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A mitochondrial regulator protein, mitofusin 2, is elevated in the maternal blood of women with preeclampsia

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Abstract

Objective To investigate the expression of mitofusin 2 (Mfn2) in the placenta and peripheral blood of patients with early-onset preeclampsia (eoPE) and late-onset preeclampsia (loPE), and to evaluate its possibility as a diagnostic and therapeutic target for preeclampsia.

Methods A total of 68 pregnant women with preeclampsia in Jiaxing Maternal and Child Health Hospital from June 2022 to June 2024 were selected, including 32 patients with eoPE and 36 patients with loPE, and 68 term pregnant women as negative controls. Real-time fluorescence reverse transcription (RT-qPCR) was used to determine the expression level of Mfn2 mRNA in placenta and peripheral blood, and the expression of Mfn2 was analyzed; enzyme-linked immunosorbent assay (ELISA) was used to determine the level of Mfn2 in peripheral blood of patients, and the outcomes of pregnant women (placental weight, neonatal birth weight, 1 min Apgar) were recorded. The correlation between the level of Mfn2 in peripheral blood and the severity of preeclampsia and pregnancy outcomes was analyzed.

Result The expression of Mfn2 mRNA in the placenta tissue of the eoPE group was significantly lower than that of the term pregnancy group and the loPE group ($P < 0.001$), while the expression of Mfn2 in the placenta tissue of the loPE group was only lower than that of the term pregnancy group, with no significant difference($P > 0.05$). The expression of Mfn2 mRNA in the peripheral blood of eoPE and loPE was significantly higher than that of term pregnancy group (all $P < 0.001$). In the peripheral blood, the levels of Mfn2 in eoPE group and loPE group were significantly higher than that of the term pregnancy group (all $P < 0.001$). The Pearson correlation analysis showed that the expression level of Mfn2 protein in peripheral blood of patients are positively correlated with blood pressure and urinary protein, and negatively correlated with neonatal birth weight and 1 min Apgar score.

Conclusion In early-onset placenta, the expression of Mfn2 is significantly lower than that in full-term pregnancy, while in late-onset eclampsia, it is not, indicating that the abnormal expression of Mnf2 in placenta is related to the occurrence period of preeclampsia and the progression of the disease; Mfn2 in peripheral blood can be used as a biological marker to evaluate the occurrence and progression of preeclampsia.

Keywords Early-onset preeclampsia, Late-onset preeclampsia, Mitofusin 2, Pregnancy outcomes, Biological marker

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Introduction

Preeclampsia (PE) is an obstetric disease characterized by new-onset hypertension after 20 weeks of gestation, accompanied by proteinuria or other organ dysfunction [1]. The global prevalence of preeclampsia is 2–8%. Approximately 76,000 pregnant women and 500,000 perinatal infants die from preeclampsia and related hypertensive diseases each year, making it one of the major causes of morbidity and mortality in pregnant women and perinatal infants [2]. Preeclampsia can be divided into early-onset preeclampsia (eoPE) and late-onset preeclampsia (loPE), postpartum PE (within 48 h after delivery), and delayed PE (48 h to 2 weeks after delivery) according to gestational age. eoPE and loPE begin to show clinical signs and symptoms and delivery around 34 weeks of gestation, respectively.

The placenta is the site for material exchange between the fetus and the mother, and its structure and function are very important for maintaining normal physiological functions of cells [3]. Insufficient placental nutrient and oxygen transport leads to shallow placental implantation, which is one of the pathological characteristics of preeclampsia, accompanied by changes in placental mitochondrial function. Mitochondria are organelles with multiple functions that can respond to a variety of stimuli, such as cellular energy requirements under normal physiological conditions or changes in oxidative phosphorylation and signal transduction under stress conditions. Emerging evidence suggests that mitochondrial dysfunction contributes to preeclampsia pathogenesis, including impaired oxidative phosphorylation and increased reactive oxygen species [4–5]. However, preeclampsia is a multifactorial disorder, and mitochondrial abnormalities may represent one component of its complex etiology.

Mitofusin 2 (Mfn2) is a transmembrane protein with guanosine triphosphatase activity. In mammalian cells, Mfn2 is localized on the outer membrane of mitochondria and the surface of the endoplasmic reticulum. It can anchor mitochondria to the endoplasmic reticulum and participate in the bridging of mitochondria and the endoplasmic reticulum [6]. Yu et al. [7] showed that Mfn2 expression was reduced in the placental tissue of patients with preeclampsia, mitochondrial fusion defects, accelerated mitochondrial fragmentation, and increased trophoblast apoptosis. The above suggests that Mfn2 may play a role in the occurrence and development of preeclampsia, but it has not yet been distinguished between eoPE and loPE. There is clear evidence that there are significant differences in placental pathology between eoPE and loPE. In early-onset PE, due to the remodeling disorder of the uterine spiral arteries, insufficient placental blood perfusion occurs, and pathological and physiological changes such as ischemia and hypoxia occur. In late-onset PE, poor remodeling of the uterine spiral arteries is rarely observed, and compared with normal pregnant women, the placental blood perfusion level can be maintained at normal or even higher [8]. Therefore, it is necessary to distinguish eoPE from loPE (although they present with the same maternal characteristics, signs, and symptoms of preeclampsia) to more accurately clarify that Mfn2 plays an important role in the development of preeclampsia.

In this study, we detected the expression of Mfn2 in the placenta and peripheral blood of term pregnancy, eoPE patients, and loPE patients to clarify that there are differences in the expression of Mfn2 with the occurrence of preeclampsia during pregnancy and disease progression. This will provide a reference for further research on the differences in the pathogenesis of eoPE and loPE. By detecting and analyzing the correlation between serum Mfn2 levels and the severity of preeclampsia and pregnancy outcomes, it will provide support for clinical prediction, diagnosis and early treatment of preeclampsia.

Materials and methods

Patients and sample collection

This study included 68 pregnant women with preeclampsia who gave birth at Jiaxing Maternal and Child Health Hospital between June 2022 and June 2024, including 32 patients with eoPE (eoPE group), 36 patients with loPE (loPE group), and 68 term pregnant women negative controls (normal group). Data recorded included maternal age, gestation at delivery, blood pressure on admission, proteinuria, baby weight and 1 min Apgar score. All women were non-smoking and had no family history of preeclampsia. Preeclampsia was defined as a maternal systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg measured on two occasions separated by at least 6 h, and proteinuria > 300 mg on a 24 h urinary collection or qualitatively, > 1+, after 20 weeks of gestation following the guidelines of the International Society for the Study of Hypertension in Pregnancy (ISSHP). eoPE was defined as occurring at less than 34 weeks, and loPE occurs after 34 weeks. Placental tissue was taken from the central area around the umbilical cord immediately after delivery, avoiding infarcts and calcified areas. The specimens were then washed with cold phosphate-buffered saline(PBS)and stored at-80℃ until further use. Maternal venous blood was collected before delivery, and serum was separated and stored at -80℃. This study adhered to the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Jiaxing Municipal Maternal and Child Health Care Hospital affiliated to Jiaxing University, and participants signed informed consent.

Table 1 The sequences of primers used in this study

Genes	Forward	Reverse
Mfn2	5′-ATCTGTGCCAGCAAGTTGACA-3′	5′-AAGTGAATC-CAGAGCCTCGAC-3′
β-actin	5′ATTGCCGACAGGATGCAGAA-3′	5′GCTGATCCA-CATCTGCTGGA-3′

Reverse transcription-quantitative polymerase chain reaction (RT-qPCR)

Placenta tissue and peripheral blood were ground with Trizol and total RNA was extracted. For the detection of Mfn2 expression, a PrimeScript II 1st Strand cDNA Synthesis Kit was used to synthesize cDNA, and qPCR was performed using the SYBR® Premix Ex Taq™ kit on an Applied Biosystems 7500 thermocycler.The PCR reaction conditions were: 95℃ 3 min, 95℃ 30s, 56℃ 20s, 72℃ 30s, a total of 42 cycles.The sequences of primers shown in Table 1. Relative Mfn2 mRNA expression in the placenta and peripheral blood was determined with $2^{-\Delta\Delta Ct}$ method, β-actin gene was used as an internal reference, as described in our previous publications [9].

Enzyme-Linked Immunosorbent (ELISA) Assay

Peripheral blood was drawn before delivery and placed in a non-anticoagulant tube to separate the serum. Mfn2 content was determined using the Mfn2 ELISA kit (Cloud-Clone, Katy, TX, USA) according to the kit instructions. The absorbance (OD value) of each well solution was measured using an enzyme-labeled instrument at a wavelength of 450 nm.

Statistical analysis

Statistical analysis was performed using SPSS 20.0 software. Measurement data were expressed as mean ± standard deviation (SD). One-way analysis of variance was used for comparison, and LSD-t test was used for pairwise comparison. Correlation analysis was performed using Pearson correlation analysis or Spearman rank correlation analysis. All data considering p values < 0.05 as statistically significant.

Results

Clinical characteristics of pregnancies with and without preeclampsia

The general information and statistical data of the three groups of patients are shown in Table 2. As a result, there were significant differences between eoPE and normal group in the gestational age at delivery, systolic blood pressure, diastolic blood pressure, proteinuria, birth weight, and 1 min Apgar score, as well as between loPE and NC groups ($P < 0.001$). Moreover, significant differences existed between eoPE and loPE groups in the gestational age at delivery ($P < 0.001$), birth weight ($P < 0.001$), 1 min Apgar score ($P < 0.001$) and Proteinuria ($P < 0.05$). No significant difference existed in other clinical features.

The effect of Mfn2 on eoPE is different from that on loPE

To investigate the differential expression of Mfn2 in patients with eoPE and loPE, we detected the expression of Mfn2 mRNA in the placenta and peripheral blood. As shown in Fig. 1A, the expression levels of Mfn2 mRNA in the placenta increased sequentially in the eoPE group, loPE group, and normal group. The eoPE group was significantly lower than the normal group ($P < 0.001$) and the loPE group ($P < 0.05$), but there was no significant difference between the loPE group and the normal group ($P > 0.05$). The expression level of Mfn2 mRNA in peripheral blood decreased sequentially in the eoPE group, loPE group, and normal group. The eoPE group was significantly higher than the normal group ($P < 0.001$) and the loPE group ($P < 0.05$), and the loPE group was significantly higher than the normal group ($P < 0.001$). To exclude gestational age as a potential confounder of Mfn2 levels, the analysis of covariance were performed with gestational age as the covariate, consistent with the previous results, supporting its association with PE independent of pregnancy stage.The level of Mfn2 mRNA in the placenta of pregnant women with eoPE is negatively correlated with the level of Mfn2 mRNA in peripheral blood (r=-0.471, $P < 0.01$), but not in loPE. The above results indicate that the mechanism of action of Mfn2 on eoPE patients is different from that on loPE patients and the abnormal expression of Mnf2 in placenta is related to

Table 2 Clinical baseline data of term pregnancy, early-onset preeclampsia, and late-onset preeclampsia

Clinical features	Normal group	Early-onset preeclampsia	Late-onset sever preeclampsia
Age (year)	28.59 ± 3.0	30.25 ± 5.14	29.61 ± 4.59
Gestational age at delivery (week)	39.09 ± 0.66	31.03 ± 1.79***	37.14 ± 1.59***###
Number of childbirths	1.29 ± 0.46	1.41 ± 0.56	1.44 ± 0.74
Systolic Blood Pressure (mm Hg)	120.07 ± 9.59	150.28 ± 10.26***	150.69 ± 14.07
Diastolic Blood Pressure (mm Hg)	73.09 ± 11.02	98.91 ± 7.89***	97.69 ± 6.84
Proteinuria (g/24 h)	0.19 ± 0.05	2.58 ± 0.54***	2.31 ± 0.50***#
Birth weight (g)	3587.65 ± 364.86	2430.59 ± 254.49***	2833.83 ± 301.58***###
1 min Apgar score	9.59 ± 0.55	7.88 ± 1.04***	8.64 ± 0.76***###

***$P < 0.001$ vs. Normal group. #$P < 0.05$ vs. Early-onset preeclampsia; ###$P < 0.001$ vs. Early-onset preeclampsia

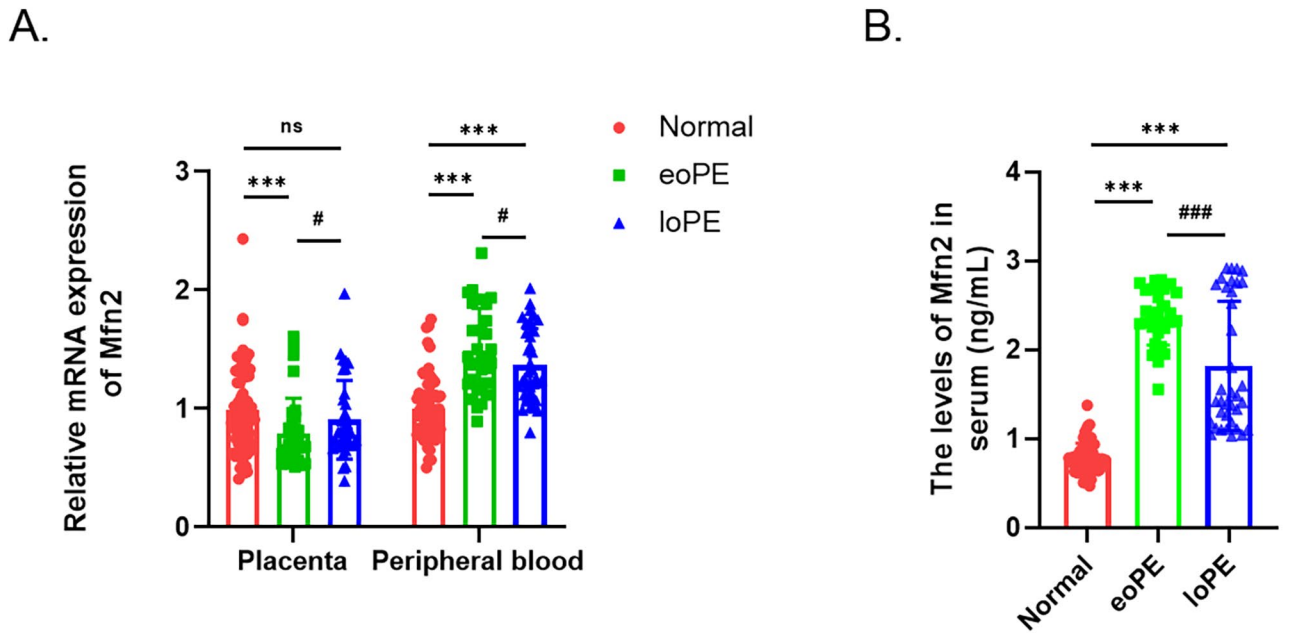

Fig. 1 Mfn2 expression level in subjects. (**A**) Comparison of Mfn2 mRNA levels in placenta and peripheral blood of normal group, eoPE, and loPE. (**B**) Comparison of Mfn2 protein levels in the serum of normal group, eoPE, and loPE (***$P<0.001$ vs. normal group. ###$P<0.001$, #$P<0.05$ vs. eoPE)

the occurrence period of preeclampsia and the progression of the disease.

Correlation analysis between serum Mfn2 protein level and severity of preeclampsia

After confirming that the mRNA level of Mfn2 in peripheral blood of patients with preeclampsia was significantly higher than that of the normal group, the protein level of Mfn2 in serum was also detected. As shown in Fig. 1B, the eoPE group was significantly higher than the normal group ($P<0.001$) and the loPE group ($P<0.001$), and the loPE group was significantly higher than the normal group ($P<0.001$). To determine the correlation between serum Mfn2 protein levels and the severity of preeclampsia, as shown in Fig. 2, the levels of Mfn2 in patients with eoPE and loPE are positively correlated with systolic blood pressure ($r=0.891$, $P<0.01$ and $r=0.791$, $P<0.01$), diastolic blood pressure ($r=0.694$, $P<0.01$ and $r=0.252$, $P>0.05$), and proteinuria ($r=0.604$, $P<0.01$ and $r=0.560$, $P<0.01$), with a stronger correlation observed in eoPE.

Correlation analysis between serum Mfn2 protein levels and the outcomes in patients with preeclampsia

Meanwhile, to further confirm whether the protein level of Mfn2 in peripheral blood is correlated with the outcomes in patients with preeclampsia, we analyzed the correlation between Mfn2 and birth weight as well as 1 min Apgar score in patients with eoPE and loPE. The results showed that the levels of Mfn2 in patients with eoPE and loPE are negatively correlated with birth weight (r=-0.690, $P<0.01$ and r=-0.648, $P<0.01$) and 1 min Apgar score (r=-0.532, $P<0.01$ and r=-0.488, $P<0.01$), with a stronger correlation observed in eoPE (Fig. 3).The above results indicate that the levels of Mfn2 in serum are correlated with the severity of preeclampsia and pregnancy outcomes, especially in eoPE, which will provide support for clinical prediction, diagnosis, and early treatment of preeclampsia.

Discussion

Preeclampsia is a dynamic disease that progresses continuously and occurs after 20 weeks of pregnancy. Its pathogenesis is not yet fully understood. This disease seriously affects the health of mothers and infants and is one of the leading causes of maternal and perinatal mortality. Currently, termination of pregnancy is the only treatment and strategy [10]. Preeclampsia has been shown to impose another burden on mothers and children because it can have long-term effects on both, such as a higher risk of developing cardiovascular disease in later life [11]. Therefore, elucidating the pathogenesis of preeclampsia has become an important clinical issue in obstetrics.

The stability of mitochondrial structure and function is essential for normal cell metabolism and survival. It will regulate the cell's stress response to cope with the stimulation [12]. Mitochondrial dysfunction is associated with a series of diseases, including neurological diseases, cardiovascular system, etc [13, 14]. Studies have shown that mitochondrial dysfunction can have serious consequences on neuronal function and structure [15, 16]. In terms of cardiac dysfunction, studies have found that long-term lack of Mfn2 may lead to more severe

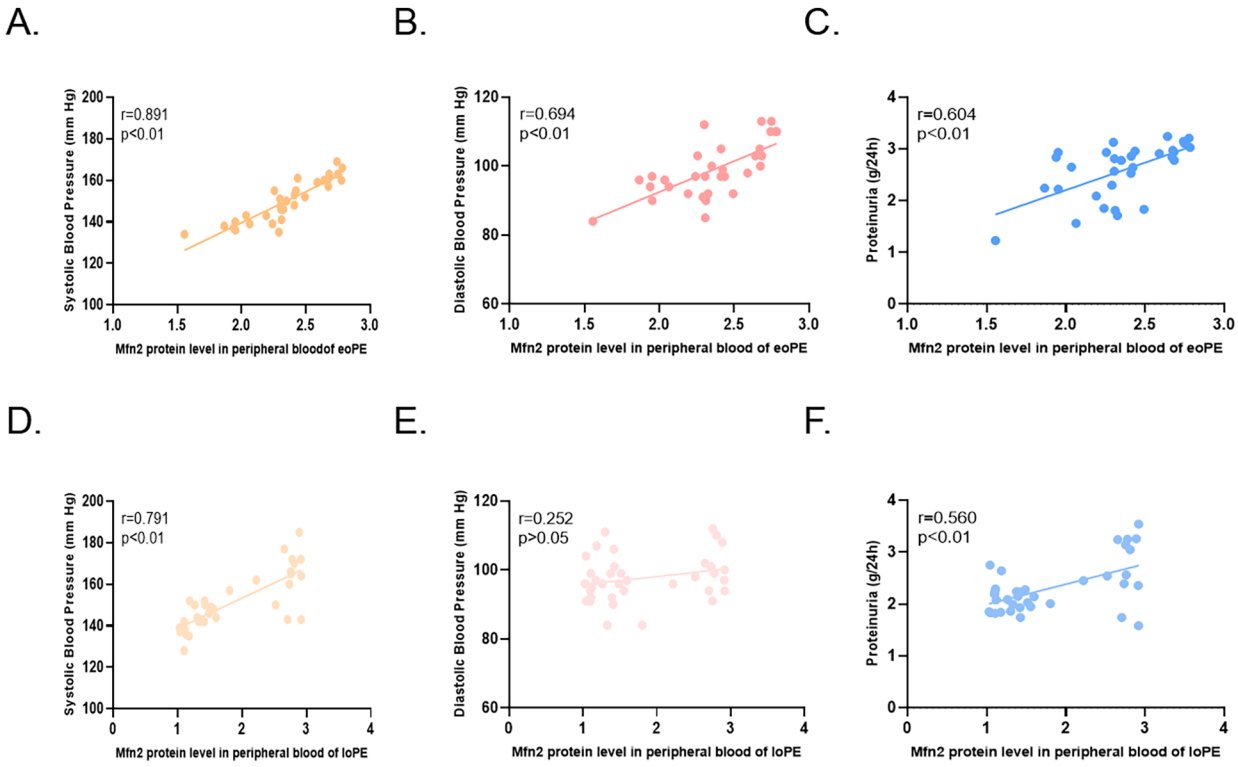

Fig. 2 Correlation analysis between serum Mfn2 protein level and severity of preeclampsia. The levels of Mfn2 in patients with eoPE and loPE are positively correlated with systolic blood pressure (**A**, $r=0.891$, $P<0.01$ and **D**, $r=0.791$, $P<0.01$), diastolic blood pressure (**B**, $r=0.694$, $P<0.01$ and **E**, $r=0.252$, $P>0.05$), and proteinuria (**C**, $r=0.604$, $P<0.01$ and **F**, $r=0.560$, $P<0.01$)

cardiomyopathy defects due to lack of fusion [17, 18]. It can be seen that the common characteristics of these diseases are mitochondrial dysfunction and increased cell apoptosis. For the metabolically active placental tissue, the focus can also be on mitochondrial dysfunction to study the involvement of mitochondrial dysfunction in the onset of preeclampsia. By balancing mitochondrial dynamics to treat the onset of preeclampsia, the prognosis of preeclampsia patients and fetuses can be improved.

Studies have shown that eoPE is caused by specific trophoblast cell defects, while loPE is caused by maternal metabolic defects [19, 20]. eoPE is characterized by impaired villous growth in early pregnancy, superficial invasion of exotrophoblast cells, insufficient transformation of uterine spiral arteries, changes in placental perfusion and maternal blood (the flow rate of maternal blood from insufficiently transformed spiral arteries into the interstitial space is higher), and changes in perfusion of basic organs of the fetus, including the placenta. Therefore, the fetal growth curve of this case showed a clear trend of growth restriction. loPE is characterized by an increasing mismatch between normal maternal perfusion and the metabolic needs of the placenta and fetus, coupled with maternal genetic susceptibility to cardiovascular and metabolic diseases and high body mass index. The fetal growth curve of this case did not show a clear trend of growth restriction. The possible mechanism is that in patients with loPE, the villous trophoblast is affected in some or larger parts, and other parts of the placenta may be sufficient to compensate so that the fetus can grow and develop normally.

However, the disorder of placental spiral artery remodeling causes the placenta to be in a state of low blood perfusion and hypoxia, and the reactive oxygen and reactive nitrogen produced by mitochondria are produced in large quantities [21]. Mitochondria should fuse/fission in response to stress conditions such as hypoxia. When the antioxidant capacity of mitochondria and the body is insufficient, reactive oxygen will attack mitochondria and cause mitochondrial damage, while promoting cell apoptosis, trophoblast proinflammatory cytokines and chemokines, and trophoblast cell fragments are released into the maternal circulation, causing endothelial cell dysfunction and systemic inflammatory response, thereby inducing clinical manifestations of preeclampsia [22]. It can be seen that there are differences in the mechanism of action of mitochondria in eoPE and loPE, and it may play a more important role in eoPE.

Mitofusin 2 (Mfn2) is one of the mitochondrial outer membrane proteins that regulates mitochondrial

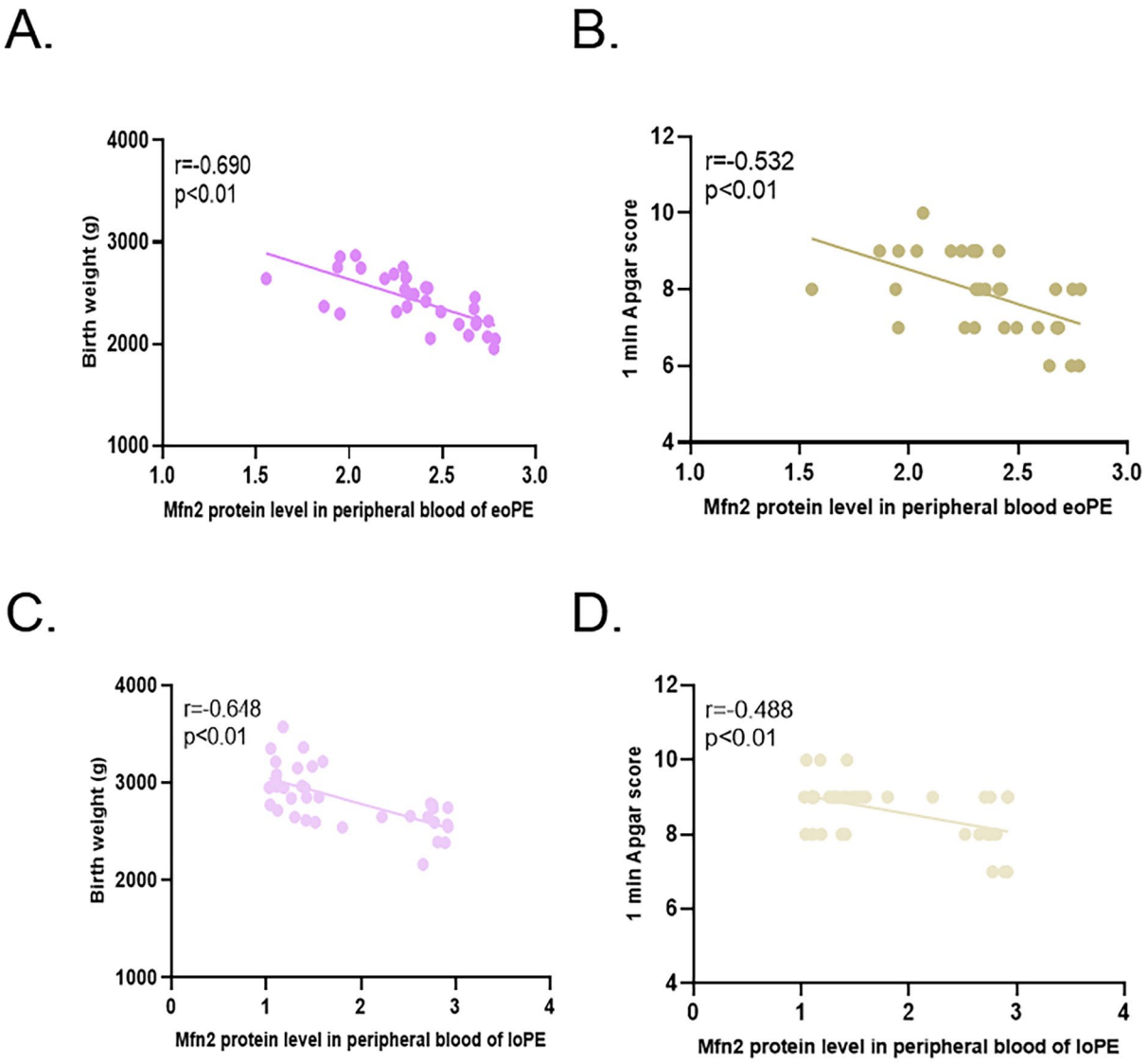

Fig. 3 Correlation analysis between serum Mfn2 protein levels and the outcomes in patients with preeclampsia. The levels of Mfn2 in patients with eoPE and loPE are negatively correlated with birth weight (**A**, r=-0.690, $P<0.01$ and **C**, r=-0.648, $P<0.01$) and 1 min Apgar score (**B**, r=-0.532, $P<0.01$ and **D**, r=-0.488, $P<0.01$)

homeostasis, including processes such as mitochondrial fusion and fission [6]. Mfn2 also plays a role in regulating many cellular functions such as cell proliferation, apoptosis, energy metabolism, and signal transduction [23, 24]. Studies have shown that low expression of Mfn2 can cause mitochondrial dysfunction, and low expression of Mfn2 increases cell apoptosis [25, 26]. However, there are few reports on whether Mfn2 participates in preeclampsia and its expression characteristics in early-onset and late-onset preeclampsia. In this study, we divided the patients into three groups: term pregnancy group, eoPE group, and loPE group. The results confirmed that the expression of Mfn2 in the placental tissue of the eoPE group was significantly lower than that of the term pregnancy group and the loPE group, while the expression of Mfn2 in the placental tissue of the loPE group was only lower than that of the term pregnancy group, with no significant difference. This shows that the expression of Mfn2 in the placental tissue of patients during eoPE is reduced, and it can be inferred that the mitochondrial dysfunction of eoPE is more serious than that of loPE, and eoPE is mainly caused by placental dysfunction. However, the expression of Mfn2 in the placental tissue of the loPE group was not significantly reduced. It can be inferred that the pathogenesis of eoPE and loPE may be different, and placental damage in loPE patients accounts for a small proportion of the pathogenesis.

Meanwhile, the serum of eoPE, loPE and term pregnancy groups was collected for ELISA analysis to test the expression of Mfn2 in the patients' serum. Because normal full-term cesarean section pregnant women have no obvious oxidative stress, inflammatory immune response, endothelial cell damage during pregnancy, and the mitochondrial structure and function are normal, the Mfn2 protein is at a stable level. The expression of Mfn2 in the eoPE group and loPE patients is higher than that in the term pregnancy group and loPE group. The increased Mfn2 levels in maternal serum may reflect placental mitochondrial damage and subsequent release into circulation, though contributions from maternal vascular endothelium cannot be ruled out. Further studies using tissue-specific markers or in vitro models are needed to confirm the origin of serum Mfn2. By correlating the expression of Mfn2 in serum with the severity of eclampsia and pregnancy outcome, it can be concluded that the level of Mfn2 in serum is proportional to the severity of preeclampsia, but negatively correlated with pregnancy outcome, and the correlation of eoPE is stronger than that of late-onset eclampsia. Therefore, we can use the Mfn2 indicator to predict preeclampsia and the degree of disease progression. It follows that the downregulation of placental Mfn2 in eoPE likely reflects mitochondrial dysfunction and cellular stress, while the elevated serum Mfn2 may result from compensatory release of damaged mitochondrial proteins into circulation. This discrepancy suggests that serum Mfn2 could serve as a biomarker of placental pathology, though the exact mechanisms warrant further investigation.

However, there were some limitations in our study that still need to be thoroughly investigated. First, this study did not evaluate Mfn2 expression in each trimester, which could help elucidate its role in the progression of preeclampsia. Future longitudinal studies are needed to track Mfn2 levels throughout pregnancy. Also, while our study demonstrates correlations between serum Mfn2 and PE severity, its clinical utility as a pre-delivery biomarker requires validation in larger cohorts. Future research should assess whether Mfn2 levels can predict PE onset before clinical symptoms, enabling early intervention. In addition, this study did not further explore the differences in the specific pathogenesis of eoPE and loPE, and more research is needed to further confirm it.

In summary, this is the few studies to distinguish Mfn2 expression patterns between eoPE and loPE, providing evidence that mitochondrial dysfunction may play distinct roles in these subtypes. Our findings also propose serum Mfn2 as a potential biomarker for PE severity and progression. The difference in the expression of Mfn2 in eoPE and loPE placental tissues can be considered that the pathogenesis of the two periods is different, and the pathogenesis of loPE is more likely to be caused by maternal metabolic defects. The expression of mitochondrial fusion protein 2 is related to the onset of preeclampsia and the degree of disease progression. The earlier it is found in serum, the more severe the disease is and the higher the expression level is. Therefore, we can detect the expression of Mfn2 in peripheral blood to predict and evaluate the occurrence and severity of preeclampsia in patients.

Abbreviations

Mfn2	Mitofusin 2
eoPE	Early-onset preeclampsia
loPE	Late-onset preeclampsia
RT-qPCR	Real-time fluorescence reverse transcription
ELISA	Enzyme-linked immunosorbent assay
PE	Preeclampsia

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None.

Author contributions
LA conceived the study. DDS searched the literature and collected the data. HJZ, YTW, JWZ performed the statistical analysis. DDS drafted the manuscript. LA reviewed the manuscript. All authors have read and approved the final paper.

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Data availability
All data generated or analyzed during this study are included within the article.

Declarations

Ethics approval and consent to participate
With the informed consent of the donor, obtain tissue samples. The study was approved by the Ethics Committee of Jiaxing Municipal Maternal and Child Health Care Hospital.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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