Journal of the American Heart Association

ORIGINAL RESEARCH

Endothelial Activation and Stress Index Is Associated With Adverse Maternal and Perinatal Outcomes in Preeclampsia

Anna S. Scholz, MD; Annabel Kussner; Michael Elsässer, MD; Thomas Luft, MD, PhD; Stephanie Wallwiener, MD; Alexandra von Au, MD

BACKGROUND: Endothelial dysfunction represents a key driver in the development of preeclampsia. The Endothelial Activation and Stress Index (EASIX) is a validated predictor of endothelial-related complications in diverse clinical settings beyond obstetrics. Therefore, we aimed to assess the predictive performance of EASIX for adverse maternal and perinatal outcomes in pregnancies with preeclampsia.

METHODS: This retrospective study analyzed data from 986 patients with preeclampsia who delivered at Heidelberg University Hospital between 2017 and 2022. The primary end points were adverse maternal (death; kidney failure; pulmonary edema; eclampsia; disseminated intravascular coagulation; hemorrhage; cerebrovascular event; and hemolysis, elevated liver enzymes, low platelets syndrome); and perinatal events (death, stillbirth, preterm delivery, placental abruption, respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis). EASIX was calculated as a product of lactate dehydrogenase and creatinine, both divided by platelet counts.

RESULTS: Five hundred forty-two patients were eligible for the analysis. EASIX was significantly elevated in patients with a maternal adverse event (1.41±0.86 versus 0.87±0.5, P<0.0001) or perinatal adverse event (1.05±0.65 versus 0.93±0.59, P=0.046) compared with patients without an adverse event. EASIX was independently associated with adverse maternal (adjusted odds ratio [aOR], 2.90 [2.00–4.19]) and perinatal events (aOR, 2.02 [1.21–3.39]). These associations were emphasized when stratifying for early-onset preeclampsia. EASIX levels of the highest tertile were associated with the shortest remaining time to delivery (adjusted hazard ratio, 2.10 [1.66–2.66]).

CONCLUSIONS: Our findings underline EASIX as an easily available predictive marker of the risk of maternal and perinatal adverse outcomes in patients with preeclampsia. We propose that EASIX may be useful to stratify the individual risk of adverse events, especially in patients with early-onset preeclampsia.

Key Words: adverse maternal outcome ■ adverse perinatal outcome ■ endothelial dysfunction ■ prediction ■ preeclampsia

With an incidence of up to 8% of all pregnancies, preeclampsia constitutes one of the most feared obstetric challenges.[1] Preeclampsia is defined as hypertension combined with features of multiorgan dysfunction and can progress rapidly to severe adverse outcomes affecting both the mother and the fetus.[2] Preeclampsia-related complications, such as hemolysis, elevated liver enzymes, and low platelets syndrome; stroke; kidney failure; or intrauterine growth restriction aggravate both maternal and perinatal morbidity and mortality.[2] Prediction tools to accurately identify vulnerable patients with preeclampsia prone to develop adverse maternal and perinatal outcomes are of paramount importance to guide clinical care and to

Correspondence to: Anna S. Scholz, MD, Heidelberg University Hospital, Department of Gynecology and Obstetrics, Im Neuenheimer Feld 440, Heidelberg 69120, Germany. Email: anna.scholz@med.uni-heidelberg.de

This article was sent to Tochukwu M. Okwuosa, DO, Associate Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.125.041059

For Sources of Funding and Disclosures, see page 9.

JAHA is available at: www.ahajournals.org/journal/jaha

RESEARCH PERSPECTIVE

What Is New?

- The Endothelial Activation and Stress Index (EASIX) represents a new, simple, easily available score consisting of lactate dehydrogenase, creatinine, and platelet counts, and is a validated predictor for endothelial-related complications in various clinical settings beyond obstetrics.
- For the first time, EASIX was assessed in a retrospective cohort of 542 patients with preeclampsia, showing a significant association with the risk for both adverse maternal and perinatal outcomes.
- The predictive performance for adverse events was enhanced when stratifying for early-onset preeclampsia, and patients with the highest EASIX values demonstrated a significantly reduced remaining duration of pregnancy.

What Question Should Be Addressed Next?

- Our findings underline EASIX as a promising marker of elevated endothelial dysfunction in the prediction of preeclampsia-related adverse outcomes, especially in patients with early-onset preeclampsia.
- This work will stimulate future research on how to integrate EASIX into clinical care to aid individual risk stratification and guide clinical decision-making on application of antenatal corticosteroids and timing of delivery.
- Future studies should focus on a further characterization of EASIX in the context of hypertensive disorder of pregnancy.

Nonstandard Abbreviations and Acronyms

CPR	cerebro-placental ratio
EASIX	Endothelial Activation and Stress Index

optimize administration of antenatal corticosteroids to enhance fetal lung maturity before 34 weeks' gestation and the timing of delivery.

Endothelial dysfunction represents one of the key drivers in the pathophysiology of preeclampsia and is the result of insufficient trophoblast invasion in early gestation, chronic placental hypoxia, and a proinflammatory and antiangiogenic environment.[3] Changes in endothelial and vascular function in preeclampsia have been demonstrated through reduced flow-mediated vasodilation as a result of reduced availability of NO,[4] which potentially persists up to several years postpartum.[4] In addition, video capillaroscopy was able to visualize a reduced microvascular perfusion mediated by glycocalyx degradation.[5] These vascular remodeling processes characterize preeclampsia as a female-specific cardiovascular risk factor[6] for long-term cardiovascular, cerebrovascular, and renal complications after preeclampsia.[7–9]

Until now, there was no validated, simple biomarker available representing endothelial dysfunction with prognostic value for preeclampsia-related outcomes. Beyond this background, we aimed to investigate if the Endothelial Activation and Stress Index (EASIX) might help to predict the clinical course of preeclampsia. The EASIX is based on the routine parameters lactate dehydrogenase (LDH), creatinine, and platelet counts, thus integrating different mechanisms of systemic endothelial dysfunction. Endothelial dysfunction often targets kidney dysfunction, is typically associated with increased LDH release by endothelial cells, and the interaction between endothelial cells and platelets induces platelet aggregation and consumption. Originally, EASIX was developed by Luft et al as a simple score to predict endothelial-related complications after allogenic stem cell transplantation[10] and to predict the risk of sepsis even before conditioning therapy.[11,12] Subsequent studies revealed that EASIX can be used as a marker of endothelial complications and survival in various clinical settings: EASIX was shown to be associated with the severe course of COVID-19 disease[13] and predicted death of patients with coronary artery disease, irrespective of the timing of coronary catheterization.[14]

This strong link of EASIX and endothelial-related diseases and complications led us to hypothesize that EASIX might be a systemic marker of endothelial dysfunction in the context of preeclampsia. The individual parameters of EASIX have been shown to be predictive for the development of maternal adverse outcomes in preeclampsia.[15,16] To our knowledge, this is the first study that evaluated the predictive performance of EASIX for adverse maternal and perinatal outcomes in patients with preeclampsia.

METHODS

Study Design and Population

This was a single-center retrospective analysis of routinely collected data recorded at the Department of Gynecology and Obstetrics, University Hospital Heidelberg, Heidelberg, Germany. The local ethics committee of the medical faculty of the Ruprecht-Karls University Heidelberg (S-680/2023) approved the study and confirmed that no written informed consent was required from the study participants. The data that support the findings of this study are available from the corresponding author upon reasonable request. The

study adheres to the Strengthening the reporting of observational studies in epidemiology (STROBE) guidelines for observational cohort studies, including the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) extension, and all methods were performed in accordance with the Declaration of Helsinki. All patients with documented *International Classification of Diseases, Tenth Revision* (*ICD-10*) codes O10 (chronic hypertension), O11 (superimposed preeclampsia), O13 (pregnancy-induced hypertension), and O14 (preeclampsia) who delivered at our department between 2017 and 2022 were considered eligible for the analysis. *ICD-10* codes were extended to hypertensive disorders beyond preeclampsia, because the definition of preeclampsia had changed during the observational period.[2] Individual patient records were reviewed to confirm the diagnosis of preeclampsia according to the International Society for the Study of Hypertension in Pregnancy 2021 defined as elevated blood pressure in pregnancy in combination with any end-organ dysfunction.[2]

We excluded women who had a history of severe cardiovascular or renal disease, SARS-CoV-2 infection during pregnancy as potential confounder of endothelial dysfunction, and any other diseases that could affect the level of platelets, LDH, or creatinine. If a woman had multiple pregnancies complicated by preeclampsia during the observational period, only the outcome of the first pregnancy was analyzed. Women who presented with a preeclampsia-related adverse event directly at the time of the first EASIX measurement were also excluded. Further exclusion criteria were any fetal chromosomal, genetic, or structural anomalies and missing data such as incomplete patient files or missing laboratory parameters. Multiples were included, and the data of the neonate with the worse outcome were documented.

Endothelial Activation and Stress Index

Routinely assessed laboratory parameters were used to calculate the EASIX constructed by LDH (units per liter)×creatinine (milligrams per deciliter) divided by platelet count (cells per nanoliter). The first available EASIX score after diagnosis of preeclampsia was used for the analysis.

Outcomes

The primary outcome was the occurrence of any maternal and/or perinatal adverse event. The composite adverse maternal outcome included death, acute kidney failure according to the Kidney Disease Improving Global Outcomes definition (increase in creatinine of ≥0.3 mg/dL [≥26.5 μmoL/L] within 48 hours, an increase of ≥1.5 times from baseline within 7 days, or urine volume <0.5 mL/kg per hour for 6 hours),[17] pulmonary edema, eclampsia or any other cerebrovascular event, disseminated intravascular coagulation, postpartum hemorrhage, and the hemolysis, elevated liver enzymes, low platelets syndrome defined as increased transaminases more than twice the upper reference interval with platelets <100 cells/nL with at least 1 hemolysis criterion (LDH ≥2 times the upper reference limit or indirect bilirubin >1.2 mg/dL or haptoglobin <0.3 g/L). The composite perinatal end point consisted of death during the first week after delivery, stillbirth, preeclampsia-related preterm delivery <34 weeks, placental abruption, respiratory distress syndrome, intraventricular hemorrhage, and necrotizing enterocolitis.

Secondary end points included individual events of the composite outcomes and intrauterine growth restriction, admission to the intensive care unit, and thromboembolism.

The maternal and perinatal outcomes covered the core outcome set for preeclampsia.[2,18]

Statistical Analysis

Descriptive statistics are presented as means±SDs or medians with interquartile ranges for continuous variables and absolute numbers and percentages for categorical variables. Distribution was evaluated by inspection of histograms. *P* values <0.05 were considered statistically significant and were calculated using the Mann-Whitney *U* test, *t* test, or χ^2 test. Univariate predictors for the multivariate logistic regression model were chosen a priori and included maternal and gestational age, body mass index, gestational diabetes, estimated fetal weight, cerebro-placental ratio, glutamic oxaloacetic transaminase, C-reactive protein, and uric acid. These risk factors have been reported to be altered in patients with preeclampsia or to be associated with adverse pregnancy outcomes.[19,20] These potential confounders and EASIX were added to the multivariate model in a backward stepwise logistic regression model. Logarithmic transformations were used for estimated fetal weight, glutamic oxaloacetic transaminase, and C-reactive protein to normalize skewed distribution. Our data revealed a parametric distribution of EASIX. Existing literature reports the log2-transformed EASIX,[14,21] and we additionally calculated the regression models with the log2-transformed EASIX. The final multivariate model included EASIX, body mass index, gestational age, and uric acid. Odds ratios with 95% CIs were calculated. Receiver operating characteristic curve analyses were performed to evaluate the discriminatory power of EASIX levels in association with preeclampsia-related adverse events. The estimates of the Preeclampsia Integrated Estimate of Risk (fullPIERS)[22,23] model were calculated by implementing the logistic regression term into our database (–logit(pi)=2.68+[–5.41×10^{-2}; gestational age at eligibility]+1.23[chest pain or dyspnea]+[–2.71×10^{-2};

creatinine]+[2.07×10^{-1}; platelets]+[4.00×10^{-5}; platelets^2]+[1.01×10^{-2}; aspartate transaminase]+[−3.05×10^{-6}; aspartate aminotransferase^2]+[2.50×10^{-4}; creatinine ×platelet]+[−6.99×10^{-5}; platelet×aspartate transaminase)+(−2.56×10^{-3}; platelet×Spo_2]).[24] Kaplan-Meier curves were calculated for EASIX stratified into tertiles based on the analysis set of all women with preeclampsia to compare the remaining time until delivery. Cox proportional hazards models were calculated for the second and third tertile, with the lowest tertile as the reference. The adjusted model included the covariates of the aforementioned multivariate model. Subgroup analyses were performed for early-onset and late-onset preeclampsia depending on the diagnosis of preeclampsia before or after 34 weeks of gestation. To evaluate a possible effect modification by these subgroups, we conducted an interaction term approach. Statistical analyses were conducted in IBM SPSS Statistics 29.0 (IBM, Armonk, NY) and Prism 9.5.0 (GraphPad Prism Software, San Diego, CA).

RESULTS

A total of 986 patients who delivered at our hospital and had a preeclampsia-related diagnosis between 2017 and 2022 were screened for eligibility. Of those, 542 patients fulfilled the criteria and were included in the final analysis (Figure S1). Mean gestational age was 34.5 weeks at diagnosis of preeclampsia and 35.3 weeks at delivery. The cohort included 197 (36%) patients with early-onset preeclampsia and 86% of patients with preeclampsia developed de novo. Baseline and birth characteristics stratified for adverse maternal and perinatal outcomes are shown in Tables 1 and 2. Several patients experienced >1 adverse event. No maternal death was observed.

Table 1. Baseline Characteristics According to Adverse Maternal Outcome

Variable	No adverse maternal event, n=450	Adverse maternal event, n=92	*P* value
Maternal age, y	32.0±5.5	31.5±5.9	0.464
Prepregnancy body mass index, kg/m^2	28.3±7.2	25.7±6.0	0.001*
Nulliparous	306 (68%)	70 (76%)	0.125
Use of assisted reproductive technology	41 (9%)	10 (11%)	0.599
Multiple pregnancy	47 (10%)	12 (13%)	0.466
Gestational diabetes	88 (20%)	10 (11%)	0.049*
>1 Antihypertensive medication	59 (13%)	26 (28%)	<0.001*
Medical history			
Previous preeclampsia	44 (10%)	7 (8%)	0.516
Diabetes	24 (5%)	3 (3%)	0.405
Chronic hypertension	59 (13%)	15 (16%)	0.416
Birth characteristics			
Gestational age at delivery, wk	35.7±3.4	33.6±3.9	<0.001*
Birth weight, g	2378±857	1913±843	<0.001*
Female sex	224 (50%)	50 (54%)	0.424
Ultrasound parameters at admission			
Estimated fetal weight (percentile)	16 (2–43)	8 (2–30)	0.082
Umbilical artery PI (absolute)	1.10±0.39	1.15±0.32	0.384
Middle cerebral artery PI (absolute)	1.57±0.39	1.59±0.33	0.766
Cerebro-placental ratio (absolute)	1.47±0.51	1.40±0.41	0.452
Laboratory parameters at admission			
C-reactive protein	6.3 (3.0–10.8)	5.6 (2.4–12.8)	0.738
GOT, U/L	25 (19–34)	33 (23–55.5)	<0.001*
Uric acid	5.7±1.6	6.5±2.3	0.002*
Creatinine, mg/dL	0.63±0.13	0.71±0.15	<0.001*
Lactate dehydrogenase, U/L	273±72	325±120	<0.001*
Platelets, cells/nL	223±66	186±59	<0.001*
EASIX	0.87±0.50	1.41±0.86	<0.001*

Data are presented as either absolute or relative numbers (percent), mean±SD, or median (interquartile range) and were compared with a *t* test, Mann-Whitney *U* test, or χ^2 test where appropriate. EASIX indicates Endothelial Activation and Stress Index; GOT, glutamic oxaloacetic transaminase; and PI, pulsatility index.
*indicates statistical significance.

Table 2. Baseline Characteristics According to Adverse Perinatal Outcome

Variable	No adverse perinatal event, n=385	Adverse perinatal event, n=157	*P* value
Maternal age, y	31.8±5.6	32.1±5.6	0.478
Prepregnancy body mass index, kg/m^2	28.0±7.3	27.5±6.5	0.497
Nulliparous	273 (71%)	103 (66%)	0.224
Use of assisted reproductive technology	34 (9%)	17 (11%)	0.470
Multiple pregnancy	46 (12%)	13 (8%)	0.214
Gestational diabetes	83 (22%)	15 (10%)	<0.001*
>1 Antihypertensive medication	37 (10%)	48 (31%)	<0.001*
Medical history			
Previous preeclampsia	31 (8%)	20 (13%)	0.090
Diabetes	22 (6%)	5 (3%)	0.220
Chronic hypertension	40 (10%)	34 (22%)	<0.001*
Birth characteristics			
Gestational age at delivery, wk	37.1±1.7	30.9±3.1	<0.001*
Birth weight, g	2696±639	1325±533	<0.001*
Female sex	197 (51%)	77 (49%)	0.654
Ultrasound parameters at admission			
Estimated fetal weight (percentile)	23 (6–49)	2 (2–14)	<0.001*
Umbilical artery PI (absolute)	0.99±0.23	1.3±0.48	<0.001*
Middle cerebral artery PI (absolute)	1.61±0.37	1.53±0.40	0.133
Cerebro-placental ratio (absolute)	1.60±0.46	1.28±0.48	<0.001*
Laboratory parameters at admission			
C-reactive protein, mg/L	5.8 (2.8–10.1)	7.2 (3.2–13.4)	0.018*
GOT, U/L	25 (20–35)	27 (21–39)	0.130
Uric acid, mg/dL	5.8±1.9	5.9±1.3	0.616
Creatinine, mg/dL	0.64±0.14	0.65±0.13	0.515
Lactate dehydrogenase, U/L	276±83	294±85	0.022*
Platelets, cells/nL	219±68	211±62	0.202
EASIX	0.93±0.59	1.05±0.65	0.046*

Data are presented as either absolute and relative numbers (percent), mean±SD, or median (interquartile range) and were compared with a *t* test, Mann-Whitney *U* test, or χ^2 test where appropriate. EASIX indicates Endothelial Activation and Stress Index; GOT, glutamic oxaloacetic transaminase; and PI, pulsatility index.
*indicates statistical significance.

One neonate died during the first week after delivery. The distribution of EASIX according to the outcomes is visualized in Figure 1. According to other cardiovascular risk factors, EASIX levels were not significantly different when comparing superimposed (0.92±0.53) versus de novo preeclampsia (0.97±0.62, *P*=0.456), and no differences were found between patients with versus without diabetes (0.94±0.66 versus 0.97±0.61, *P*=0.856).

Maternal Adverse Outcome

The composite of maternal adverse outcomes occurred in 92 (17%) patients with preeclampsia. Although 28% of the patients with an adverse event needed multiple antihypertensive medications, only 13% of patients without an adverse event took >1 antihypertensive medication (*P*<0.001) (Table 1). Patients who experienced at least 1 adverse maternal event were delivered earlier (33.6 versus 35.7 weeks, *P*<0.001), with a lower birth weight (1913 versus 2378 g, *P*<0.001), had a lower body mass index before pregnancy (25.7 versus 28.3 kg/m^2, *P*=0.001), and had lower rates of gestational diabetes (20% versus 11%, *P*=0.049). Significant differences in laboratory parameters were observed for liver transaminases, uric acid, as well as for the individual parameters of EASIX (LDH, creatinine, platelets). EASIX values were significantly higher in those patients with a composite adverse maternal outcome compared with those without (1.41±0.86 versus 0.87±0.5, *P*<0.001). Receiver operating characteristics curves demonstrated a significant discrimination for prediction of maternal adverse events by EASIX, with an area under the curve (AUC) of 0.73 (95% CI, 0.68–0.78). In contrast, the validated fullPIERS model[23] only yielded an AUC of 0.67 (95% CI, 0.61–0.73) for predicting adverse maternal events. EASIX was associated with a >3-fold increased risk of

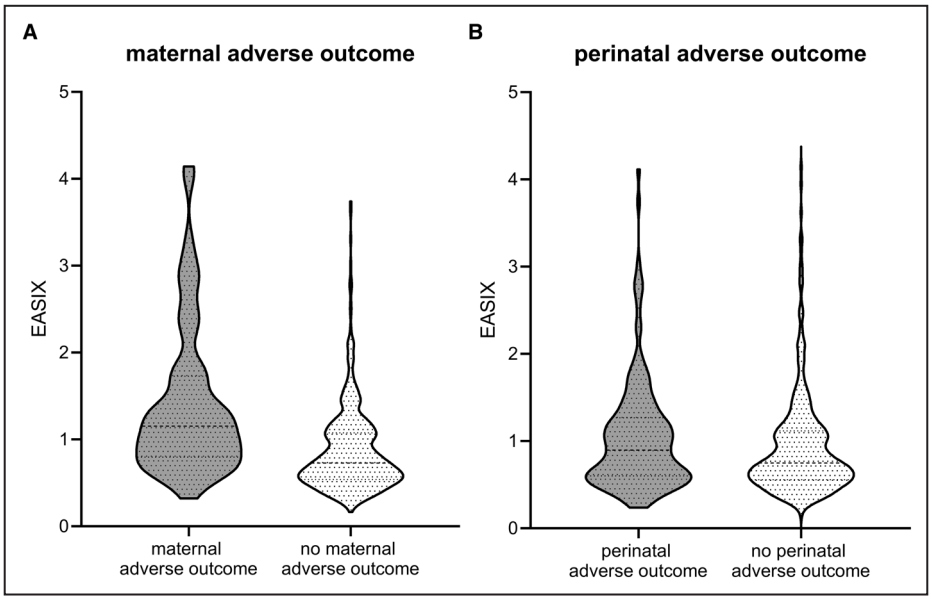
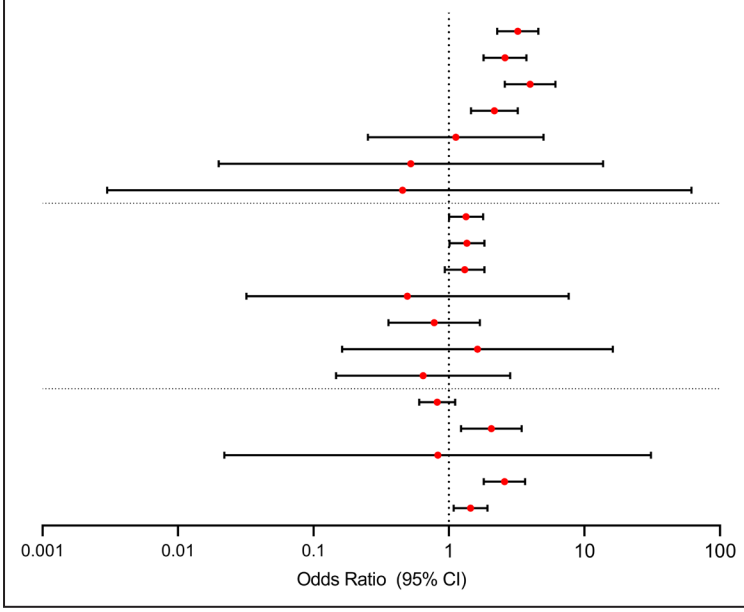


Figure 1. Violin plots of EASIX.
A, EASIX according to maternal adverse outcome and (**B**) according to perinatal adverse outcome. In each violin plot, the horizontal dashed lines represent the median and the lower and upper quartile. EASIX indicates Endothelial Activation and Stress Index.

a subsequent maternal adverse event in patients with preeclampsia (odds ratio [OR], 3.22 [95% CI, 2.27–4.57]). A descriptive analysis of EASIX and individual primary and secondary end points is reported in Figure 2. EASIX revealed a significant association for hemolysis, elevated liver enzymes, low platelets syndrome (OR, 3.97 [95% CI, 2.58–6.10]), acute kidney failure (OR, 2.59 [95% CI, 1.90–3.73]), and postpartum hemorrhage (OR, 2.16 [95% CI, 1.45–3.22]). No association between EASIX and any other secondary maternal end point was detected. In multivariate regression analysis, EASIX remained independently associated with the risk



	n	OR (95% CI)	p value
all maternal events	92	3.22 (2.27-4.57)	<0.001
acute kidney injury	49	2.59 (1.9-3.73)	<0.001
HELLP syndrome	29	3.97 (2.58-6.1)	<0.001
postpartum hemorrhage	36	2.16 (1.45-3.22)	<0.001
pulmonary edema	4	1.12 (0.25-5)	0.879
eclampsia	2	0.52 (0.02-13.74)	0.697
cerebrovascular	1	0.46 (0.003-61.71)	0.753
all perinatal events	157	1.34 (1.00-1.79)	0.49
preterm delivery <34 weeks	138	1.36 (1.01-1.83)	0.043
respiratory distress syndrome	90	1.31 (0.93-1.83)	0.119
necrotizing enterocolitis	3	0.49 (0.03-7.65)	0.612
intraventricular hemorrhage	24	0.78 (0.36-1.69)	0.528
death during first week	1	1.62 (0.16-16.18)	0.681
placental abruption	8	0.64 (0.15-2.83)	0.56
FGR	190	0.82 (0.6-1.11)	0.2
transfusion	18	2.05 (1.23-3.44)	0.006
thrombosis	1	0.83 (0.02-31.00)	0.918
ICU maternal	264	2.57 (1.81-3.65)	<0.001
ICU neonatal	177	1.44 (1.09-1.92)	0.012

Figure 2. EASIX and individual outcome events.
Forest plots illustrating EASIX as predictor of the risk of the composite maternal and perinatal outcomes and descriptive analysis of its individual components and other secondary end points. Values are presented as absolute and relative numbers of patients experiencing the indicated event and OR (95% CI). EASIX indicates Endothelial Activation and Stress Index; FGR, fetal growth restriction; HELLP, hemolysis, elevated liver enzymes, low platelets; ICU, intensive care unit; and OR, odds ratio.

Table 3. Univariate and Multivariate Logistic Regression Analysis for the Prediction of Adverse Maternal and Perinatal Outcomes

	Maternal adverse outcome		Perinatal adverse outcome	
	Univariate	Multivariate*	Univariate	Multivariate*
Variable	OR (95% CI)	aOR (95% CI)	OR (95% CI)	aOR (95% CI)
EASIX (all)	3.2 (2.27–4.57)	2.90 (2.00–4.19)	1.34 (1.0–1.79)	2.02 (1.21–3.39)
EASIX (early-onset)	3.52 (1.99–6.20)	3.10 (1.74–5.53)	4.43 (1.76–11.19)	3.61 (1.23–10.66)
EASIX (late-onset)	3.26 (2.04–5.22)	2.71 (1.66–4.42)	1.1 (0.38–3.17)	1.04 (0.32–3.42)

aOR indicates adjusted odds ratio; EASIX, Endothelial Activation and Stress Index; and OR, odds ratio.
*The multivariate model was calculated by backward stepwise logistic regression and resulted in a model including EASIX, body mass index, gestational age, and uric acid.

of maternal adverse events after adjusting for the a priori defined risk factors (adjusted OR [aOR], 2.90 [95% CI, 2.00–4.19]) (Table 3). When stratifying for early-onset preeclampsia, the performance of EASIX was enhanced for prediction of adverse maternal outcomes (aOR, 3.10 [95% CI, 1.74–5.53]). ORs calculated for a 2-fold change of EASIX (log2-transformed) are reported in Table S1 and revealed comparable results.

Perinatal Adverse Outcome

The rate of perinatal adverse outcomes in patients with preeclampsia was 29%. Patients with perinatal adverse outcomes were more likely to have chronic hypertension and to take >1 antihypertensive medication (P<0.001) (Table 2). They had lower rates of gestational diabetes (P<0.001) and delivered significantly earlier (30.9 versus 37.1 weeks, P<0.001) with subsequently lower birth weights. Prenatal ultrasound parameters such as estimated fetal weight, umbilical artery pulsatility index, and C-reactive protein differed significantly between patients with and without an adverse perinatal outcome. Significant differences in laboratory measurements were observed only for C-reactive protein and LDH. Patients with a perinatal adverse outcome revealed significantly higher EASIX values compared with patients without adverse outcomes (1.05±0.65 versus 0.93±0.59, P=0.046). Receiver operating characteristic curve analysis revealed a weak albeit significant discrimination for the prediction of adverse perinatal events by EASIX, with an AUC of 0.56 (95% CI, 0.51–0.62; P=0.022). The predictive capacity of EASIX was enhanced when stratifying for early-onset preeclampsia (AUC, 0.73 [95% CI, 0.65–0.81]; P<0.001) (Table S2). In multivariate analysis, EASIX was significantly associated with a doubled risk of perinatal adverse outcomes (aOR, 2.02 [95% CI, 1.21–3.39]), which was more pronounced when stratifying for early-onset preeclampsia (aOR, 3.61 [95% CI, 1.23–10.66]) (Table 3). ORs per log2 increase of EASIX showed the same associations (Table S1).

Time to Delivery Analysis

The mean time to delivery was 5.5 days (range, 0–43 days). Women who remained pregnant for >7 days had significantly lower EASIX levels than patients being delivered within <2 days (0.61 [0.45–0.83] versus 0.91 [0.65–1.28], P<0.0001) (Figure S2). Kaplan-Meier curves were used to analyze the remaining time until delivery stratified by EASIX tertiles (Figure 3). After a week, only 20 of 181 (11%) patients with the highest

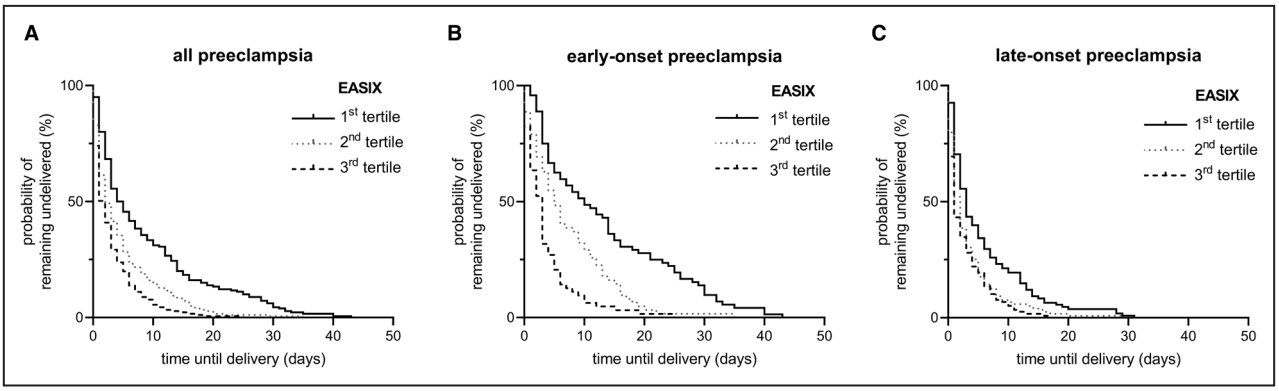


Figure 3. Time to delivery analyses.
The Kaplan-Meier curves summarize the remaining pregnancy duration of patients stratified according to EASIX tertiles (first tertile <0.634 [——], second tertile 0.634–1.036 [····], third tertile >1.036 [– – –]) for the whole cohort (**A**), early-onset (**B**), and late-onset preeclampsia (**C**). EASIX indicates Endothelial Activation and Stress Index.

EASIX tertile remained pregnant. EASIX levels of the highest tertile were associated with the shortest latency until delivery for the total cohort and patients with early- and late-onset preeclampsia (Figure 3A through 3C). Patients with an EASIX value above the third tertile had an >2-fold increased risk for imminent delivery compared with those of the lowest tertile (hazard ratio [HR], 2.25 [95% CI, 1.81–2.8]; adjusted HR [aHR], 2.10 [95% CI, 1.66–2.66]). These effects were pronounced when evaluating patients with early-onset preeclampsia (HR, 3.36 [95% CI, 2.31–4.87]; aHR, 2.88 [95% CI, 1.93–4.30]). For a detailed description of the Cox proportional hazards models see Table S3.

DISCUSSION

To our knowledge, this is the first study that investigated EASIX in the context of preeclampsia as a predictive marker for the risk of adverse maternal and perinatal outcomes. We demonstrated that (1) patients who experienced a preeclampsia-related adverse maternal or perinatal event had elevated EASIX levels; (2) that EASIX was independently associated with an increased risk for adverse events; and (3) that patients with higher EASIX levels were more likely to deliver early.

Endothelial dysfunction is a common pathophysiological link between preeclampsia and multiple other diseases. Because the endothelial response patterns are highly heterogeneous depending on the location, it is difficult to capture the systemic effects of endothelial dysfunction in 1 universal marker. EASIX was originally based on typical laboratory changes of transplant-associated thrombotic microangiopathy, a potentially life-threatening complication after allogenic stem cell transplantation, which is characterized by high LDH and creatinine levels combined with low platelet counts.[10] Similar rises in LDH and creatinine with reduced platelet counts are reported for the closely related atypical hemolytic uremic syndrome.[25] Endothelial dysfunction typically affects kidney function and is characterized by increased LDH release due to cell damage. Damaged endothelial cells interact with circulating platelets leading to platelet activation and aggregation,[26] which subsequently provokes platelet consumption. Angiogenic factors, such as soluble fms-like tyrosine kinase-1/placental growth factor and soluble endoglin were found to correlate with the individual parameters of EASIX in preeclampsia (soluble fms-like tyrosine kinase-1/placental growth factor versus creatinine r=0.55,[27] soluble endoglin versus platelets r=−0.35,[28] soluble endoglin versus LDH r=0.29[28]), whereas EASIX itself correlates with markers of endothelial dysfunction such as angiopoietin-2, soluble thrombomodulin, and interleukin-18.[13] Although our retrospective study cannot provide comparisons with these endothelial biomarkers, our results further highlight preeclampsia as an endothelial disease and suggest how to potentially mirror the extent of the endothelial dysfunction in affected women.

EASIX aims to reflect a preexisting subclinical or clinical endothelial defect that may lead to endothelial complications and mortality. We did not exclude patients with preexisting vascular risk factors, such as hypertension or diabetes, to examine whether EASIX can represent the individual predisposition of an otherwise intact endothelium of becoming dysfunctional only after a triggering event such as a pregnancy or other second hits.[29] In our cohort, patients with superimposed preeclampsia and patients with diabetes did not have significantly more adverse outcomes compared with those without the preexisting disease.

In view of the increased risks of long-term cardiovascular, cerebrovascular, and renal disease after a pregnancy complicated by preeclampsia,[7] a persistence of systemically damaged endothelium must be taken into consideration. Recently, Honigberg et al revealed that the microvascular dysfunction in preeclampsia also involves a reduced coronary function, as demonstrated through cardiac positron emission tomography in the early postpartum period following preeclampsia.[9] There is an unmet urgent clinical need of early detection of patients at risk, especially for preeclampsia-related adverse outcomes. Various laboratory parameters and prognostic tools, such as the fullPIERS model,[22] have been investigated to guide clinical care and to identify those patients at greatest risk and those suitable for expectant management. The fullPIERS model was developed to predict severe preeclampsia-related maternal complications and yielded an excellent discriminatory ability, with an AUC of 0.88 in the original cohort[22] with proven external validity. In contrast, the fullPIERS model performed poorly in our cohort, with an AUC of 0.67. Our findings are supported by Ukah et al, who assessed the fullPIERS model in a cohort of women in tertiary hospitals in the United States and Canada and also reported a low predictive performance for adverse maternal outcomes (AUC, 0.67 [95% CI, 0.58–0.76])[30] and by Mirkovic et al, who found a nonsignificant AUC of 0.63 (95% CI, 0.44–0.82).[31] The authors hypothesized that this discrepancy may be explained by different hospital settings and preeclampsia management protocols,[30] because the fullPIERS cohort was originally developed in settings with a general policy of expectant management.[22] There are some overlapping criteria between fullPIERS and EASIX such as creatinine and platelets. A major concern of the clinical usefulness of fullPIERS is the inclusion of 6 variables and the requirement of an online tool, making it cumbersome compared with the EASIX score, which can be calculated easily.

Binder et al evaluated the predictive potential of longitudinal maternal laboratory measurements for preeclampsia-related adverse outcomes[15] and demonstrated high stand-alone predictive accuracy of the individual parameters of EASIX for adverse maternal outcomes (LDH AUC 0.73, creatinine AUC 0.71, platelets AUC 0.65), which are comparable to the observed high accuracy of EASIX in our study (AUC, 0.73 [95% CI, 0.68–0.78]). Soluble fms-like tyrosine kinase-1/placental growth factor reached a similarly high predictive accuracy for maternal events, with an AUC of 0.72 (95% CI, 0.62–0.81) according to data published by Binder et al.[15]

Interestingly, EASIX revealed an enhanced predictive performance in our cohort after stratification for women with only early-onset preeclampsia. It has been increasingly recognized that women with early- and late-onset preeclampsia present with different clinical features, suggesting distinct underlying pathophysiological mechanisms.[32] Different profiles of angiogenic factors and a different extent of endothelial dysfunction may be responsible for the higher benefit of EASIX in our cohort or soluble fms-like tyrosine kinase-1/placental growth factor as reported by others[15] for the prediction of adverse events in early-onset preeclampsia in contrast to the late-onset group. Recently, Chaiworapongsa et al suggested 3 subgroups of preeclampsia, with 1 early group and 2 groups of preeclampsia at term based on their angiogenic profile.[33] These 2 groups of preeclampsia at term revealed different demographics, clinical characteristics, and preeclampsia-related prognosis. In addition to predicting adverse preeclampsia-related outcomes, EASIX was correlated to the latency until delivery. Patients with the highest EASIX tertiles demonstrated a significantly reduced remaining duration of pregnancy. It is of paramount importance to develop simple, quickly available tools to accurately identify those highly vulnerable patients and to guide individualized obstetric monitoring and care. Especially in patients with early-onset preeclampsia, EASIX showed a high potential to discriminate for patients with a high risk for an early delivery.

Strengths and Limitations

We evaluated EASIX in a large cohort assessing pregnancies with preeclampsia. For the first time, we introduced EASIX in the context of preeclampsia, thus highlighting the predominant role of endothelial dysfunction in the pathophysiology of preeclampsia. Additionally, our study evaluated the totality of preeclampsia and did not only focus on early-onset preeclampsia.

Given the inherent nature of retrospective data analysis, some limitations must be addressed. First, based on the case records, a detailed description of clinical symptoms was often not fully available; especially, ethnic background was not ubiquitously documented. In light of the increased risk of preeclampsia in women with a Afro-Caribbean or South Asian background, expanding our analyses to ethnically diverse populations would be relevant to prove the generalizability of EASIX. Second, because the definition of preeclampsia was extended to any hypertension in pregnancy in combination with at least 1 end-organ manifestation,[2] there were cases that were not diagnosed as preeclampsia during their past hospital stay but needed to be classified as preeclampsia retrospectively. Thus, we cannot exclude that clinical management would have possibly been changed with the knowledge of diagnosed preeclampsia according to current definitions. Third, we analyzed EASIX only at 1 center. Further studies to validate our observations are needed.

PERSPECTIVES

EASIX represents a new, simple, easily available score consisting of LDH, creatinine, and platelet counts. We propose that EASIX may be used to stratify the individual risk of maternal and perinatal adverse outcomes in patients with preeclampsia. The good prognostic performance of EASIX, for both maternal and perinatal adverse events, especially in patients with early-onset preeclampsia, presumably relies on the integration of biomarkers reflecting different mechanisms of systemic endothelial dysfunction, which represents the hallmark of preeclampsia as a multiorgan disease. This work will stimulate future research to further characterize EASIX in the context of preeclampsia and its use for clinical management of preeclampsia.

ARTICLE INFORMATION

Received January 6, 2025; accepted June 6, 2025.

Affiliations

Department of Gynecology and Obstetrics (A.S.S., A.K., M.E., A.v.A.), and Department of Internal Medicine V, Hematology, Oncology and Rheumatology, University Hospital Heidelberg, Heidelberg, Germany (T.L.) and Department of Obstetrics and Fetal Medicine, University Hospital Halle (Saale), Halle, Germany (S.W.).

Sources of Funding

This work was funded by a research grant from the Ernst and Berta Grimmke Foundation (awarded to A. Scholz and A. von Au). For the publication fee we acknowledge financial support by Heidelberg University. The funders had no influence on the study design, data collection and analysis, decision to publish, or preparation of the article.

Disclosures

None.

Supplemental Material

Tables S1–S3
Figures S1–S2

REFERENCES

1. Bruno AM, Allshouse AA, Metz TD, Theilen LH. Trends in hypertensive disorders of pregnancy in the United States from 1989 to 2020. *Obstet Gynecol*. 2022;140:83–86. doi: 10.1097/AOG.0000000000004824
2. Magee LA, Brown MA, Hall DR, Gupte S, Hennessy A, Karumanchi SA, Kenny LC, McCarthy F, Myers J, Poon LC, et al. The 2021 international society for the study of hypertension in pregnancy classification, diagnosis & management recommendations for international practice. *Pregnancy Hypertens*. 2022;27:148–169. doi: 10.1016/j.preghy.2021.09.008
3. Opichka MA, Rappelt MW, Gutterman DD, Grobe JL, McIntosh JJ. Vascular dysfunction in preeclampsia. *Cells*. 2021;10:3055. doi: 10.3390/cells10113055.
4. Weissgerber TL, Milic NM, Milin-Lazovic JS, Garovic VD. Impaired flow-mediated dilation before, during, and after preeclampsia: a systematic review and meta-analysis. *Hypertension*. 2016;67:415–423. doi: 10.1161/HYPERTENSIONAHA.115.06554
5. Weissgerber TL, Garcia-Valencia O, Milic NM, Codsi E, Cubro H, Nath MC, White WM, Nath KA, Garovic VD. Early onset preeclampsia is associated with glycocalyx degradation and reduced microvascular perfusion. *J Am Heart Assoc*. 2019;8:e010647. doi: 10.1161/JAHA.118.010647
6. Garovic VD, Dechend R, Easterling T, Karumanchi SA, McMurtry Baird S, Magee LA, Rana S, Vermunt JV, August P; American Heart Association Council on Hypertension; Council on the Kidney in Cardiovascular Disease, Kidney in Heart Disease Science Committee; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Lifestyle and Cardiometabolic Health; Council on Peripheral Vascular Disease; and Stroke Council. Hypertension in pregnancy: diagnosis, blood pressure goals, and pharmacotherapy: a scientific statement from the american heart association. *Hypertension*. 2022;79:e21–e41. doi: 10.1161/HYP.0000000000000208
7. Scholz AS, Hassdenteufel K, Gutsfeld R, Muller M, Goetz M, Bauer A, Wallwiener M, Brucker SY, Joos S, Colombo MG, et al. Observational database study on preeclampsia and postpartum medical care up to 7.5years after birth. *Sci Rep*. 2022;12:21230. doi: 10.1038/s41598-022-25596-2
8. Hassdenteufel K, Muller M, Gutsfeld R, Goetz M, Bauer A, Wallwiener M, Brucker SY, Joos S, Colombo MG, Hawighorst-Knapstein S, et al. Long-term effects of preeclampsia on maternal cardiovascular health and postpartum utilization of primary care: an observational claims data study. *Arch Gynecol Obstet*. 2022;307:275–284. doi: 10.1007/s00404-022-06561-w
9. Honigberg MC, Economy KE, Pabon MA, Wang X, Castro C, Brown JM, Divakaran S, Weber BN, Barrett L, Perillo A, et al. Coronary microvascular function following severe preeclampsia. *Hypertension*. 2024;81:1272–1284. doi: 10.1161/HYPERTENSIONAHA.124.22905
10. Luft T, Benner A, Jodele S, Dandoy CE, Storb R, Gooley T, Sandmaier BM, Becker N, Radujkovic A, Dreger P, et al. Easix in patients with acute graft-versus-host disease: a retrospective cohort analysis. *Lancet Haematol*. 2017;4:e414–e423. doi: 10.1016/S2352-3026(17)30108-4
11. Korell F, DeFilipp Z, Schreck N, Luft T; Taskforces Allogeneic Stem Cell T. Validation of pre-conditioning easix for prediction of sepsis after allogeneic stem cell transplantation. *Intensive Care Med*. 2023;49:1408–1410. doi: 10.1007/s00134-023-07193-7
12. Korell F, Penack O, Mattie M, Schreck N, Benner A, Krzykalla J, Wang Z, Schmitt M, Bullinger L, Müller-Tidow C, et al. Easix and severe endothelial complications after cd19-directed car-t cell therapy-a cohort study. *Front Immunol*. 2022;13:877477. doi: 10.3389/fimmu.2022.877477
13. Luft T, Wendtner CM, Kosely F, Radujkovic A, Benner A, Korell F, Kihm L, Bauer MF, Dreger P, Merle U. Easix for prediction of outcome in hospitalized sars-cov-2 infected patients. *Front Immunol*. 2021;12:634416. doi: 10.3389/fimmu.2021.634416
14. Finke D, Hund H, Frey N, Luft T, Lehmann LH. Easix (endothelial activation and stress index) predicts mortality in patients with coronary artery disease. *Clin Res Cardiol*. 2024.
15. Binder J, Palmrich P, Kalafat E, Haberl C, Schirwani N, Pateisky P, Khalil A. Longitudinal assessment of angiogenic markers in prediction of adverse outcome in women with confirmed pre-eclampsia. *Ultrasound Obstet Gynecol*. 2023;62:843–851. doi: 10.1002/uog.26276
16. Burwick RM, Rincon M, Beeraka SS, Gupta M, Feinberg BB. Evaluation of hemolysis as a severe feature of preeclampsia. *Hypertension*. 2018;72:460–465. doi: 10.1161/HYPERTENSIONAHA.118.11211
17. Khwaja A. Kdigo clinical practice guidelines for acute kidney injury. *Nephron Clin Pract*. 2012;120:c179–c184. doi: 10.1159/000339789
18. Lai J, Syngelaki A, Nicolaides KH, von Dadelszen P, Magee LA. Impact of new definitions of preeclampsia at term on identification of adverse maternal and perinatal outcomes. *Am J Obstet Gynecol*. 2021;224:518.e511
19. Rana S, Powe CE, Salahuddin S, Verlohren S, Perschel FH, Levine RJ, Lim KH, Wenger JB, Thadhani R, Karumanchi SA. Angiogenic factors and the risk of adverse outcomes in women with suspected preeclampsia. *Circulation*. 2012;125:911–919. doi: 10.1161/CIRCULATIONAHA.111.054361
20. Tangeras LH, Austdal M, Skrastad RB, Salvesen KA, Austgulen R, Bathen TF, Iversen AC. Distinct first trimester cytokine profiles for gestational hypertension and preeclampsia. *Arterioscler Thromb Vasc Biol*. 2015;35:2478–2485. doi: 10.1161/ATVBAHA.115.305817
21. Luft T, Benner A, Terzer T, Jodele S, Dandoy CE, Storb R, Kordelas L, Beelen D, Gooley T, Sandmaier BM, et al. Easix and mortality after allogeneic stem cell transplantation. *Bone Marrow Transplant*. 2020;55:553–561. doi: 10.1038/s41409-019-0703-1
22. von Dadelszen P, Payne B, Li J, Ansermino JM, Broughton Pipkin F, Cote AM, Pipkin FB, Douglas MJ, Gruslin A, Hutcheon JA, et al. Prediction of adverse maternal outcomes in pre-eclampsia: development and validation of the fullpiers model. *Lancet*. 2011;377:219–227. doi: 10.1016/S0140-6736(10)61351-7
23. Ukah UV, Payne B, Hutcheon JA, Ansermino JM, Ganzevoort W, Thangaratinam S, Magee LA, von Dadelszen P. Assessment of the fullpiers risk prediction model in women with early-onset preeclampsia. *Hypertension*. 2018;71:659–665. doi: 10.1161/HYPERTENSIONAHA.117.10318
24. Boutot M, Margueritte F, Boukeffa N, Coste Mazeau P, Aubard Y, Gauthier T. Validation externe du modele FullPIERS dans la pré-éclampsie à partir d'une série française de 4ans. *Gynecol Obstet Fertil Senol*. 2020;48:167–173. doi: 10.1016/j.gofs.2020.01.002
25. Bitzan M, Hammad RM, Bonnefoy A, Al Dhaheri WS, Vezina C, Rivard GE. Acquired thrombotic thrombocytopenic purpura with isolated cfhr3/1 deletion-rapid remission following complement blockade. *Pediatr Nephrol*. 2018;33:1437–1442. doi: 10.1007/s00467-018-3957-8
26. Michelson AD, Barnard MR, Krueger LA, Valeri CR, Furman MI. Circulating monocyte-platelet aggregates are a more sensitive marker of in vivo platelet activation than platelet surface p-selectin: studies in baboons, human coronary intervention, and human acute myocardial infarction. *Circulation*. 2001;104:1533–1537. doi: 10.1161/hc3801.095588
27. Molvarec A, Szarka A, Walentin S, Szucs E, Nagy B, Rigo J Jr. Circulating angiogenic factors determined by electrochemiluminescence immunoassay in relation to the clinical features and laboratory parameters in women with pre-eclampsia. *Hypertens Res*. 2010;33:892–898. doi: 10.1038/hr.2010.92
28. Leanos-Miranda A, Navarro-Romero CS, Sillas-Pardo LJ, Ramirez-Valenzuela KL, Isordia-Salas I, Jimenez-Trejo LM. Soluble endoglin as a marker for preeclampsia, its severity, and the occurrence of adverse outcomes. *Hypertension*. 2019;74:991–997. doi: 10.1161/HYPERTENSIONAHA.119.13348
29. Luft T, Dreger P, Radujkovic A. Endothelial cell dysfunction: a key determinant for the outcome of allogeneic stem cell transplantation. *Bone Marrow Transplant*. 2021;56:2326–2335. doi: 10.1038/s41409-021-01390-y
30. Ukah UV, Payne BA, Hutcheon JA, Chappell LC, Seed PT, Conti-Ramsden FI, Ansermino JM, Magee LA, von Dadelszen P. Placental growth factor for the prognosis of women with preeclampsia (fullpiers model extension): context matters. *BMC Pregnancy Childbirth*. 2020;20:1–9.
31. Mirkovic L, Tulic I, Stankovic S, Soldatovic I. Prediction of adverse maternal outcomes of early severe preeclampsia. *Pregnancy Hypertens*. 2020;22:144–150. doi: 10.1016/j.preghy.2020.09.009
32. Powers RW, Roberts JM, Plymire DA, Pucci D, Datwyler SA, Laird DM, Sogin DC, Jeyabalan A, Hubel CA, Gandley RE. Low placental growth factor across pregnancy identifies a subset of women with preterm preeclampsia: type 1 versus type 2 preeclampsia? *Hypertension*. 2012;60:239–246. doi: 10.1161/HYPERTENSIONAHA.112.191213
33. Chaiworapongsa T, Romero R, Gotsch F, Suksai M, Gallo DM, Jung E, Krieger A, Chaemsaithong P, Erez O, Tarca AL. Preeclampsia at term can be classified into 2 clusters with different clinical characteristics and outcomes based on angiogenic biomarkers in maternal blood. *Am J Obstet Gynecol*. 2023;228:569. e561–e524