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Evaluating maternal serum sortilin levels: a potential biomarker for predicting preeclampsia

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Abstract

Objective To determine the role of sortilin in the pathogenesis of preeclampsia by examining serum sortilin levels in maternal blood.

Methods This prospective case-control study was conducted from May to November 2023 at the Perinatology Clinic of Ankara Etlik City Hospital. The study cohort was divided into two groups: Group 1 consisted of 44 pregnant women diagnosed with preeclampsia, and Group 2 served as the control group, comprising 44 healthy pregnant women. The groups were matched individually, with controls selected based on similar maternal age and gestational age at the time of sample collection.

Results Maternal sortilin levels were significantly elevated in preeclampsia patients compared to controls. Using a cut-off value of > 3.57 ng/mL, sortilin levels could distinguish preeclampsia cases with a sensitivity of 90.9%, a specificity of 45.5%, and an area under the curve (AUC) of 0.679 ($p = 0.002$). At a cut-off of > 3.57 ng/mL, it was significantly associated with composite adverse neonatal outcomes, with a sensitivity of 89.6%, a specificity of 36.1%, and an AUC of 0.620 ($p = 0.045$). In addition, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and protein in 24-hour urine, which are important components in the diagnosis and severity of preeclampsia, were significantly correlated maternal blood sortilin levels.

Conclusion Our findings indicate that maternal sortilin levels are elevated in patients with preeclampsia compared to those in a healthy pregnant control group. Furthermore, maternal sortilin levels may predict adverse neonatal outcomes. In addition, sortilin levels are correlated key clinical markers of preeclampsia severity.

Keywords Preeclampsia, Sortilin, Maternal blood, Perinatal outcomes, Neonatal outcomes

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Introduction

Preeclampsia is a condition characterized by the onset of high blood pressure after the 20th week of pregnancy, accompanied by proteinuria or other signs of organ damage [1]. This condition affects 2–8% of pregnancies and is a significant contributor to maternal and neonatal morbidity and mortality [2]. Maternal adverse outcomes include placental abruption, HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome, pulmonary edema, and severe renal failure [2]. Adverse neonatal outcomes include fetal growth restriction, oligohydramnios, low Apgar scores at birth, the need for neonatal intensive care unit, and increased fetal mortality [3]. Biomarkers such as placental growth factor (PLGF) and soluble fms-like tyrosine kinase-1 (sFLT-1) have demonstrated predictive value in identifying preeclampsia; however, their sensitivity and specificity are limited, and additional biomarkers are needed to better understand its complex pathophysiology and improve early diagnostic capabilities [4, 5].

Sortilin was first identified in human brain membrane proteins and is encoded by the SORT1 gene, located on chromosome 1 at band 1p13.3 [6]. It is a transmembrane protein that belongs to the Vacuolar protein sorting 10 protein (VPS10P) receptor family [7]. Sortilin is synthesized as prosortilin and remains inactive in its proform [8]. It is abundantly expressed in tissues such as the brain, spinal cord, heart, and skeletal muscle in adult humans, and found at lower levels in the liver, kidney, pancreas, spleen, and small intestine [9]. Elevated levels of sortilin are linked to a range of cardiovascular and metabolic disorders, such as atherosclerosis, abnormalities in lipoprotein metabolism, vascular calcification, and obesity [9]. It contributes to an increase in free oxygen radicals, leading to a significant decrease in nitric oxide (NO) levels, which is an oxidative marker that inhibits vasodilation [10]. Additionally, an independent effect of sortilin on the inflammatory process has been reported [11]. Given the role of sortilin plays in these diseases, it is considered a potential therapeutic target and biomarker.

Although evidence suggests that maternal endothelial dysfunction—characterized by reduced vasodilation, increased levels of oxygen free radicals, systemic inflammation, and thrombosis—contributes to the pathogenesis of preeclampsia, the detailed underlying mechanisms of this condition remain elusive [3]. Previous research has identified sortilin as a significant regulator of vascular function, closely associated with endothelial dysfunction and hypertension [7, 10]. Our study aims to explore the role of sortilin in the pathogenesis of preeclampsia by analyzing serum sortilin levels in the maternal blood of pregnant women diagnosed with preeclampsia.

Materials and methods

This prospective case-control study was conducted from May to November 2023 at the Perinatology Clinic of Ankara Etlik City Hospital. The study cohort was divided into two groups: Group 1 consisted of 44 pregnant women diagnosed with preeclampsia, and Group 2 served as the control group, comprising 44 healthy pregnant women. The groups were matched individually, with controls selected based on similar maternal age and gestational age at the time of sample collection. The study protocol was approved by the Ethics Committee of Ankara Etlik City Hospital (approval number: AESH-EK1-2023-253). The patients who participated in the study were informed and their written informed consent was obtained. This study complied with the provisions of the Declaration of Helsinki.

Preeclampsia, typically emerging after the 20th week of pregnancy, is defined by elevated blood pressure measurements (a systolic pressure of 140 mm Hg or higher and a diastolic pressure of 90 mm Hg or higher on two separate occasions at least four hours apart) in addition to one or more of the following new-onset conditions: significant proteinuria (300 mg or more in a 24-hour urine collection or a protein/creatinine ratio of 0.3 or higher in a random urine sample), or in the absence of proteinuria, new indicators of end-organ dysfunction such as thrombocytopenia (platelet count less than 100,000/μL), renal insufficiency (serum creatinine levels greater than 1.1 mg/dL or a doubling from the baseline level in the absence of other renal pathology), impaired liver function (elevated blood levels of liver enzymes to twice the normal concentration), pulmonary edema, or new-onset severe headache unresponsive to medication and not accounted for by alternative diagnoses, or visual disturbances [12].

Gestational weeks were calculated from the first day of the last menstrual period and confirmed via ultrasound examinations. Fetal biophysical profiles, amniotic fluid measurements, and non-stress tests were conducted. The systolic/diastolic ratio (S/D) and the pulsatility index (PI) of the umbilical artery were also recorded. Exclusion criteria for the study included multiple pregnancies, chronic maternal diseases (such as hypertension, diabetes, thyroid dysfunction disorders etc.), premature rupture of membranes cases, fetal growth restriction cases, fetal doppler abnormalities, oligohydramnios or polyhydramnios cases, multiple pregnancies, smoking, alcohol consumption, and congenital anomalies.

Demographic and medical information, including maternal age, weight gained during pregnancy, body mass index (BMI), and previous pregnancy history (gravida, parity, and abortion), was collected for all participants. Peripheral venous blood samples were collected during routine antenatal visits in the preeclampsia and

control groups. These samples were analyzed to measure hemoglobin, white blood cells (WBC), platelets, aspartate aminotransferase (AST), alanine aminotransferase (ALT), uric acid, and fibrinogen levels. Additionally, 24-hour urine samples were collected from participants in the PE group to measure protein excretion. Neonatal outcomes were recorded at birth. The composite adverse neonatal outcome was defined as the occurrence of at least one of the following situations: APGAR score at 5th minute < 7, respiratory distress syndrome (RDS), and admission to neonatal intensive care unit (NICU).

Sample collection

Maternal blood samples were collected at the time of preeclampsia diagnosis for the preeclampsia group and at matched gestational ages for the control group during routine prenatal visits. 5 mL of peripheral venous blood samples were collected and after centrifugation at 3000 rpm for 15 min, the serum was stored at − 80 °C in accordance with the recommendations provided with the kit. Sortilin concentrations were quantified in ng/mL using the Sortilin (SORT1) Human Elisa Kit (SEC895Mu) (USCNK brand, China). In the analysis, we used the Combiwash model from the Human Diagnostic brand (Germany) for washing and the Alisei model from the Next Level brand (Italy) as the spectrophotometer for reading the results.

Statistical analysis

Statistical analyses were conducted using the RStudio software (Affero General Public License v3; published 2011), which provides an integrated development environment for statistical computation. The variables were investigated using analytic methods (Kolmogrov-Simirnov/Shapiro-Wilk's test) to determine whether or not they are normally distributed. The Levene test was utilized to evaluate variance homogeneity. For variables following a normal distribution, descriptive statistics were presented as means and standard deviations (SDs). The Independent Samples T-test was employed to compare these parameters between groups. In contrast, for variables not normally distributed, medians and interquartile ranges (Q1-Q3) were reported, and the Mann-Whitney U test was used for group comparisons. The p-value for maternal sortilin levels was adjusted for BMI using regression analysis. Categorical variables were analyzed using frequencies and percentages, and their associations were examined through the Chi-square test or Fisher's exact test, the latter being used when the assumptions for the Chi-square test were not met due to low expected frequencies. The Spearman test was applied to explore the correlations between variables. The predictive ability of maternal serum sortilin levels to predict preeclampsia and composite neonatal outcomes was assessed using Receiver Operating Characteristics (ROC) curve analysis, reporting sensitivity, specificity, and the Area Under the Curve (AUC) value when a significant threshold was identified. A p-value less than 0.05 was considered indicative of statistical significance.

The required sample size for the study was determined using the G-Power 3.1.9.7 software (University of Dusseldorf, Dusseldorf, Germany). The sample size was estimated using a Student's Paired t-Test with an 80% power, a significance level of $\alpha = 0.05$, and a medium Cohen effect size. Based on these parameters, the minimum sample size required to achieve adequate statistical power was calculated to be at least 36 patients for each group, ensuring the robustness of the study's findings.

Results

Maternal characteristics and perinatal outcomes of the pregnant woman included in the study are shown in Table 1. Our analysis revealed no statistically significant differences between the groups in terms of maternal age, gravida, parity, number of abortions, and the gestational age at the time of blood sampling ($p = 0.148$, $p = 0.197$, $p = 0.287$, $p = 0.124$, and $p = 0.316$, respectively). Weight gained during pregnancy was similar between groups, but BMI at during test was higher in the preeclampsia group ($p = 0.001$). The median gestational week at the diagnosis of preeclampsia was 33 weeks, with a range of 30 to 36 weeks. There were no significant differences observed in levels of hemoglobin, WBC, platelet, ALT, and fibrinogen between the two groups ($p = 0.181$, $p = 0.278$, $p = 0.392$, $p = 0.066$, and $p = 0.078$, respectively). However, AST and uric acid levels were significantly elevated in the preeclampsia group ($p = 0.001$ and $p < 0.001$, respectively). The average 24-hour urine protein level among preeclampsia patients was 578 mg/day, ranging from 374 to 2834 mg/day. The systolic/diastolic (S/D) ratio and the pulsatility index (PI) of the umbilical artery showed no significant differences between the groups. Maternal blood sortilin levels were significantly higher in the preeclampsia group, with an average of 5.27 ng/mL (Q1–Q3: 4.22–8.49) compared to 4.09 ng/mL (Q1–Q3: 2.85–6.13) in the control group ($p = 0.004$, BMI-adjusted $p = 0.034$).

Maternal blood sortilin levels for each week between preeclampsia and control groups are shown in Table 2. In both groups, lower sortilin values were noted at gestational ages of < 34 weeks and at 36 weeks, in comparison to other evaluated time intervals.

Birth characteristics and neonatal outcomes of the newborns are examined in Table 3. The gestational age at delivery was significantly lower in the preeclampsia group ($p < 0.001$), with a significantly higher incidence of preterm births ($p = 0.002$). Cesarean section rates were higher in the preeclampsia group compared to the

Table 1 Maternal characteristics and perinatal outcomes of the pregnant woman included in the study

	Preeclampsia *n* = 44	Control *n* = 44	Total *n* = 88	*p*
Maternal age (year)	30 (24–34)	28 (24–32)	29 (24–33)	0.148
Weight gained during pregnancy (kg)	10 (8–14)	12 (9–16)	10 (8–15)	0.161
BMI at during test (kg/m^2)	33.3 (28.9–39.6)	28.2 (25.9–32.2)	30.9 (26.5–36.8)	0.001
Gravida	2 (1–3)	2 (1–3)	2 (1–3)	0.197
Parity	1 (0–1)	1 (0–1)	1 (0–1)	0.287
Parity				0.129
Nulliparous	22 (50)	14 (31.8)	36 (40.9)	
Multiparous	22 (50)	30 (68.2)	52 (59.1)	
Abortion	0 (0–0)	0 (0–1)	0 (0–0)	0.124
Diagnosis week (week)	33 (30–36)	-	-	N/A
Blood sample collection time (week)	35 (32–37)	34 (32–36)	34 (32–36)	0.316
Hemoglobin (g/dL)	12.1 ± 1.56	11.7 ± 1.29	11.9 ± 1.44	0.181
WBC (*10^3/mm^3)	11.2 (9.4–12.9)	10.5 (8.8–12.4)	10.8 (8.9–12.6)	0.278
Platelet (*10^3/mm^3)	248 (187–286)	240 (210–299)	244 (200–289)	0.392
AST (U/L)	19 (15–23)	15 (12–18)	17 (13–20)	0.001
ALT (U/L)	11 (9–17)	10 (8–13)	11 (8–14)	0.066
Uric acid (mg/dL)	5.3 (4.3–6.4)	3.9 (3.2–5.3)	4.7 (3.6–5.7)	< 0.001
Fibrinogen (mg/dL)	539 (443–596)	465 (434–537)	488 (439–567)	0.078
Protein in 24-hour urine (mg/day)	578 (374–2834)	-	-	N/A
HELLP syndrome	2 (4.5)	0 (0)	2 (2.3)	0.494
Abruption placenta	2 (4.5)	0 (0)	2 (2.3)	0.494
Eclampsia	1 (2.3)	0 (0)	1 (1.1)	N/A
Maternal blood Sortilin levels (ng/mL)	5.27 (4.22–8.49)	4.09 (2.85–6.13)	4.75 (3.42–6.98)	0.004 *
Umblical arterial systolic/diastolic (S/D) ratio	2.7 (2.1–3.3)	2.6 (2.3–3.1)	2.6 (2.3–3.2)	0.880
Umblical arterial pulsatility index (PI)	1.0 (0.8–1.2)	0.9 (0.8-1.0)	0.9 (0.8–1.1)	0.235

BMI: Body mass index, WBC: White blood cell, AST: Aspartate aminotransferase, ALT: Alanin aminotransferase, HELLP: Hemolysis-Elevated Liver enzymes-Low platelets

Data are expressed as mean ± SD, median and quartiles (Q1–Q3), or number (percentage) where appropriate. A p value of < 0.05 indicates a significant difference. * BMI-adjusted p values = 0.034

Table 2 Maternal blood sortilin levels for each week between preeclampsia and control groups

Maternal blood Sortilin levels (ng/mL)	mean ± SD	median	minimum-maxium
Preeclampsia			
< 34 weeks (*n* = 16)	7.38 ± 7.19	4.56	2.20-31.37
34 weeks (*n* = 5)	5.94 ± 1.60	5.62	4.60–8.69
35 weeks (*n* = 5)	7.47 ± 2.56	6.80	4.31–10.29
36 weeks (*n* = 5)	5.21 ± 4.31	3.72	2.35–12.72
≥ 37 weeks (*n* = 13)	24.1 ± 63.60	5.91	4.01-235.57
Control			
< 34 weeks (*n* = 17)	12.5 ± 26.05	4.75	2.20-109.02
34 weeks (*n* = 8)	4.0 ± 2.19	3.79	1.58–8.56
35 weeks (*n* = 5)	5.24 ± 2.20	6.48	2.35–7.32
36 weeks (*n* = 13)	13.9 ± 37.31	2.96	0.64-137.79
≥ 37 weeks (*n* = 1)	2.96	2.96	2.96–2.96
Total			
< 34 weeks (*n* = 33)	10.0 ± 19.24	4.75	2.20-109.02
34 weeks (*n* = 13)	4.8 ± 2.15	4.60	1.58–8.69
35 weeks (*n* = 10)	6.4 ± 2.54	6.55	2.35–10.29
36 weeks (*n* = 18)	11.9 ± 31.67	3.19	0.64-137.79
≥ 37 weeks (*n* = 14)	22.5 ± 61.36	5.62	2.96-235.57

control group ($p = 0.043$). While fetal sex ratios were similar between the groups, birth weight was significantly lower in the preeclampsia group than in the control group [(2310 (Q1–Q3: 1560–2875) vs. 3170 (Q1–Q3: 2885–3495), $p < 0.001$]. Additionally, the incidence of low birth weight infants was significantly higher in the preeclampsia group [20 (45.4%) vs. 2 (4.5%), $p < 0.001$]. Although the 1-minute and 5-minute APGAR scores were lower in the preeclampsia group ($p = 0.003$ and $p < 0.001$, respectively), the prevalence of newborns with a 5-minute APGAR score below 7 was similar between the groups ($p = 0.494$). Although RDS rates were similar between both groups ($p = 0.237$), NICU admission was significantly higher in the preeclampsia group ($p = 0.003$). The occurrence of composite adverse neonatal outcomes was significantly higher in the preeclampsia group compared to the control group (34.1% vs. 6.8%, $p = 0.001$).

Spearman's correlation between maternal blood sortilin levels and maternal-perinatal characteristics are examined in Table 4. The analysis revealed a negative correlation of maternal blood sortilin levels with parity (r=-0.326, $p = 0.031$) and fibrinogen levels (r=-0.273, $p = 0.010$). Conversely, a positive correlation was observed with WBC count ($r = 0.248$, $p = 0.020$), AST levels ($r = 0.311$, $p = 0.040$), ALT levels ($r = 0.273$, $p = 0.010$), and protein levels in 24-hour urine samples ($r = 0.263$, $p = 0.013$).

The sensitivity and specificity of maternal serum sortilin levels for predicting preeclampsia were assessed using ROC analysis. The analysis demonstrated that maternal blood sortilin levels are significantly associated with preeclampsia when using a threshold of > 3.57 ng/mL, yielding a sensitivity of 90.9% and a specificity of 45.5%. The AUC was 0.679 (95% Confidence Interval (CI): 0.571–0.774, $p = 0.002$), indicating the potential utility of sortilin levels as a biomarker for preeclampsia detection (Fig. 1). Additionally, it was also significantly associated with composite adverse neonatal outcomes at a cut-off value of > 3.57 ng/mL. This cut-off achieved a sensitivity

Table 3 Birth characteristics and neonatal outcomes of the participants

	Pre-eclampsia *n* = 44	Control *n* = 44	Total *n* = 88	*p*
Gestational age at delivery (week)	37 (34–37)	39 (37–39)	37 (36–39)	< 0.001
Preterm birth (< 37 week)	20 (46.5)	6 (13.6)	26 (29.9)	0.002
Birth method				0.043
Vaginal birth	10 (22.7)	20 (45.5)	30 (34.1)	
Cesarean section	34 (77.3)	24 (54.5)	58 (65.9)	
Primary cesarean section	21 (47.7)	7 (15.9)	28 (31.8)	
Previous cesarean section history	13 (29.5)	17 (38.6)	30 (34.1)	
Gender				0.286
Male	19 (43.2)	25 (56.8)	44 (50)	
Female	25 (56.8)	19 (43.2)	44 (50)	
Birth weight (gram)	2310 (1560–2875)	3170 (2885–3495)	2885 (2300–3229)	< 0.001
Low birth weight (< 2500 gram)	20 (45.4)	2 (4.5)	22 (25)	< 0.001
Antenatal corticosteroid therapy	36 (81.8)	5 (11.6)	41 (47.1)	< 0.001
APGAR Score at 1st minute	9 (8–9)	9 (9–9)	9 (8–9)	0.003
APGAR Score at 5th minute	10 (9–10)	10 (10–10)	10 (9–10)	< 0.001
APGAR Score at 5th minute < 7	2 (4.5)	0	2 (2.3)	0.494
RDS	5 (11.4)	2 (4.5)	7 (7.9)	0.237
NICU admission	14 (31.8)	3 (6.8)	17 (19.3)	0.003
Composite adverse neonatal outcomes *	15 (34.1)	3 (6.8)	18 (20.4)	0.001

RDS: Respiratory distress syndrome, NICU: Neonatal intensive care unit

* The composite adverse neonatal outcome was defined as the occurrence of at least one of the following situations: APGAR Score at 5th minute < 7, respiratory distress syndrome (RDS), and admission to neonatal intensive care unit (NICU)

Data are expressed as mean ± SD, median and quartiles (Q1–Q3), or number (percentage) where appropriate. A p value of < 0.05 indicates a significant difference

of 89.6%, a specificity of 36.1%, and an AUC of 0.620 (95% CI: 0.510–0.721, $p = 0.045$), suggesting statistical significance in their ability to predict neonatal outcomes (Fig. 2).

Discussion

The study showed that sortilin levels, an indicator of oxidation and inflammation, in maternal blood samples from preeclampsia patients were significantly higher than in the maternal blood of healthy pregnant women. High sortilin levels were associated with preeclampsia, with a cut-off point of > 3.57 ng/mL indicating a sensitivity of 90.9%, a specificity of 45.5%, and an AUC: 0.679 (95% CI: 0.571–0.774, $p = 0.002$). In addition to demonstrating high sensitivity in detecting preeclampsia among pregnant women, at a cut-off point of > 3.57 ng/mL, showed 89.6% sensitivity, 36.1% specificity, and an AUC of 0.620 (95% CI: 0.510–0.721, $p = 0.045$) for predicting composite adverse neonatal outcomes. Furthermore, AST, ALT, and protein in 24-hour urine, which are important components in the diagnosis and severity of preeclampsia, were significantly correlated maternal blood sortilin levels.

Table 4 Spearman's correlation between maternal blood sortilin levels and maternal-perinatal characteristics

	r	*p*
Maternal age	-0.032	0.834
Weight gain	-0.029	0.785
BMI	-0.226	0.140
Parity	-0.326	0.031
Blood sample collection time	-0.252	0.099
Hemoglobin	0.004	0.971
WBC	0.248	0.020
Platelet	-0.019	0.858
AST	0.311	0.040
ALT	0.273	0.010
Uric acid	-0.295	0.055
Fibrinogen	-0.273	0.010
Protein in 24-hour urine	0.263	0.013
Umblical arterial systolic/diastolic (S/D) ratio	-0.060	0.700
Umblical arterial pulsatility index (PI)	0.032	0.839
Gestational age at delivery	-0.107	0.491
Birth weight	-0.187	0.225
APGAR Score at 1st minute	-0.236	0.122
APGAR Score at 5th minute	-0.212	0.168

BMI: Body mass index, WBC: White blood cell, AST: Aspartate aminotransferase, ALT: Alanin aminotransferase

Although preeclampsia is one of the most important causes of maternal mortality and morbidity, the underlying pathophysiology is not yet fully understood [3, 13]. Redman et al. demonstrated that in patients with preeclampsia, the syncytiotrophoblasts of the placenta become dysfunctional under oxidative stress, leading to an increased release of proinflammatory cytokines and subsequent endothelial dysfunction [14]. Salafia et al. identified acute atherotic plaques, which contribute to fibrin accumulation and endothelial damage, as key elements in the pathogenesis of preeclampsia. These plaques promote hypoperfusion of the placenta and ischemia-related pathology [15]. In their study, Devisme et al. linked preeclampsia to placental infarction and thrombosis [16]. In their examination of the pathophysiology of preeclampsia, Nirupama et al. highlighted abnormal placentation, altered angiogenic-antiangiogenic balance (e.g., decrease in NO, increase in sFlt-1, decrease in PLGF), and endothelial dysfunction [17]. Despite evidence indicating that maternal endothelial dysfunction—characterized by reduced NO production

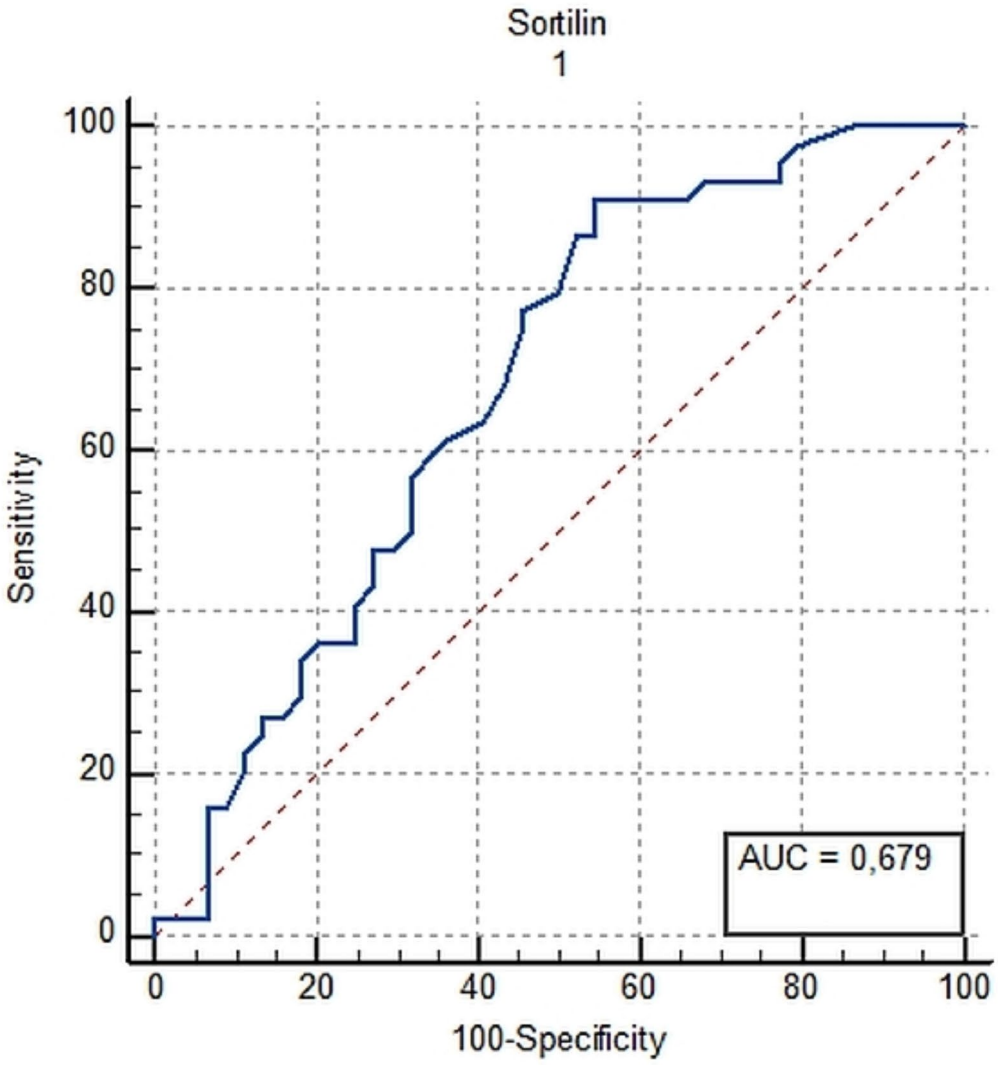

Fig. 1 Maternal blood sortilin levels are significantly associated with preeclampsia, with a threshold of > 3.57 ng/mL (AUC = 0.679, $p = 0.002$)

and vasodilation, increased oxidative stress and reactive oxygen species, as well as atherosis and thrombosis—contributes to the etiology of preeclampsia, the full pathophysiology of this condition remains incompletely understood. Based on this uncertainty, we initiated this investigation by hypothesizing that sortilin, a marker linked to oxidative stress, endothelial dysfunction and inflammation, may play a critical role in the pathophysiology of preeclampsia. Specifically, our analysis determined that a sortilin level exceeding 3.57 ng/mL could predict the occurrence of preeclampsia with a high sensitivity of 90.9%. This finding not only serves as an indicator of sortilin's potential pathophysiological involvement in the development of preeclampsia but also positions sortilin as a promising biomarker for its early detection. Furthermore, it underscores the imperative for additional studies to unravel sortilin's underlying mechanisms and explore its potential therapeutic applications in managing preeclampsia. In their investigation into the role of sortilin in hypertension, Avvisato et al. found that sortilin levels were significantly higher in the blood samples of individuals with hypertension, suggesting its involvement in the disease's pathogenesis [7]. Similarly, research by Mortensen et al. established a link between sortilin and key cardiovascular issues such as atherosclerosis, vascular inflammation, and endothelial dysfunction [18]. Echoing these findings, Goettsch et al., in their exploration of sortilin's relationship with metabolic diseases, also highlighted its association with atherosclerosis and endothelial dysfunction, underlining the broader implications of sortilin in vascular health [19].

This study demonstrated that maternal blood sortilin levels are not only highly sensitive in the pathophysiology of preeclampsia, but also play a significant role in

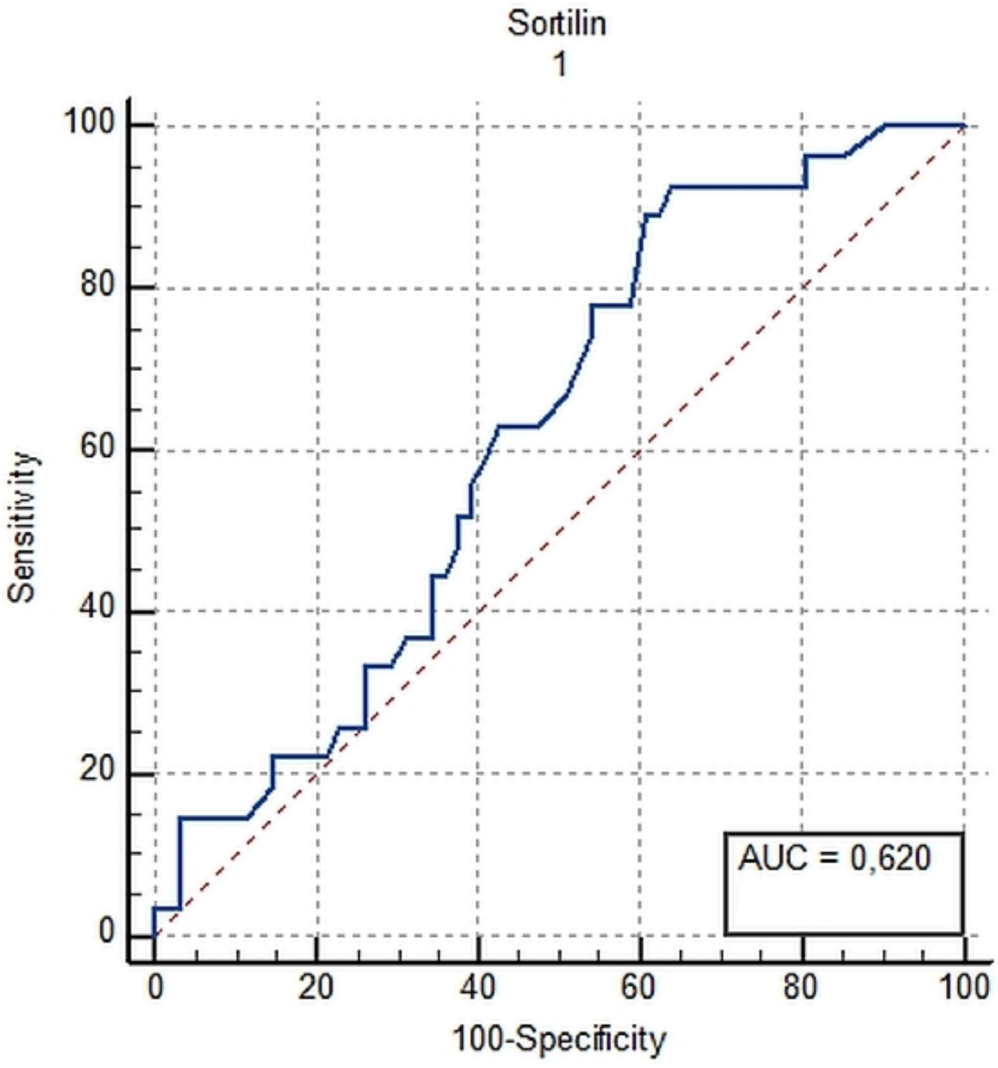

Fig. 2 Maternal blood sortilin levels are significantly associated with composite adverse neonatal outcomes, with a cut-off value of > 3.57 ng/mL (AUC = 0.620, $p = 0.045$)

predicting composite adverse neonatal outcomes. To our knowledge, there is no study in the literature examining maternal blood sortilin levels and composite adverse neonatal outcomes. Palmrich et al. investigated serum catestatin levels in preeclampsia patients. Cathestatin concentrations in the preeclampsia group were lower than in the control group, and admission to neonatal intensive care and low birth weight were significantly higher in newborns born to mothers with preeclampsia. However, in this study, the relationship between serum catestatin levels and adverse neonatal outcomes was not investigated [20]. Yilmaz et al. investigated renalase levels in preeclampsia patients. They showed that renalase levels were higher in preeclampsia patients. Adverse neonatal outcomes were significantly higher in the preeclampsia group than in the control group, but the relationship between renalase level and these outcomes was not investigated [21]. In our study, consistent with the literature, it was shown that 1st and 5th minute APGAR scores were lower and the NICU admission rate increased in preeclampsia cases. In addition, our findings established a link between high sortilin levels and composite adverse neonatal outcomes.

The significant correlation between maternal blood sortilin levels and clinical parameters such as AST, ALT, and proteinuria in 24-hour urine underscores the potential role of sortilin as a biomarker not only for the pathogenesis of preeclampsia but also for its severity assessment. Elevated AST and ALT levels are indicative of liver involvement, which is a critical aspect of severe preeclampsia, often associated with the HELLP syndrome [22]. These findings suggest that sortilin may

be intricately linked to the pathological mechanisms that exacerbate organ dysfunction in preeclampsia. The relationship with proteinuria, a hallmark of preeclampsia resulting from endothelial damage and increased vascular permeability, further emphasizes the systemic involvement of sortilin in this disorder. The utility of these correlations extends beyond diagnostic value. For clinicians, the simultaneous evaluation of sortilin levels alongside AST, ALT, and proteinuria could provide a more comprehensive risk stratification framework.

Currently, the only definitive treatment for preeclampsia is delivery [23, 24], highlighting a significant gap in therapeutic options or preventetive measures for this condition. However, intriguing developments in the study of sortilin in other diseases provide a hopeful perspective for future research into preeclampsia treatment. Animal studies with sortilin have shown that sortilin antibodies increase the effectiveness of treatment in breast cancer patients [8]. Specifically, Simonian et al. have identified sortilin as being abundantly present on the surface of breast cancer cells, suggesting that targeting sortilin with antibodies could offer a novel therapeutic approach [25]. Similarly, Chen et al. have highlighted the disruption of the sortilin signaling pathway as a promising strategy for neuroprotection in Parkinson's disease, marking it as an innovative target for treatment. These findings suggest that sortilin's role in other diseases—such as its regulation of oxidative stress and inflammation—could be relevant to preeclampsia. By modulating these mechanisms, which are central to the pathogenesis of preeclampsia, sortilin-targeted therapies may help mitigate the condition's progression [25]. Further investigation is warranted to explore whether targeting sortilin-mediated pathways could lead to effective preventive or therapeutic strategies for preeclampsia, potentially addressing this critical unmet medical need.

This study has several limitations. First, while the sample size was considered adequate for preliminary findings, the relatively small number of participants may limit the generalizability of the results and the statistical power to detect smaller effect sizes. Future studies should use a larger group of patients to provide a more comprehensive assessment of the efficacy of sortilin as a predictive marker for preeclampsia. Second, the study did not stratify preeclampsia cases by severity (mild vs. severe) or by onset timing (early-onset vs. late-onset preeclampsia). All participants in the preeclampsia group were included based on general diagnostic criteria without further stratification. Categorizing cases based on severity and onset timing could have provided deeper insights into whether sortilin levels differ between these subgroups, potentially offering a better understanding of its role in disease progression. Future studies should incorporate such stratification to explore these relationships more effectively. Third, although the study results showed that AST, ALT, and protein in 24-hour urine, which are important components in the diagnosis and severity of preeclampsia, were significantly correlated with maternal blood sortilin levels, the correlation coefficients were relatively small (< 0.4). Fourth, the study did not include longitudinal measurements of sortilin levels throughout pregnancy, which could better evaluate the temporal relationship between sortilin levels and the development of preeclampsia. Collecting serial measurements starting from the first trimester would provide critical insights into whether sortilin can serve as an early predictive biomarker. Finally, we did not measure sortilin levels in fetal cord blood, an area that could provide valuable insight into the fetal effects of high maternal sortilin levels. Investigating fetal sortilin levels could potentially uncover new aspects of preeclampsia's impact on neonatal health. Despite these limitations, the study's significant strength lies in its novelty; it represents the first investigation into the serum sortilin levels in preeclampsia patients, establishing a foundation for future research in this critical area.

In conclusion, our findings demonstrate that maternal sortilin levels are elevated in patients with preeclampsia compared to those in a healthy pregnant control group. This study contributes to the understanding of preeclampsia by highlighting the potential role of sortilin—a marker linked to oxidative stress, endothelial dysfunction, and inflammation—in the disease's etiology. The identification of a specific cut-off point for sortilin levels (> 3.57 ng/mL) with a high sensitivity underscores its potential utility as a biomarker for the detection of preeclampsia. Furthermore, maternal sortilin levels may predict adverse neonatal outcomes. Additionally, significant correlations were observed between sortilin levels and key diagnostic markers of preeclampsia severity, such as AST, ALT, and proteinuria.

Author contributions

GK: Conceptualization, Methodology, Writing – Review & Editing. BB: Methodology, Resources, Writing – Review & Editing. ZS: Formal Analysis, Writing – Review & Editing. BTC: Resources, Writing – Review & Editing. GA: Resources, Formal Analysis. STS: Writing – Review & Editing. NVT: Resources, Writing – Review & Editing. UK: Writing – Review & Editing. DK: Resources. ATC: Supervision.

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Data availability

The data supporting this study are available from the corresponding authors upon reasonable request.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of Ankara Etlik City Hospital (approval number: AESH-EK1-2023-253). The patients who

participated in the study were informed and their written informed consent was obtained. This study complied with the provisions of the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Dimitriadis E, Rolnik DL, Zhou W, Estrada-Gutierrez G, Koga K, Francisco RPV, et al. Pre-eclampsia. Nat Rev Dis Primer. 2023;9(1):8.
2. Rolnik DL, Nicolaides KH, Poon LC. Prevention of preeclampsia with aspirin. Am J Obstet Gynecol. 2022;226(2S):S1108–19.
3. Burton GJ, Redman CW, Roberts JM, Moffett A. Pre-eclampsia: pathophysiology and clinical implications. BMJ. 2019;366:l2381.
4. Zeisler H, Llurba E, Chantraine F, Vatish M, Staff AC, Sennström M, et al. Predictive value of the sFlt-1:PlGF ratio in women with suspected preeclampsia. N Engl J Med. 2016;374(1):13–22.
5. Stepan H, Herraiz I, Schlembach D, Verlohren S, Brennecke S, Chantraine F, et al. Implementation of the sFlt-1/PlGF ratio for prediction and diagnosis of pre-eclampsia in Singleton pregnancy: implications for clinical practice. Ultrasound Obstet Gynecol. 2015;45(3):241–6.
6. Petersen CM, Nielsen MS, Nykjaer A, Jacobsen L, Tommerup N, Rasmussen HH, et al. Molecular identification of a novel candidate sorting receptor purified from human brain by receptor-associated protein affinity chromatography. J Biol Chem. 1997;272(6):3599–605.
7. Avvisato R, Jankauskas SS, Varzideh F, Kansakar U, Mone P, Santulli G. Sortilin and hypertension. Curr Opin Nephrol Hypertens. 2023;32(2):134–40.
8. Al-Akhrass H, Pietilä M, Lilja J, Vesilahti EM, Anttila JM, Haikala HM, et al. Sortilin-related receptor is a druggable therapeutic target in breast cancer. Mol Oncol. 2022;16(1):116–29.
9. Mitok KA, Keller MP, Attie AD. Sorting through the extensive and confusing roles of sortilin in metabolic disease. J Lipid Res. 2022;63(8):100243.
10. Varzideh F, Jankauskas SS, Kansakar U, Mone P, Gambardella J, Santulli G. Sortilin drives hypertension by modulating sphingolipid/ceramide homeostasis and by triggering oxidative stress. J Clin Invest. 2022;132(3):e156624.
11. Han W, Wei Z, Zhang H, Geng C, Dang R, Yang M, et al. The association between sortilin and inflammation in patients with coronary heart disease. J Inflamm Res. 2020;13:71–9.
12. Gestational Hypertension and Preeclampsia. ACOG practice bulletin, number 222. Obstet Gynecol. 2020;135(6):e237–60.
13. Gölbaşı C, Gölbaşı H, Gültekin CK, Gülseren V, Akşit MZ, Bayraktar B, et al. Ischemia modified albumin levels in intrauterine growth restriction: levels are increased in fetal cord blood but not in maternal blood. Ginekol Pol. 2022;93(12):993–8.
14. Redman CWG, Staff AC. Preeclampsia, biomarkers, syncytiotrophoblast stress, and placental capacity. Am J Obstet Gynecol. 2015;213(4, Supplement):S9.e1-S9.e4.
15. Salafia CM, Pezzullo JC, Ghidini A, Lopèz-Zeno JA, Whittington SS. Clinical correlations of patterns of placental pathology in preterm pre-eclampsia. Placenta. 1998;19(1):67–72.
16. Devisme L, Merlot B, Ego A, Houfflin-Debarge V, Deruelle P, Subtil D. A case-control study of placental lesions associated with pre-eclampsia. Int J Gynaecol Obstet Off Organ Int Fed Gynaecol Obstet. 2013;120(2):165–8.
17. Nirupama R, Divyashree S, Janhavi P, Muthukumar SP, Ravindra PV. Preeclampsia: pathophysiology and management. J Gynecol Obstet Hum Reprod. 2021;50(2):101975.
18. Mortensen MB, Kjolby M, Bentzon JF. Sortilin and atherosclerosis. Oncotarget. 2015;6(23):19352–3.
19. Goettsch C, Kjolby M, Aikawa E. Sortilin and its multiple roles in cardiovascular and metabolic diseases. Arterioscler Thromb Vasc Biol. 2018;38(1):19–25.
20. Palmrich P, Schirwani-Hartl N, Haberl C, Haslinger P, Heinzl F, Zeisler H, et al. Catestatin-A potential new therapeutic target for women with preeclampsia?? An analysis of maternal serum catestatin levels in preeclamptic pregnancies. J Clin Med. 2023;12(18):5931.
21. Yılmaz ZV, Akkaş E, Yıldırım T, Yılmaz R, Erdem Y. A novel marker in pregnant with preeclampsia: Renalase. J Matern-Fetal Neonatal Med Off J Eur Assoc Perinat Med Fed Asia Ocean Perinat Soc Int Soc Perinat Obstet. 2017;30(7):808–13.
22. Mei JY, Afshar Y. Hypertensive complications of pregnancy: hepatic consequences of preeclampsia through HELLP syndrome. Clin Liver Dis. 2023;22(6):195–9.
23. Ramos JGL, Sass N, Costa SHM, Preeclampsia. Rev Bras Ginecol E Obstet Rev Fed Bras Soc Ginecol E Obstet. 2017;39(9):496–512.
24. Vural T, Karaca SY, Bayraktar B, Gölbaşı C, Ekin A, Özeren M. Clinical significance of isolated gestational proteinuria: A prospective analysis of maternal and neonatal outcomes. J Clin Obstet Gynecol. 2024;34(4):132–40.
25. Simonian M, Haji Ghaffari M, Salimi A, Mirzadegan E, Sadeghi N, Ebrahimnezhad N, et al. Monoclonal antibody against sortilin induces apoptosis in human breast cancer cells. Avicenna J Med Biotechnol. 2022;14(1):37–45.

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