vascular injury, suggesting that the brain is involved in the occurrence of preeclampsia [26]. In addition, for preeclampsia, reactive oxygen species (ROS) are produced by oxidative stress, which can increase S100B levels in amnion [27]. In a previous study, the severe preeclampsia showed higher S100B levels than the mild preeclampsia or normotensive [28]. Levels of S100B remained higher in women who had experienced preeclampsia in one year postpartum than those with previous normal pregnancies [29, 30]. S100B should be a potential biomarker of the central nervous system (CNS), as well as in perinatal development and damage [31]. S100B is also applied to monitor the effect of maternal prenatal treatment, such as the administration of NO and glucocorticoids [32]. In this study, compared to the control, increased expression levels of S100B protein in maternal blood and amniotic fluid of pregnant women with early-onset severe preeclampsia were found.

Previous studies reported that ELISA can be used to detect changes in S100B concentration in serum and cerebrospinal fluid (CSF) with high sensitivity and specificity, and it should be a simple diagnosis tool for preeclampsia [32, 33]. SPRi is a label-free, real-time method to monitor and diagnose fetal diseases [34, 35]. This study indicated that there are significant differences in concentrations of S100B in maternal blood between the two groups assayed by ELISA and SPRi. Previous studies showed that high S100B protein levels indicate development of PBI [24]. Additionally, the Youden index of SPRi-S100B in pregnant women's blood and amniotic fluid were higher than the control, indicating a greater diagnostic value. Based on these results, it was believed that the SPRi-S100B used as an indicator of early-onset severe preeclampsia is better than that of ELISA-S100B. Overall, our experiments provide real-time, non-invasive, and relative quantitative estimates of early-onset severe preeclampsia, as well as preliminary evidence for monitoring, diagnosing, and predicting early-onset severe preeclampsia.

Limitations

This is a study with fewer cases from a single center, so results may not accurately represent populations in different geographic areas. Future studies will require more patients and careful matching of key clinical indicators to ultimately quantify the potential clinical value of PBI and early onset of severe preeclampsia using the SPRi-S100B.

CONCLUSIONS

Increased levels of S100B are found in maternal blood and amniotic fluid of pregnant women with early-onset severe preeclampsia compared to healthy pregnant women. There was a positive correlation in S100B concentration between maternal blood and amniotic fluid. SPRi-S100B is sensitive to ELISA-S100B for the diagnosis of early onset of severe preeclampsia and PBI.

Article information and declarations

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Conflict of interest

The authors declare that they have no competing interests.

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