

Article

Combination of Maternal Serum ESM-1 and PLGF with Uterine Artery Doppler PI for Predicting Preeclampsia

Xianjing Xie ^{1,2,†}, Dan Chen ^{1,2,3,†}, Xingyu Yang ^{1,2,4}, Yunyun Cao ¹, Yuna Guo ^{1,*} and Weiwei Cheng ^{1,2,*} 

¹ International Peace Maternity and Child Health Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200030, China

² Shanghai Key Laboratory of Embryo Original Diseases, Shanghai 200030, China

³ Department of Obstetrics and Gynecology, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200127, China

⁴ Institute of Birth Defects and Rare Diseases, School of Medicine, Shanghai Jiao Tong University, Shanghai 200030, China

* Correspondence: gyna@live.com (Y.G.); wwcheng29@shsmu.edu.cn (W.C.);
Tel./Fax: +86-21-64070434 (Y.G. & W.C.)

† These authors contributed equally to this work.

Abstract: Objective: This study aimed to determine whether the combination of pregnancy-associated endothelial cell-specific molecule 1 (ESM-1), the placental growth factor (PLGF) in the first- and second-trimester maternal serum, and the uterine artery Doppler pulsatility index (PI) in the second trimester can predict preeclampsia (PE). Methods: The serum levels of ESM-1 and PLGF in 33 severe preeclampsia (SPE) patients, 18 mild preeclampsia patients (MPE), and 60 age-matched normal controls (CON) were measured. The Doppler ultrasonography was performed, and the artery pulsatility index (PI) was calculated for the same subjects. Results: The 2nd PLGF level was significantly lower and the 2nd PI was higher than those in the MPE group. Combining the 2nd PLGF with the 2nd PI yielded an AUC of 0.819 (83.33% sensitivity and 70.00% specificity). In the SPE group, the 1st ESM-1 level and the 2nd PLGF level were significantly lower, and the 2nd ESM-1 level and the 2nd PI were significantly higher in the SPE group. The combination of the 1st ESM-1, the 2nd PLGF, and the 2nd PI yielded an AUC of 0.912 (72.73% sensitivity and 95.00% specificity). Conclusions: The 1st ESM-1 and the 2nd PLGF levels and the 2nd PI were associated with PE. The combination of serum biomarkers and the PI improved the screening efficiency of the PE prediction, especially for SPE.

Keywords: preeclampsia; ESM-1; PLGF; uterine artery Doppler; PI; prediction



Citation: Xie, X.; Chen, D.; Yang, X.; Cao, Y.; Guo, Y.; Cheng, W. Combination of Maternal Serum ESM-1 and PLGF with Uterine Artery Doppler PI for Predicting Preeclampsia. *J. Clin. Med.* **2023**, *12*, 459. <https://doi.org/10.3390/jcm12020459>

Academic Editor: Silvia Lobmaier

Received: 6 December 2022

Revised: 27 December 2022

Accepted: 3 January 2023

Published: 6 January 2023



Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Preeclampsia (PE) is a major cause of morbidity and mortality among pregnant women and infants, resulting in an estimated 76,000 maternal deaths and 500,000 fetal and newborn deaths every year [1]. The etiology of PE is still an enigma; currently, the most widely accepted theory for the development of PE is the “two-stage” theory. The first stage is reduced placental perfusion, and the second stage is generalized maternal endothelial dysfunction. Abnormal vascular growth and impaired endothelial function are considered to be the main components of the pathogenesis [2]. The imbalance between the antiangiogenic and proangiogenic factors is considered to be the link between the two stages. The expression of the antiangiogenic and angiogenic factors is altered in PE [3].

Endocan, an antiangiogenic factor which is also called endothelial cell-specific molecule-1 (ESM-1), was originally identified in cultured endothelial cells [4]. Several studies have shown that ESM-1 could be a novel biomarker of various diseases with endothelial dysfunction and inflammation, such as newly diagnosed hypertension [5]. A recent meta-analysis suggested that women with PE had a higher level of circulating ESM-1 than women with normal pregnancies [6].

Placental growth factor (PLGF), produced by villous syncytiotrophoblasts, is thought to induce nonbranching angiogenesis, leading to a low-resistance placental vascular network [7,8]. Limited angiogenesis in early PE pregnancies, with a shallow vascular invasion of the maternal spiral arteries, results in the subsequent placental hypoperfusion [9]. Many studies have revealed that angiogenic factors such as PLGF are decreased in the serum of PE patients [10,11]. PLGF has been proven to be a useful screening tool for PE prediction [12].

Spiral artery transformation failure in PE could lead to an increase in uterine artery blood flow resistance [13], which could be captured as an abnormality, such as by the presence of an impedance on the uterine artery Doppler. These changes support the uterine artery Doppler velocimetry-based screening of patients who are at risk of developing PE [14]. Furthermore, some studies have shown that uterine artery PI is a promising marker for predicting PE [15,16].

The objective of our study was to evaluate the maternal serum ESM-1 and the PLGF levels in the first and second trimesters and the uterine artery Doppler PI in the second trimester and to determine whether the integration of these biomarkers with the 2nd PI would be helpful in the prediction of PE.

2. Patients and Methods

2.1. Patients

This was a prospective study. Women with singleton pregnancies who presented at the International Peace Maternity and Child Health Hospital, Shanghai, China, from 2020 to 2021 for prenatal examination were eligible for inclusion. The exclusion criteria were multiple pregnancies, chronic hypertension, chronic renal disease or pre-existing proteinuria, diabetes, malignancy, autoimmune disorders, acute systemic inflammation, fever, premature rupture of membranes, preterm labor, or major congenital fetal anomaly. The study was conducted according to the Declaration of Helsinki guidelines and the approval of the National Ethics Committee for Science and Technology (number: GKLW2020-03). All the participants were followed from the first trimester to delivery, with pregnancy outcomes recorded and written informed consent provided.

The definition of the severe preeclampsia (SPE) group was as follows:

- (1) Blood pressure $\geq 160/110$ mm Hg on two occasions at least 4 h apart (unless antihypertensive therapy was initiated before this time);
- (2) Thrombocytopenia: platelet count $<100 \times 10^9/L$;
- (3) Renal insufficiency: serum creatinine concentrations >1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal diseases;
- (4) Impaired liver function: elevated blood concentrations of liver transaminases to twice the normal concentration;
- (5) Pulmonary edema;
- (6) New-onset headache unresponsive to medication and not accounted for by alternative diagnoses or visual symptoms.

The mild preeclampsia (MPE) group was described as follows:

- (1) Blood pressure $\geq 140/90$ mmHg on two occasions at least 4 h apart after 20 weeks of gestation in a woman with previously normal blood pressure;
- (2) Three hundred milligrams or more per 24 h of urine collection (or this amount extrapolated from a timed collection) or a protein/creatinine ratio ≥ 0.3 mg/dL or a dipstick reading of 2+.

2.2. Maternal Serum Analytes

Peripheral venous blood samples were collected from all the participants during two different periods: the first trimester, at 9–13⁺⁶ weeks of gestation, and the second trimester, at 24–28 weeks of gestation. All the blood samples were centrifuged at 3000 rpm for 10 min, and the serum samples were stored at -80 °C until use.

All the samples from the subsequently diagnosed PE patients based on the ACOG guidelines [17] and gestational age and storage time-matched control (CON) pregnancies

were retrieved. The ESM-1 and PLGF levels were measured using the enzyme-linked immunosorbent assay (ELISA) (R&D Systems, Minneapolis, MN, USA) by technicians who were blinded to the identity of the samples. The accuracy and stability of the ELISA method were validated in the pilot experiments. Each sample was measured three times and the average level was used as the final value for the sample. The ESM-1 kit detection range was 10.3–2500 pg/mL. The kit performance characteristics were a sensitivity of 1.08 pg/mL and a coefficient of variation (CV%) of <10. The PLGF kit detection range was 2.88–700 pg/mL. The kit performance characteristics were a sensitivity of 1.9 pg/mL and a coefficient of variation (CV%) of <10.

2.3. Uterine Artery PI

The patients without fetal defects on routine ultrasound performed at 22–28 weeks of gestation also underwent a bilateral uterine artery Doppler assessment. The uterine artery PI was determined as the average PI from three continuous similar waveforms. All the examinations were evaluated by ultrasound by simultaneous B-mode scanning (GE Healthcare, Milwaukee, WI, USA). The carrier frequency was from 1 to 5 MHz for the transabdominal probes.

2.4. Statistical Analysis

The data analysis was performed using SPSS 25.0 (SPSS Inc., Chicago, IL, USA) and MedCalc (version 11.4.2.0). The data are presented as the mean \pm SD or median (min-max). Logistic regression analysis was used to evaluate the combination of these indicators. Receiver operating characteristic (ROC) curve analysis was performed to assess the predictive value. Statistically significant differences were estimated utilizing the Student's *t*-tests or chi-square tests. A *p* value < 0.05 was considered statistically significant.

3. Results

In total, 2086 pregnant women were recruited for the study. Among them, 1927 pregnant women completed the study, and 159 (7.6%) did not give birth in our hospital and were lost to the follow-up. Fifty-one women developed PE (severe preeclampsia (SPE) 33 cases and mild preeclampsia (MPE) 18 cases), with an incidence rate of 2.6%, which was consistent with that in the literature [18]. The CON group comprised 60 women with normal pregnancies who were randomly chosen and matched for gestational age to the women with PE. The flowchart of our prospective cohort study was shown in Figure 1.

The clinical and demographic characteristics of the participants are presented in Table 1. Compared with those in the CON group, the blood pressures of all those in the PE groups were higher ($p < 0.001$). The gestational age at delivery and the fetal weights were significantly lower in the PE group, especially in the SPE group ($p < 0.001$). The placental weights were lower in the SPE group ($p < 0.05$). However, there was no significant difference in maternal age, pre-pregnancy BMI, or the 5' Apgar scores among the groups.

The results of the serum analytes from the PE group and the CON group samples collected in the first and second trimesters are shown in Table 2 and Figures 2–4. In the first trimester, compared with those in the gestational age-matched controls, the ESM-1 level (285.82 ± 89.53 vs. 357.61 ± 80.40 , $p < 0.001$) in the SPE group was significantly lower. There was no significant difference in the ESM-1 level between the control and the MPE groups (Figure 2A). Additionally, there was also no significant difference in the PLGF level between the control group and any PE group (Figure 2B). In the second trimester, compared with those in the gestational age-matched controls, the ESM-1 level (206.24 ± 132.53 vs. 152.35 ± 29.00 , $p = 0.0032$) in the SPE group was significantly higher and the PLGF level (14.03 ± 6.21 vs. 29.52 ± 17.26 , $p < 0.001$) in the SPE group was significantly lower (Figure 3A,B). Moreover, compared to those in the control group, the PLGF level was significantly lower (16.82 ± 6.25 vs. 29.52 ± 17.26 , $p < 0.001$) in the MPE group (Figure 3B). There was no significant difference in the ESM-1 level between the control and the MPE groups (Figure 3A). Compared with those in the gestational age-matched controls, the 2nd

PI (1.35 ± 0.39 vs. 0.89 ± 0.22 , $p < 0.001$) in the SPE group and the 2nd PI (1.15 ± 0.34 vs. 0.89 ± 0.22 , $p < 0.001$) in the MPE group were also significantly higher (Figure 4).

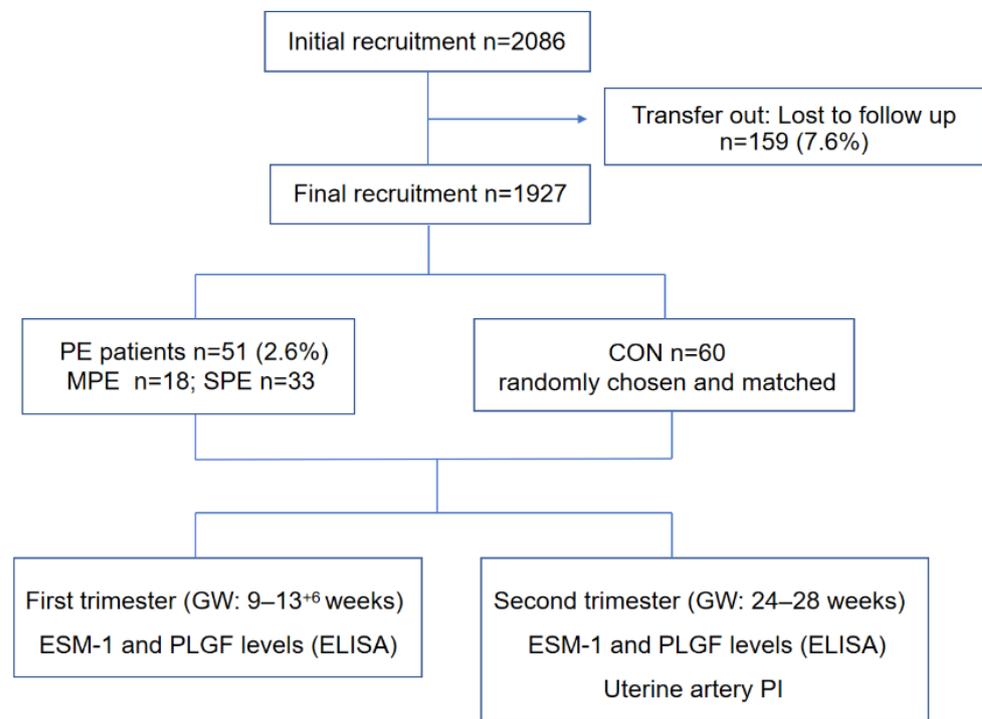


Figure 1. The flowchart of the prospective cohort study. CON, control group; MPE, mild preeclampsia group; SPE, severe preeclampsia group; GW, gestational week.

Table 1. Demographic characteristics of the participants.

Characteristic	SPE (n = 33)	MPE (n = 18)	CON (n = 60)
Maternal age, y	31.06 ± 4.34	31.89 ± 4.38	30.03 ± 3.61
Pre-BMI, kg/m ²	21.02 ± 2.55	21.51 ± 2.02	20.60 ± 1.82
SBP (mmHg)	166.18 ± 9.74 **	144.39 ± 5.38 **	117.00 ± 9.39
DBP (mmHg)	97.91 ± 8.91 **	92.33 ± 5.24 **	74.78 ± 9.11
Nulliparous, n (%)	29 (87.88%)	16 (88.89%)	52 (86.67%)
GA at delivery, weeks	37.09 ± 3.01 **	38.73 ± 1.20 *	39.45 ± 0.81
Fetal weight, g	2660.45 ± 754.43 **	3161.39 ± 266.34 *	3375.50 ± 297.29
Placental weight, g	537.27 ± 165.52 *	622.50 ± 84.53	614.08 ± 67.01
5' Apgar score	9.33 ± 1.83	9.61 ± 0.61	9.81 ± 0.62

SPE, severe preeclampsia; MPE, mild preeclampsia; CON, control; pre-BMI: pre-pregnancy body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; GA, gestational age. * $p < 0.05$; ** $p < 0.001$ compared to the CON.

Furthermore, the details of the AUCs are shown in Table 3, and the ROC curves for the biomarkers in the SPE prediction are presented in Figure 5. The ROC analysis for the SPE and control subjects yielded AUCs for the 1st ESM-1, the 2nd PLGF, and the 2nd PI of 0.714 (95% CI: 0.611–0.803, $p = 0.0002$), 0.802 (95% CI: 0.706–0.877, $p < 0.0001$), and 0.843 (95% CI: 0.753–0.911, $p < 0.0001$), respectively. Logistic regression analysis was used to evaluate the combination of these indicators. In the SPE group, the AUCs for the combinations of the 1st ESM-1 and 2nd PLGF, the 1st ESM-1 and 2nd PI, and the 2nd PLGF and 2nd PI were 0.856 (93.90% sensitivity and 66.70% specificity), 0.876 (84.85% sensitivity and 80.00% specificity), and 0.890 (69.70% sensitivity and 95.00% specificity), respectively. The combination of the 1st ESM-1, the 2nd PLGF, and the 2nd PI yielded an AUC of 0.912 (72.73% sensitivity and 95.00% specificity) ($p < 0.0001$ for all).

Table 2. Comparison of biomarker levels among study groups.

	SPE (n = 33)	MPE (n = 18)	CON (n = 60)	p Value	
				SPE	MPE
1st ESM-1 (pg/mL)	285.82 ± 89.53	304.00 ± 121.59	357.61 ± 80.40	<0.001 **	0.093
2nd ESM-1 (pg/mL)	206.24 ± 132.53	142.58 ± 60.68	152.35 ± 29.00	0.0032 *	0.347
1st PLGF (pg/mL)	2.67 ± 1.07	2.87 ± 1.27	3.13 ± 1.10	0.0524	0.400
2nd PLGF (pg/mL)	14.03 ± 6.21	16.82 ± 6.25	29.52 ± 17.26	<0.001 **	<0.001 **
2nd PI	1.35 ± 0.39	1.15 ± 0.34	0.89 ± 0.22	<0.001 **	<0.001 **

SPE, severe preeclampsia; MPE, mild preeclampsia; CON, control; ESM-1, endothelial cell-specific molecule 1; PLGF, placental growth factor; PI, pulsatility index. 1st/2nd ESM-1, ESM-1 level measured in the first/second trimester; 1st/2nd PLGF, PLGF level measured in the first/second trimester; 2nd PI, PI measured in the second trimester. * $p < 0.05$; ** $p < 0.001$ compared to the CON.

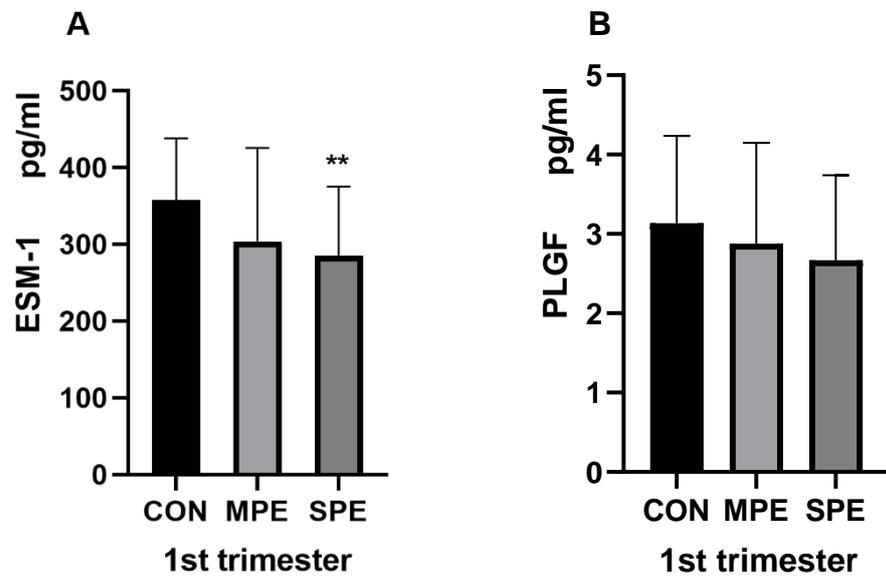


Figure 2. ESM-1 and PLGF in first-trimester maternal serum (A,B). CON, n = 60; MPE, n = 18; SPE, n = 33, ** $p < 0.001$.

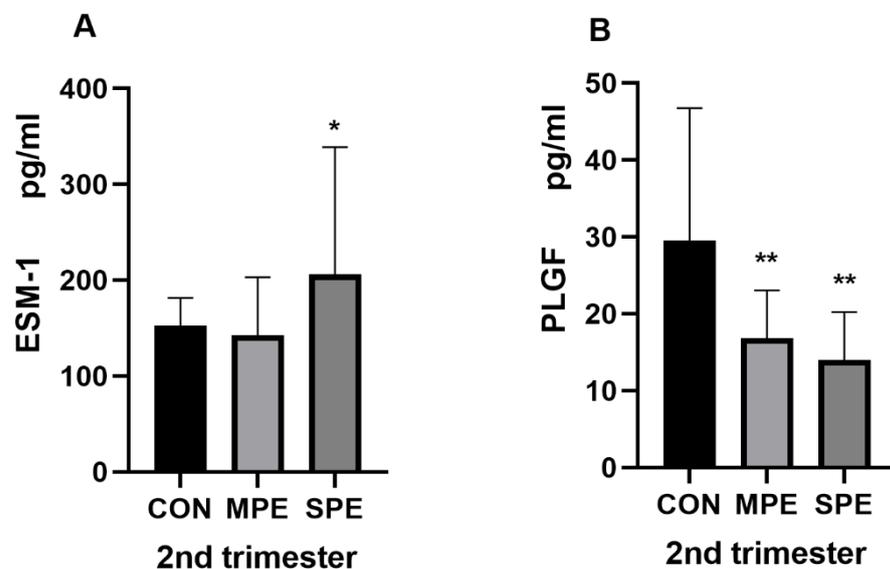


Figure 3. ESM-1 and PLGF in second-trimester maternal serum (A,B). CON, n = 60; MPE, n = 18; SPE, n = 33, * $p < 0.05$, ** $p < 0.001$.

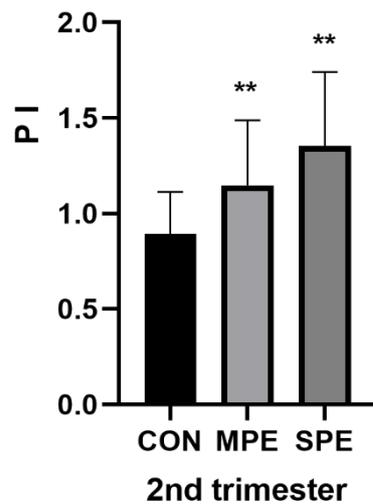


Figure 4. Uterine artery Doppler PI in the second trimester. CON, $n = 60$; MPE, $n = 18$; SPE, $n = 33$, $** p < 0.001$.

Table 3. Predictive efficiency of biomarker levels and PI for severe preeclampsia.

Variable	AUC	<i>p</i> Value	95%CI	Cutoff	Specificity (%)	Sensitivity (%)
1st ESM-1	0.714	0.0002	0.611–0.803	262.33	91.67	45.50
2nd PLGF	0.802	<0.0001	0.706–0.877	19.12	70.00	84.85
2nd PI	0.843	<0.0001	0.753–0.911	1.12	86.67	75.76
1st ESM-1 + 2nd PLGF	0.856	<0.0001	0.767–0.920	-	66.70	93.90
1st ESM-1 + 2nd PI	0.876	<0.0001	0.792–0.935	-	80.00	84.85
2nd PLGF + 2nd PI	0.890	<0.0001	0.808–0.945	-	95.00	69.70
1st ESM-1 + 2nd PLGF + 2nd PI	0.912	<0.0001	0.835–0.961	-	95.00	72.73

CI: confidence interval; ESM-1, endothelial cell-specific molecule 1; PLGF, placental growth factor; PI, pulsatility index; 1st/2nd ESM-1, ESM-1 level measured in the first/second trimester; 1st/2nd PLGF, PLGF level measured in the first/second trimester.

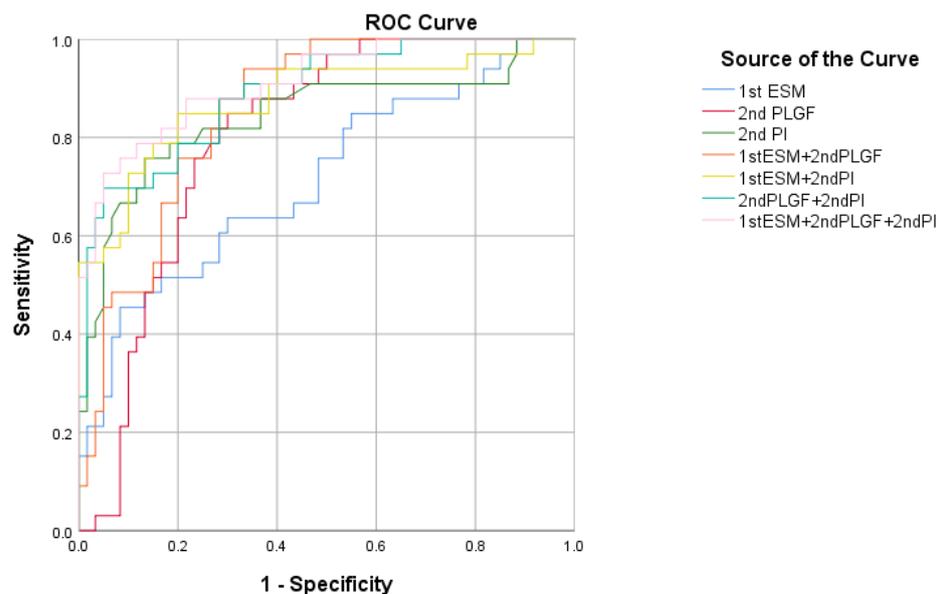


Figure 5. Receiver operating characteristic curve showing the clinical discrimination of different markers alone or in combination in the detection of severe preeclampsia.

The ROC curves for the biomarkers in the MPE prediction are presented in Figure 6. The ROC analysis for the MPE and control subjects yielded areas under the curve (AUCs)

for the 2nd PLGF and the 2nd PI of 0.738 (95% CI: 0.626–0.831, $p < 0.0001$) and (95% CI: 0.636–0.839, $p = 0.0007$), respectively. In the MPE group, combining the 2nd PLGF with the 2nd PI yielded an AUC of 0.819 (83.33% sensitivity and 70.00% specificity).

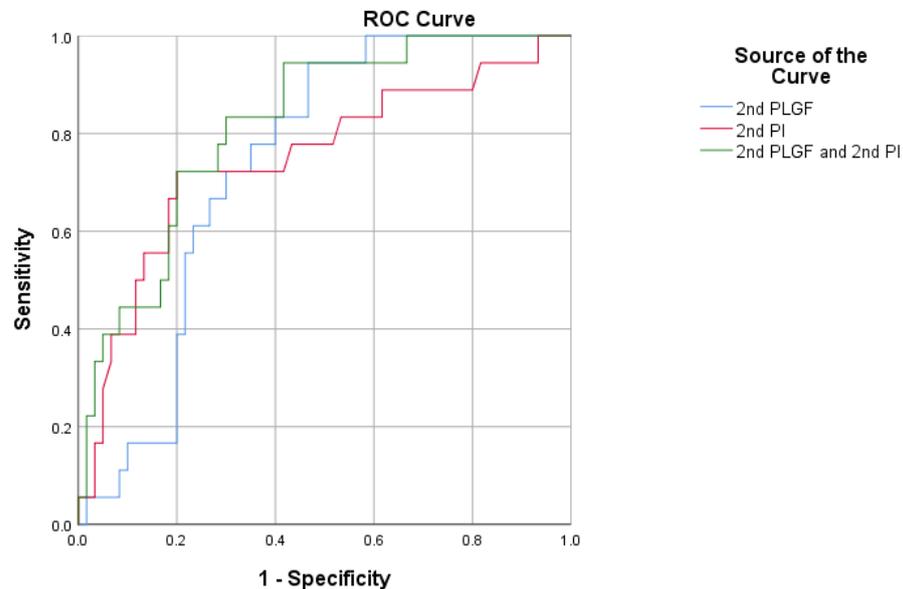


Figure 6. Receiver operating characteristic curve showing the clinical discrimination of different markers alone or in combination in the detection of mild preeclampsia.

4. Discussion

Accumulative evidence has revealed that inflammation and endothelial dysfunction are vitally important to the pathophysiology of PE [19]. ESM-1 might be involved in endothelial-related processes, including cell adhesion, angiogenesis, inflammation, and endothelial dysfunction [20]. Thus, ESM-1 could be regarded as a biomarker for hypertension [5,21], sepsis [22], malignancy [23], and PE [6].

The results showed that the ESM-1 level in the maternal plasma was lower during the first trimester (12–16 weeks of gestation) but increased in the second and third trimesters (≥ 24 weeks of gestation) in the SPE group [24]. Some studies in 2015 and 2016 reported higher ESM-1 concentrations in PE maternal plasma and a negative correlation with the clinical data, indicating its crucial role in the pathogenesis of PE progression [25,26]. Moreover, the stratified results from a meta-analysis conducted to determine the potential role of ESM-1 in PE suggested the upregulation of ESM-1 levels in PE [6]. The results obtained in our study were consistent with these studies, except that ESM-1 was detected earlier in the first trimester in our study.

As an explanation for the lower 1st ESM-1 level in PE, some researchers have suggested that ESM-1 functions as a protective cytokine by inhibiting leukocyte aggregation to protect tissues and organs from inflammatory damage and is consumed in early pregnancy [25]. It was also indicated that a positive feedback loop exists between the vascular endothelial growth factor (VEGF) and ESM-1 [27]; therefore, as the results revealed, the 2nd ESM-1 level was reduced with the advancement of the placental vasculature in the CON group and PE groups. In addition, ESM-1 can be upregulated by proinflammatory factors and growth factors, such as TNF- α , IL-6, and VEGF [28]. With the development of PE, the inflammatory response and endothelial dysfunction were aggravated, and the ESM-1 level was elevated in the second and third trimesters. Regarding the lack of a significant difference in the ESM-1 level between the MPE group and the normal pregnancy group in the first and second trimesters, it was speculated that inflammation and endothelial dysfunction were too minor to distinguish.

PLGF, which is expressed in the human placenta, heart, and lungs, is a member of the VEGF family [29]. It can directly activate its angiogenic pathway through PLGF/VEGFR1

(known as FLT1) and compete with VEGF-A for VEGFR1, further stimulating angiogenesis via the VEGFA/VEGFR2 (known as FLK1) interaction. During normal pregnancy, the PLGF level is relatively low in the first trimester. It gradually increases with the advancement of the utero-placental circulation and remodeling of the myometrial spiral arteries and finally reaches its peak at approximately 30 weeks of gestation, after which it drops [8]. Given the vital role of the placenta in PE, the usefulness of PLGF in PE prediction was investigated. A previous study revealed that at 9–12⁺⁶ weeks of gestation, the PLGF expression was significantly lower in PE pregnancies than in the CON pregnancies [30]. Another study examined the concentrations of PLGF in women with PE during two periods (8–14 weeks of gestation and 20–34 weeks of gestation). The results suggested that the PLGF level in the PE group was significantly lower in the first period, but no difference was found in the second period between the PE group and the CON group [31]. The study investigated the remarkably lower PLGF level in PE pregnancies at 24–28 weeks of gestation [32], and another study found that the PLGF concentration was also significantly lower before 35 weeks in the PE pregnancy compared to the normal pregnancy [33]. Moreover, the PLGF change was relevant to disease severity [34]. Our study had similar results. Specifically, a lack of a significant difference in the 1st PLGF level was found between the PE group and the CON group. Additionally, the 2nd PLGF concentrations were elevated compared to the 1st PLGF concentrations, but they were significantly lower than the 2nd PLGF concentration in the CON group, especially for SPE. With pregnancy progression in PE, the PLGF might compete with the VEGF for binding to sFlt-1, resulting in a significant drop emerging in the second trimester before the onset of PE symptoms [8].

Some studies have shown that uterine artery PI is a significant marker for predicting PE. The Doppler ultrasound of the maternal uterine artery PI might be the most effective method for screening women with PE in the second trimester [35]. In our study, 75.76% sensitivity and 86.67% specificity were achieved with the uterine artery PI. The uterine artery PI was increased in the second-trimester pregnancies in the PE patients, especially the SPE patients, which was consistent with the reported literature.

Many recent studies have suggested that the combination of biochemical indicators and the uterine artery Doppler could improve the screening efficiency for the prediction of PE [36,37]. Notably, our study similarly indicated that the overall predictive efficiency for SPE achieved by combining serum biomarkers and the uterine artery Doppler PI was improved compared with the single use of any marker alone.

5. Conclusions

The 1st ESM-1, 2nd PLGF levels and the 2nd uterine artery Doppler PI were associated with PE. The combination of serum biomarkers and the uterine artery Doppler PI strengthened the screening efficiency for the prediction of PE, especially for SPE. Our study is the first to assess the predictive combination of the 1st ESM-1, the 2nd PLGF, and the 2nd uterine artery Doppler PI for PE. Unfortunately, due to the COVID-19 outbreak, the blood samples of the participants in the third trimester were lost, resulting in a lack of data on the serum concentrations of ESM-1 and PLGF. Further studies are needed in a larger population to determine the potential for use of the aforementioned indicators.

Author Contributions: Conception and design, X.X. and D.C.; acquisition of data, X.X., D.C., and Y.C.; analysis and interpretation of data, X.X. and X.Y.; drafting of the manuscript, X.X. and D.C.; critical revision of the manuscript, X.X., D.C., Y.G. and W.C. All authors have read and agreed to the published version of the manuscript.

Funding: This study was supported by the Shanghai Municipal Health Commission (20194Y0050), the project of International Peace Maternal and Child Health Hospital Affiliated to Shanghai Jiaotong University (CR2018WX04), the National Natural Science Foundation of China (81370727), the Interdisciplinary Program of Shanghai Jiao Tong University (ZH2018ZDA31), and the establishment of preeclampsia–eclampsia cohort database (Clinical Research Plan of SHDC, SHDC2020CR6021).

Institutional Review Board Statement: The study was conducted according to the Declaration of Helsinki guidelines and the approval of the National Ethics Committee for Science and Technology (number: GKLW2020-03).

Informed Consent Statement: Written informed consent was obtained from all the participants.

Data Availability Statement: All the study data will be made available upon request to the corresponding author.

Acknowledgments: We thank all our participants for their cooperation and help during this study.

Conflicts of Interest: The authors report no conflict of interest in this work.

References

1. Kassebaum, N.J.; Barber, R.M.; Bhutta, Z.A.; Dandona, L.; Gething, P.W.; Hay, S.I.; Kinfu, Y.; Larson, H.J.; Liang, X.; Lim, S.S.; et al. Global, regional, and national levels of maternal mortality, 1990–2015: A systematic analysis for the Global Burden of Disease Study 2015. *Lancet* **2016**, *388*, 1775–1812. [[CrossRef](#)] [[PubMed](#)]
2. Roberts, J.M.; Lain, K.Y. Recent Insights into the pathogenesis of pre-eclampsia. *Placenta* **2002**, *23*, 359–372. [[CrossRef](#)] [[PubMed](#)]
3. Kornacki, J.; Wender-Ożegowska, E. Utility of biochemical tests in prediction, diagnostics and clinical management of preeclampsia: A review. *Arch. Med. Sci.* **2020**, *16*, 1370–1375. [[CrossRef](#)] [[PubMed](#)]
4. Lassalle, P.; Molet, S.; Janin, A.; Van der Heyden, J.; Tavernier, J.; Fiers, W.; Devos, R.; Tonnel, A.-B. ESM-1 is a novel human endothelial cell-specific molecule expressed in lung and regulated by cytokines. *J. Biol. Chem.* **1996**, *271*, 20458–20464. [[CrossRef](#)] [[PubMed](#)]
5. Balta, S.; Mikhailidis, D.P.; Demirkol, S.; Ozturk, C.; Kurtoglu, E.; Demir, M.; Celik, T.; Turker, T.; Iyisoy, A. Endocan—A novel inflammatory indicator in newly diagnosed patients with hypertension: A pilot study. *Angiology* **2014**, *65*, 773–777. [[CrossRef](#)]
6. Lan, X.; Liu, Z. Circulating endocan and preeclampsia: A meta-analysis. *Biosci. Rep.* **2020**, *40*, 1–9. [[CrossRef](#)]
7. Kingdom, J.; Huppertz, B.; Seaward, G.; Kaufmann, P. Development of the placental villous tree and its consequences for fetal growth. *Eur. J. Obstet. Gynecol. Reprod. Biol.* **2000**, *92*, 35–43. [[CrossRef](#)]
8. Chau, K.; Hennessy, A.; Makris, A. Placental growth factor and pre-eclampsia. *J. Hum. Hypertens.* **2017**, *31*, 782–786. [[CrossRef](#)]
9. Agrawal, S.; Shinar, S.; Cerdeira, A.S.; Redman, C.; Vatish, M. Predictive Performance of PlGF (Placental Growth Factor) for Screening Preeclampsia in Asymptomatic Women: A Systematic Review and Meta-Analysis. *Hypertension* **2019**, *74*, 1124–1135. [[CrossRef](#)]
10. Levine, R.J.; Maynard, S.E.; Qian, C.; Lim, K.-H.; England, L.J.; Yu, K.F.; Schisterman, E.F.; Thadhani, R.; Sachs, B.P.; Epstein, F.H.; et al. Circulating Angiogenic Factors and the Risk of Preeclampsia. *N. Engl. J. Med.* **2004**, *350*, 672–683. [[CrossRef](#)]
11. Polliotti, B.M.; Fry, A.G.; Saller, D.N.; Mooney, R.A.; Cox, C.; Miller, R.K. Second-trimester maternal serum placental growth factor and vascular endothelial growth factor for predicting severe, early-onset preeclampsia. *Obstet. Gynecol.* **2003**, *101*, 1266–1274. [[CrossRef](#)] [[PubMed](#)]
12. Perry, H.; Binder, J.; Kalafat, E.; Jones, S.; Thilaganathan, B.; Khalil, A. Angiogenic Marker Prognostic Models in Pregnant Women with Hypertension. *Hypertension* **2020**, *75*, 755–761. [[CrossRef](#)] [[PubMed](#)]
13. Carbillon, L.; Challier, J.; Alouini, S.; Uzan, M.; Uzan, S. Uteroplacental Circulation Development: Doppler Assessment and Clinical Importance. *Placenta* **2001**, *22*, 795–799. [[CrossRef](#)] [[PubMed](#)]
14. Lloyd-Davies, C.; Collins, S.L.; Burton, G.J. Understanding the uterine artery Doppler waveform and its relationship to spiral artery remodelling. *Placenta* **2021**, *105*, 78–84. [[CrossRef](#)]
15. Cui, S.; Gao, Y.; Zhang, L.; Wang, Y.; Zhang, L.; Liu, P.; Liu, L.; Chen, J. Combined use of serum MCP-1/IL-10 ratio and uterine artery Doppler index significantly improves the prediction of preeclampsia. *Clin. Chim. Acta* **2017**, *473*, 228–236. [[CrossRef](#)]
16. Papageorghiou, A.T.; Yu, C.K.H.; Bindra, R.; Pandis, G.; Nicolaides, K. Multicenter screening for pre-eclampsia and fetal growth restriction by transvaginal uterine artery Doppler at 23 weeks of gestation. *Ultrasound Obstet. Gynecol.* **2001**, *18*, 441–449. [[CrossRef](#)]
17. American College of Obstetricians and Gynecologists. Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin Summary, Number 222. *Obstet. Gynecol.* **2020**, *135*, 1492–1495. [[CrossRef](#)] [[PubMed](#)]
18. Ives, C.W.; Sinkey, R.; Rajapreyar, I.; Tita, A.T.; Oparil, S. Preeclampsia—Pathophysiology and Clinical Presentations: JACC State-of-the-Art Review. *J. Am. Coll. Cardiol.* **2020**, *76*, 1690–1702. [[CrossRef](#)]
19. Chappell, L.C.; Cluver, C.A.; Kingdom, J.; Tong, S. Pre-eclampsia. *Lancet* **2021**, *398*, 341–354. [[CrossRef](#)]
20. Balta, S.; Mikhailidis, D.P.; Demirkol, S.; Ozturk, C.; Celik, T.; Iyisoy, A. Endocan: A novel inflammatory indicator in cardiovascular disease? *Atherosclerosis* **2015**, *243*, 339–343. [[CrossRef](#)]
21. Oktar, S.F.; Guney, I.; Eren, S.A.; Oktar, L.; Kosar, K.; Buyukterzi, Z.; Alkan, E.; Biyik, Z.; Erdem, S.S. Serum endocan levels, carotid intima-media thickness and microalbuminuria in patients with newly diagnosed hypertension. *Clin. Exp. Hypertens.* **2019**, *41*, 787–794. [[CrossRef](#)] [[PubMed](#)]
22. Mihajlovic, D.M.; Lendak, D.F.; Draskovic, B.G.; Brkic, S.V.; Mitic, G.P.; Mikic, A.S.N.; Cebovic, T.N. Corrigendum to “Endocan is useful biomarker of survival and severity in sepsis” [*Microvasc. Res.* 93 (2014) 92–97]. *Microvasc. Res.* **2020**, *129*, 103992. [[CrossRef](#)] [[PubMed](#)]

23. Scherpereel, A.; Gentina, T.; Grigoriu, B.; Sénéchal, S.; Janin, A.; Tsicopoulos, A.; Plénat, F.; Béchar, D.; Tonnel, A.-B.; Lassalle, P. Overexpression of endocan induces tumor formation. *Cancer Res.* **2003**, *63*, 6084–6089. [[PubMed](#)]
24. Schuitemaker, J.; Woudenberg, J.; Wijbenga, G.; Scherjon, S.; van Pampus, M.; Faas, M. PPNew prognostic marker for the risk to develop early-onset preeclampsia. *Pregnancy Hypertens.* **2013**, *3*, 95–96. [[CrossRef](#)]
25. Hentschke, M.R.; Lucas, L.S.; Mistry, H.D.; Pinheiro da Costa, B.E.; Poli-de-Figueiredo, C.E. Endocan-1 concentrations in maternal and fetal plasma and placenta in pre-eclampsia in the third trimester of pregnancy. *Cytokine* **2015**, *74*, 152–156. [[CrossRef](#)]
26. Cakmak, M.; Yilmaz, H.; Bağlar, E.; Darçın, T.; Inan, O.; Aktas, A.; Celik, H.T.; Özdemir, O.; Atalay, C.R.; Akcay, A. Serum levels of endocan correlate with the presence and severity of pre-eclampsia. *Clin. Exp. Hypertens.* **2015**, *38*, 137–142. [[CrossRef](#)]
27. Roudnicky, F.; Poyet, C.; Wild, P.; Krampitz, S.; Negrini, F.; Huggenberger, R.; Rogler, A.; Stöhr, R.; Hartmann, A.; Provenzano, M.; et al. Endocan Is Upregulated on Tumor Vessels in Invasive Bladder Cancer Where It Mediates VEGF-A-Induced Angiogenesis. *Cancer Res.* **2013**, *73*, 1097–1106. [[CrossRef](#)]
28. Zhang, H.; Shen, Y.-W.; Zhang, L.-J.; Chen, J.-J.; Bian, H.-T.; Gu, W.-J.; Zhang, H.; Chen, H.-Z.; Zhang, W.-D.; Luan, X. Targeting Endothelial Cell-Specific Molecule 1 Protein in Cancer: A Promising Therapeutic Approach. *Front. Oncol.* **2021**, *11*, 687120. [[CrossRef](#)]
29. Lohela, M.; Bry, M.; Tammela, T.; Alitalo, K. VEGFs and receptors involved in angiogenesis versus lymphangiogenesis. *Curr. Opin. Cell Biol.* **2009**, *21*, 154–165. [[CrossRef](#)]
30. Myatt, L.; Clifton, R.G.; Roberts, J.M.; Spong, C.Y.; Hauth, J.C.; Varner, M.W.; Thorp, J.M.; Mercer, B.M.; Peaceman, A.M.; Ramin, S.M.; et al. First-Trimester Prediction of Preeclampsia in Nulliparous Women at Low Risk. *Obstet. Gynecol.* **2012**, *119*, 1234–1242. [[CrossRef](#)]
31. Andersen, L.B.; Dechend, R.; Jørgensen, J.S.; Luef, B.M.; Nielsen, J.; Barington, T.; Christesen, H.T. Prediction of preeclampsia with angiogenic biomarkers. Results from the prospective Odense Child Cohort. *Hypertens. Pregnancy* **2016**, *35*, 405–419. [[CrossRef](#)] [[PubMed](#)]
32. De Vivo, A.; Baviera, G.; Giordano, D.; Todarello, G.; Corrado, F.; D’Anna, R. Endoglin, PlGF and sFlt-1 as markers for predicting pre-eclampsia. *Acta Obstet. Gynecol. Scand.* **2008**, *87*, 837–842. [[CrossRef](#)] [[PubMed](#)]
33. Chappell, L.C.; Duckworth, S.; Seed, P.T.; Griffin, M.; Myers, J.; Mackillop, L.; Simpson, N.; Waugh, J.; Anumba, D.; Kenny, L.; et al. Diagnostic Accuracy of Placental Growth Factor in Women with Suspected Preeclampsia: A prospective multicenter study. *Circulation* **2013**, *128*, 2121–2131. [[CrossRef](#)] [[PubMed](#)]
34. Robinson, C.J.; Johnson, D.D.; Chang, E.Y.; Armstrong, D.M.; Wang, W. Evaluation of placenta growth factor and soluble Fms-like tyrosine kinase 1 receptor levels in mild and severe preeclampsia. *Am. J. Obstet. Gynecol.* **2006**, *195*, 255–259. [[CrossRef](#)]
35. Crossen, J.S.; Morris, R.K.; ter Riet, G.; Mol, B.W.; van der Post, J.A.; Coomarasamy, A.; Zwiderman, A.H.; Robson, S.C.; Bindels, P.J.; Kleijnen, J.; et al. Use of uterine artery Doppler ultrasonography to predict pre-eclampsia and intrauterine growth restriction: A systematic review and bivariable meta-analysis. *Can. Med. Assoc. J.* **2008**, *178*, 701–711. [[CrossRef](#)]
36. Poon, L.C.; Nicolaides, K.H. Early Prediction of Preeclampsia. *Obstet. Gynecol. Int.* **2014**, *2014*, 1–11. [[CrossRef](#)]
37. Yu, N.; Cui, H.; Chen, X.; Chang, Y. First trimester maternal serum analytes and second trimester uterine artery Doppler in the prediction of preeclampsia and fetal growth restriction. *Taiwan J. Obstet. Gynecol.* **2017**, *56*, 358–361. [[CrossRef](#)]

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.