Natural Resources for Human Health
eISSN: 2583-1194

Original Research

Received 06 May 2026
Revised 17 June 2026
Accepted 30 June 2026

Natural Resources for Human Health 2026, Vol. 6 (11s): 928–941

KEYWORDS:
TNFα, VEGF, hs-CRP, pentraxin-3, preeclampsia, and osteoprotegerin.

Artificial Neural Network-Based Prediction of Fatigue in Preeclampsia: Role of Inflammatory and Placenta-Related Biomarkers

[1]Rawaa Fadhil Kadhim, [2]Hussein Kadhem Al-Hakeim, [3]Magdy, M. Youssef, [4]Abdel-Aziz, A. El-refaay, [5]Abdel-Aziz, A.F.

[1]Department of Chemistry, College of Science,University of Mansoura, Egypt.E-mail: Rawaaalbdery1985@gmail.com
[2]Department of Chemistry, College of Science, University of Kufa, Iraq. E-mail: Headm2010@yahoo.com
ORCID: https://orcid.org/0000-0001-6143-5196.
[3]Department of Chemistry, College of Science, University of Mansoura, Egypt. E-mail: mmm_youssef@yahool.com
[4]Department of Obstetrics and Gynecology, Faculty of Medicine, University of Mansoura, Egypt. E-mail: refaeeysat@yahoo.com
[5]Department of Chemistry, College of Science, University of Mansoura, Egypt. E-mail: afaziz2012@hotmail.com

ABSTRACT:

Background. Preeclampsia (PE) is associated with inflammation and many neuropsychiatric symptoms, including fatigue. Many biomarkers are correlated with fibro fatigue (FF) scores in various diseases. In the present study, inflammatory and placenta-related biomarkers are utilized to predict fatigue severity in PE using an artificial neural network (ANN).

Methods. Two PE patient groups in the study: one with high fibro fatigue (FF) scores (PE-FF≥25, n=45) and another with lower FF (PE-FF<25, n=65). Fifty pregnant women were recruited as a control group. Pentraxin-3, VEGF, hs-CRP, osteoprotegerin, TNFα, high-sensitive C-reactive protein (hs-CRP), insulin, FABP4, and TRAIL were all measured using the ELISA method.

Results. Both patient groups' serum levels of insulin resistance indices, glucose, fasting insulin, FABP4, and PTX3 are significantly higher than those of the control group. The PE-FF≥25 group had substantially greater serum levels of TRAIL, TNFα, PAI-1, and hs-CRP than both the PE-FF<25 group and the control group. FFtotal exhibits a strong association with TRAIL, OPG, TNFα, hs-CRP, and FABP4. The ANN model's findings demonstrated 100% sensitivity and specificity in differentiating between patients with PE-FF≥25 and those with PE-FF<25. hs-CRP has the highest predictive power (100%), according to the model's predictive strength. TRAIL (97.3%), FABP4 (87.9%), TNFα (64.2%), and OPG (55.8%) are next in line.

Conclusions. Fatigue is correlated with the inflammatory and placenta-related biomarkers in PE women. The top three predictors of severe fatigue using ANN are hs-CRP, TRAIL, and FABP4, which all point to an inflammatory state in PE.

Natural Resources for Human Health
eISSN: 2583-1194

INTRODUCTION

Preeclampsia (PE) is a significant pregnancy complication marked by hypertension occurring after 20 weeks of gestation, often associated with proteinuria or other organ dysfunctions. Approximately 2-15% of pregnancies globally are impacted by preeclampsia, with higher prevalence in developing countries (1, 2). The illness increases rates of morbidity and death by posing serious threats to the health of both the mother and the fetus (2, 3). Systemic inflammation is a major contributing component to the pathophysiology of PE, which is typified by proteinuria and hypertension. Elevated levels of pro-inflammatory cytokines, such as interleukin (IL)-6, tumor necrosis factor-α (TNFα), and C-reactive protein (CRP), which are signs of an activated immune response, are symptomatic of inflammation in PE (4, 5). One of the characteristics of PE are the imbalance between pro-inflammatory and anti-inflammatory cytokines, such as IL-6 and IL-10 (5). PE has been linked to both systemic and local levels of pro-inflammatory T helper (Th)1 and Th17 cytokines, as well as suppressive Treg and Th2 cytokines (IL-10 and IL-4) (6). This inflammatory state is also associated with fatigue, a common symptom of PE, as the body's energy resources are diverted to manage the inflammatory response. Women with PE often experience fatigue, which negatively affects their overall health and quality of life (7). Research demonstrates that the incidence of fatigue in PE is high and varies depending on the demographic and terminology used (8). In addition to the symptoms of depression, anxiety, and chronic fatigue brought on by PE, the immune-inflammatory response system is activated (9). In PE, fatigue is caused by the body's reaction to ongoing inflammation, which uses a lot of energy, leading to exhaustion and fatigue (10). By altering metabolic pathways and elevating oxidative stress, the systemic inflammatory response in PE may make fatigue worse (11). In order to predict fatigue in PE, the current study uses biomarkers associated to inflammation and PE. Because of their associations with inflammation, angiogenesis, or placental components in PE, these biomarkers were selected. The most well-known indicator of systemic inflammation among these biomarkers is highly sensitive CRP (hs-CRP), which is generated by the liver in reaction to IL-6 (12). Early in pregnancy, Hs-CRP screening can be utilized to predict PE (13). Although the exact function of CRP in this respect, whether causative or consequential, has not yet been established, elevated maternal serum CRP levels may be a significant risk factor for PE (14). The levels of TNFα, IL-2, IL-4, and CRP were much higher in fatigued patients (15). These findings provide credence to the idea that chronic fatigue syndrome has an inflammatory component (15). The inflammatory response is significantly influenced by the pro-inflammatory cytokine TNFα (16), and is higher in PE patients than in those who have healthy pregnancies, indicating that it has a part in the pathophysiology of PE (16). PE is characterized by markedly high FABP4, and its elevated expression is linked to metabolic abnormalities that contribute to the pathogenesis of the illness (17). FABP4 controls inflammation and lipid metabolism (18). An acute-phase protein called pentraxin 3 (PTX3) is generated at the site of inflammation and has a role in innate immunity (19). It is regarded as a vascular inflammatory marker (20). To aid in the early detection of PE in the second trimester, PTX3 may be used as a biomarker.

Additionally, these biomarkers could show promise in predicting the severity of PE (21). Women with PE had much higher levels of PTX3, and the severity of the PE is correlated with these levels (22). Women with PE had much higher plasma levels of PAI-1 mRNA than controls, which is correlated with the severity of the illness (23). PE patients had higher amounts of PAI-1 in their plasma and placental tissues, which may be related to the pathophysiology of the condition (24). Increased levels of PAI-1, which controls fibrinolysis, can result in thrombotic changes, which are typical in PE (25). Fetal hypoxia and placental insufficiency are linked to elevated PAI-1 levels in PE, which may exacerbate systemic symptoms including exhaustion (26). The levels of PAI-1 and tissue-type plasminogen activator (t-PA) were markedly elevated in women with PE (27).

The type II transmembrane protein tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is expressed in a variety of organs, including the placenta, where it is present throughout the gestational cycle. As the gestational age increases, its levels gradually rise (28). TRAIL is proposed to be essential for developing materno-fetal immunotolerance because it shields the placenta from the assault of NK cells and maternal cytotoxic lymphocytes during a typical pregnancy (29). Atherosclerotic plaque contains osteoprotegerin (OPG) and TRAIL, which work in opposition to one another to produce the plaque (30). Osteoblastic and stromal cells release OPG, a glycoprotein that belongs to the TNF receptor family (31). OPG has a number of physiological roles in the body, but it primarily contributes to the bone metabolism pathway by preventing the development and differentiation of osteoclasts (32). When compared to a typical pregnancy, the OPG protein and mRNA levels in PE placentas were shown to be aberrant (33). The OPG protein and mRNA levels in PE were strongly correlated with its key clinical indicators. When combined, OPG and the pathophysiology of PE may be strongly connected (33). Variants in the OPG gene may be linked to severe PE that develops early (34). Vascular growth, endothelial integrity, and vascular permeability are all greatly influenced by vascular endothelial growth factor (VEGF), a glycoprotein that is expressed in placental

syncytiotrophoblasts and which attaches to its receptors 1 and 2 to produce its biological effects (35, 36), which, during pregnancy, are mostly invasive chorionic trophoblasts (37). The goal of the current investigation is to identify relationships between these biomarkers and the most effective indicators for predicting extreme fatigue in women with PE.

Contribution of the study

The key contribution of this research is that it is the first study to predict fatigue severity in PE utilizing a panel of inflammatory and placenta-related indicators using an artificial neural network. It identifies hs-CRP, TRAIL, and FABP4 as the best predictors of severe exhaustion and shows that fatigue in PE is largely driven by an inflammatory state. This provides a new, therapeutically usable model for early diagnosis of PE in women at risk of severe fatigue, with 100% sensitivity and specificity. The work links placental and systemic inflammatory processes and paves the door for biomarker-guided therapy of tiredness in preeclampsia.

SUBJECTS AND METHODS

Subjects

From October 2024 to December 2024, the current case-control research was carried out in the Al-Zahraa Obstetrics & Gynecology Hospital in the Najaf Governorate, Iraq. 110 PE patients with ages ranging from 31.13 to 5.63 years were included in the current research. To make a definitive PE diagnosis, the American College of Obstetricians and Gynecologists' criteria were applied (38). After 20 weeks of gestation, if a pregnant woman has proteinuria and a blood pressure reading of >140 mmHg systolic or ≥ 90 mmHg diastolic, she is diagnosed with PE. The woman's blood pressure should have been normal before. All of the patients in this trial met these requirements, and the dipstick test revealed positive proteinuria. They were receiving methyldopa (Aldomet®) therapy and fasted for the whole night. The last regular menstrual cycle is used to determine the gestational age of pregnancy; fundal height and/or ultrasound data were utilized for women who could not remember their last menstrual period. The total number of pregnancies, including ectopic pregnancy, termination, and any other pregnancies included on the chart, was called gravidity. The number of births beyond 28 weeks of gestation, including stillbirth and intrauterine fetal death (IUFD), is known as parity. The 12-item FF scale was used to measure the fibrofatigue scale before blood aspiration (39). Based on the FF score, the patient group was split into two groups: those with severe fatigue (PE-FF≥25, n=45 patients) and those with low fatigue (PE-FF<25, n=65 patients) (40).

As a control group, fifty pregnant women (gestational age >20 weeks) who showed no obvious anomalies were chosen. They were around the same age as the patients (31.8±5.4 years). These patients had no medical or mental illnesses and were stable. Their blood pressure, which was around 120/80 mmHg, was within the usual range. The study was conducted by international and Iraqi ethical and privacy standards. The University of Kufa's Medical Ethics Committee, Reference #: MEC-102, obtained ethical approval for this study following the Declaration of Helsinki's International Guidelines for Human Research Protection. Before their involvement in the study, each subject gave their informed consent. Standards for data security and confidentiality were strictly upheld over the course of the investigation.

Criteria for exclusion

The research excluded patients with any serious systemic disease, particularly those with diabetes, viral hepatitis, renal disease, or heart disease. Before recruitment, none of these women had a history of significant cardiovascular problems, such as autoimmune disorders, congestive heart failure, or stroke or transient ischemic event.

Measurements

Participants' fasting venous blood samples were drawn between 8:00 and 9:00 a.m. and placed in plain tubes. Prior to testing, samples were aliquoted and kept at -80 °C. The sera were separated and then divided among three fresh Eppendorf® tubes for further examination. Spectrophotometric measurements of serum glucose were performed using Spinreact® (Barcelona, Spain) kits. Utilizing commercial ELISA sandwich kits from Nanjing Pars Biochem Co., Ltd. (Nanjing, China), blood levels of TNFα, FABP4, PTX3, OPG, insulin, TRAIL, and hs-CRP were measured. As directed by the manufacturer, the processes were carried out precisely and without alteration. The accuracy inside an assay, or intra-assay coefficient of variation (CV), was less than 10.0%. Using the fasting serum insulin and glucose levels, the Homeostasis Model Assessment 2 (HOMA2) calculator© (Diabetes Trials Unit, University of Oxford; https://www.dtu.ox.ac.uk/homacalculator/download.php) was utilized to determine the β-cell function (HOMA%B), insulin sensitivity (HOMA%S), and insulin resistance (HOMA2-IR).

Biostatistical Analysis

The comparison of the variable levels between the control, PE-FF≥25, and PE-FF<25 groups was examined using the analysis of variance (ANOVA), and the post hoc test was conducted using the LSD test. To ascertain the associations between nominal variables, the χ2-test, or analysis of contingency tables, was utilized. We used a multivariate general linear model (GLM) analysis

to determine the effect of diagnosis on the biomarkers, controlling for confounding factors including age and BMI. Therefore, in order to differentiate the relationships between independent factors on biomarkers, we performed between-subjects effect testing. The complicated relationships between PE-FF≥25 and PE-FF<25 as output variables and observed biomarkers as input variables were evaluated using multilayer perceptron neural network (NN) models. Two hidden layers of processing were applied to the final feature vector in the classification stage of the current study to ascertain the influence of the input item based on each class label. We deployed two hidden layers with up to 10 nodes, up to 250 epochs, and batch training to train the NN using feedforward architecture models. We employed a holdout set (15%) to calculate the NN's predictive value, a testing sample (15%) to avoid overtraining, and a training sample (70%) to estimate network parameters. The output layer used the identity function, whereas the buried layers used the hyperbolic tangent activation function. Lastly, we calculated the area under the ROC curve with diagnostic performance, the relative error, and the significance of the explanatory factors (in an importance chart). A p-value of 0.05 was used for two-tailed testing to determine statistical significance. IBM SPSS for Windows version 26 was used for all statistical studies. Using G*Power 3.1.9.4, the predicted a priori sample size was determined and used for the primary analysis, which comprised doing a multiple regression analysis of the biomarker rating scale scores. Using an analysis of variance (ANOVA) test, the findings indicate that there are 153 people in the three research groups, with a power of 0.85 and an effect size f of 0.27.

RESULTS

Sociodemographic parameter comparison

The sociodemographic and clinical features of PE patients, as well as the control group with low and high FF levels, are displayed in Table 1. The rates of family history, prior abortions, cesarean deliveries, and vaginal births are greater in both patient groups. Patients with PE-FF≥25 had considerably higher ($p<0.001$) levels of DBP, SBP, and total FF score than patients with PE-FF<25 and the control group, which has the lowest values. Age, residence, nullpara, multipara, gestational age, parity, gravidity, and live births do not significantly differ between groups. There is no discernible difference between PE-FF<25 and PE-FF≥25 in terms of the age at which symptoms first appear and how long they last.

Biomarker comparison between groups

Serum indicators in the PE-FF < 25, PE-FF > 25, and control groups are contrasted in Table 2. When compared to the control group, the serum levels of FBG, insulin, HOMA2IR, I/G, FABP4, and PTX3 (with the exception of HOMA2%S) increased considerably in both patient groups. In contrast, the PE-FF≥25 group had considerably greater blood levels of TRAIL, TNFα, PAI-1, and hs-CRP than both the PE-FF<25 group and the control group, which had significantly lower values. HOMA2%B did not significantly differ across groups. The OPG of the PE-FF≥25 group was significantly higher than that of the PE-FF≥25 group, according to the results. Additionally, as compared to the control group, the PE-FF≥25 group's VEGF rose considerably.

The multivariate generalized linear model's (GLM) findings

The effects of PE illness with high and low FF values, as well as other cofounders, on the levels of the measured biomarkers were investigated using the multivariate generalized linear model (GLM) analysis presented in Table 3. Age, prior abortion, SBP, DBP, gravidity, multipara, gestational age, nullipara, parity, cesarean birth, and natural delivery did not significantly affect the biomarkers that were tested. According to the study, the primary significant effectors ($F=13.473$, $p<0.001$) with a substantial size impact (Partial $\eta^2 = 0.579$) are the existence of PE and FF. The between-subject effects in the table reflect the impact sizes of the diagnosis on each biomarker. Serum OPG (Partial $\eta^2 = 0.243$), TRAIL (Partial $\eta^2 = 0.217$), Hs-CRP (Partial $\eta^2 = 0.210$), TNFα (Partial $\eta^2 = 0.169$), FABP4 (Partial $\eta^2 = 0.111$), and PAI-1 (Partial $\eta^2 = 0.098$) are the parameters that were substantially impacted by the diagnosis (Partial $\eta^2 >0.09$, $p<0.001$).

FF score and other biomarker correlation

After adjusting for the characteristics of PE patients (age, SBP, DBP, age of start, and duration of symptoms), Table 4 displays the partial correlation coefficients between the total FF score and various biomarkers. FFTotal indicates a significant relationship with TRAIL ($r=0.451$, $p<0.001$), FABP4 ($r=0.208$, $p=0.009$), OPG ($r=0.385$, $p<0.001$), TNFα ($r=0.376$, $p<0.001$), and hs-CRP ($r=0.360$, $p<0.001$). All IR measures, including PAI-1, VEGF, and PTX3, do not significantly correlate with the FFTotal score after adjusting for cofounders.

The artificial neural network's outcomes

Table 5 displays the outcomes of the ANN model's performance in differentiating PE-FF≥25 patients from the PE-FF<25 group utilizing the input variables of all measured biomarkers. Two hidden layers made up the configuration used to train the feedforward network. The sum-of-squares error term in the testing sample was substantially smaller than in the training sample, indicating that the model had learnt to generalize. A good degree of discriminating was shown by the area under the receiver operating characteristic curve (AUC ROC), which came out to be 0.994. The model's capacity to distinguish between PE with high FF and low FF patients was demonstrated by its 100% sensitivity and specificity.

The model's predictive power is demonstrated by the normalized significance graph in Figure 1. Highest predictive power (100%) is shown by hs-CRP, followed by TRAIL (97.3%), FABP4 (87.9%), TNFα (64.2%), and OPG (55.8%). Conversely, the prediction of other biomarkers is less substantial (all <50%).

Discussion

The study's main conclusion is that pregnant women with PE had higher FFTotal scores than pregnant women in good health. As a consequence, PE patients were divided into two groups based on their FF scores: high (PE-FF≥25) and low (PE-FF<25). Neurological problems brought on by PE include cerebral edema and eclampsia, which are linked to dysregulation of the autonomic nervous system and decreased sensitivity to baroreceptor reflexes (41). Because the body finds it difficult to maintain homeostasis and cope with elevated stress levels, these neurological alterations may show up as weariness (41). The blood pressure of the PE group with PE-FF≥25 is greater than that of the PE-FF<25 group, suggesting that severity plays a part in making the FF symptoms worse. It has been previously documented that fatigue symptoms in PE women are correlated with blood pressure (8). Physical exhaustion may be exacerbated by mental fatigue and anxiety brought on by the psychological strain of managing a high-risk pregnancy (42). Lastly, pain and medical monitoring frequently induce sleep disruptions in PE, which can significantly impact overall energy levels and result in weariness (43).

Serum biomarkers (FBG, insulin, HOMA2IR, I/G, FABP4, and PTX3) are significantly elevated in both patient groups (except HOMA2%S) as compared to the control group. This is the second important observation. Pregnancy-related fat accumulation exacerbates this IR condition (44). By disrupting the phosphatidylinositol 3-kinase pathway and thus decreasing endothelial nitric oxide (NO) generation, vascular IR stimulates vascular contraction and accelerates the onset of PE (45). Through its effects on immunological tolerance and glycolipid metabolism, FABP4 disrupts the equilibrium of the maternal–fetal interface during pregnancy, increasing the risk of miscarriage, gestational obesity, gestational diabetes, and PE (46). FABP4 expression is elevated in the placenta and maternal blood in PE, which might be a factor in the inflammatory and metabolic alterations seen in the illness (47). The findings showed that pregnancies with PE had a statistically significantly higher amount of PTX3 than pregnancies that were judged healthy. According to earlier studies, severe PE had more PTX3 than moderate PE (21). A positive connection between PTX3 and SBP and DBP might account for this rise (48).

The third significant discovery is that in PE women, the following biomarkers rise as the FF score does: TRAIL, TNFα, OPG, PAI-1, VEGF, and hs-CRP. Moreover, FFtotal and TRAIL, OPG, TNFα, hs-CRP, and FABP4 showed a strong association in the correlation research. The impact of inflammation, seen as elevated inflammatory biomarkers on fatigue score, might be the cause (49, 50). Immunopsychiatric diseases, such as PE-related chronic fatigue symptoms, are associated with immune-inflammatory response system activation (9). High-CRP levels are a major predictor of PE patients with high-FF (7), indicating a state of inflammation in PE (51). The PE group had greater levels of maternal serum hs-CRP than the control group. Throughout pregnancy, the mother's blood pressure was linked to the hs-CRP levels (52). When compared to the control group, VEGF-A significantly increased in the high-FF PE group. VEGF levels in PE were higher than those in healthy pregnant women, according to many studies (53). The findings indicated that women with PE had a much greater VEGFR1 than controls (54). Compared to the control group, PE had considerably greater levels of serum VEGF and sVEGFR1. With an area under the curve of 97.47%, the VEGF demonstrated superior diagnostic accuracy for PE differentiation (55). Circulating sVEGFR1 levels in PE patients have been suggested to suppress physiological vasodilation, hence aggravating hypertension (56). Several clinical symptoms in PE are caused by the placental tissue's relative overproduction of VEGFR1 to VEGF (57). According to studies, women with PE experience endothelial dysfunction, hypertension, and proteinuria as a result of this elevation in VEGFR1 (58).

The development of PE can be predicted by elevated FABP4 levels in the early stages of pregnancy, indicating its potential as a biomarker for early intervention techniques (59). PE may be accurately predicted by serum FABP4 levels with excellent sensitivity and specificity (60). PTX3 may serve as a valuable biomarker for determining the degree of PE and anticipating intrauterine growth restriction (IUGR) (48). Numerous case-control studies have shown that individuals with early-onset PE toxemia had higher levels of PAI-1 than healthy controls (61). A linear regression model has assessed that severe PE toxemia

is significantly correlated with serum PAI-1 level, and a positive correlation has been established between maternal PAI-1 mRNA expression and the severity of PE in the third trimester (62). Placental microparticles, which may include TRAIL-expressing fragments, are formed in greater quantities during pregnancy and delivered into the mother's bloodstream (63). Therefore, the development of PE and other pregnancy-related hypertensive problems was linked to plasma TRAIL levels (64). OPG has been linked to vascular disorders, such as PE, and is known to shield vascular endothelial cells (65, 66). It is believed that OPG, which is expressed in the placenta, contributes to the pathophysiology of PE by shielding vascular endothelial cells (66). Severe PE has been linked to genetic variants in the OPG gene, indicating a hereditary predisposition that might affect the condition's severity (67).

The final significant conclusion is that hs-CRP has the best predictive value when it comes to differentiating PE-FF≥25 patients from the PE-FF<25 group using an artificial neural network model. This is followed by TRAIL, FABP4, TNFα, and OPG. Compared to single biomarker analysis, the capacity of ANN to examine numerous biomarker categories at once produces more accurate diagnostic results (68). PE, or uncontrolled inflammation in the early stages of pregnancy in pregnant women who are at risk of developing PE, is linked to the hs-CRP. The control group's mean hs-CRP level was 1.73 ± 0.46 mg/l, whereas moderate PE had a mean of 2.74 ± 0.53 mg/l and severe PE had a mean of 5.77 ± 1.04 mg/l. The findings of this study indicate that more severe PE is linked to elevated blood hs-CRP levels (69). Among females with PE, the prevalence of elevated maternal hs-CRP was quite high (65.5%) (70). According to these findings, PE women have higher levels of inflammation than typical pregnant women (71). One important risk factor for PE may be elevated maternal blood CRP levels (14). When compared to pregnant women with low CRP levels, the CRP cut-off value of 7.76 mg/dL had a very high odds ratio for developing PE and strong sensitivity and specificity, according to ROC analysis (72). The significance of inflammation in the manifestation of FF symptoms in PE women is only highlighted by the fact that CRP can predict PE patients with high FF. PE fatigue may result from a number of interrelated causes (73). Pregnancy-related physiological changes combined with the extra stress of PE might cause significant fatigue because of the body's increased metabolic needs (73). Second, blood flow to vital organs may be lowered by hypertension and associated vascular changes, resulting in a lower oxygen supply and feelings of exhaustion (74). The correlation between increased TNFα and PE was further supported by the fact that TNFα levels were considerably greater in women with PE than in healthy controls (75). Compared to pregnant women with normotension, individuals with PE have noticeably increased TNFα levels (76). The link between PTX3 and unfavorable neonatal outcomes, such as decreased birth weight, lends more credence to its function in PE (22). When assessing renal impairment linked to PE, PTX3's inflammatory character is superior to other indicators like hsCRP and adds to endothelial damage, a hallmark of the disease (77). Furthermore, it is well known that PE toxemia is an inflammatory disease, and inflammatory cytokines may increase the amount of PAI-1 in the blood (78). Furthermore, it has been discovered that the activation of the NF-ϰB pathway in the impaired migration of trophoblasts in PE toxemia may eventually increase PAI-1 mRNA expression (79). It should be noted that PE can be brought on by either fibrinolysis or hypoxia. Exposure to inflammatory cytokines, including VEGF and IL-1β, raises plasma levels of PAI-1 (80). The majority of research has revealed that PE is characterized by an elevated concentration of PAI-1, which is consistent with our findings (24). According to the current study, placenta-related cytokines and inflammation are linked to fatigue in PE women .

Limitations of the study

Despite promising results, this study has several limitations. First, the sample size may not be sufficient to fully generalize the predictive accuracy of the neural network across diverse populations with preeclampsia. Second, while the use of inflammatory and placenta-related biomarkers provides valuable insights, other potential confounding factors such as nutritional status, medication use, psychological variables, and comorbidities were not included in the model and may influence fatigue levels. Additionally, the cross-sectional design limits causal inference, and the fatigue assessment relied on subjective scales, which may introduce reporting bias.

CONCLUSIONS

The presence of fatigue exacerbates the rise in placenta-related and inflammatory biomarkers in women with PE. The top three predictors of severe exhaustion using ANN are hs-CRP, TRAIL, and FABP4, which all point to an inflammatory state in PE.

Acknowledgments

We acknowledge the assistance of the Asia Clinical Laboratory in Najaf for hematological and biochemical testing, as well as the personnel of the Dialysis Unit at Al-Hakeem General Hospital for sample collection .

Funding.

The current research is not specifically funded.

Conflict of interest

Regarding the submitted article, the authors state that they have no conflicts of interest with any industry or other organization.

Contributions of the authors.

Every contributing author took part equally in the manuscript's preparation .

Statement of Data Availability

After the authors have utilized the dataset, the corresponding author will make the database developed during this inquiry available upon reasonable request.

REFERENCES

[1] Chang KJ, Seow KM, Chen KH. Preeclampsia: Recent Advances in Predicting, Preventing, and Managing the Maternal and Fetal Life-Threatening Condition. Int J Environ Res Public Health. 2023;20(4).

[2] Shandilya V, Sinha N, Rani S. Preeclampsia: Prevalence, Risk Factors, and Impact on Mother and Fetus. Indian Journal of Cardiovascular Disease in Women. 2023;8:193-9.

[3] Dimitriadis E, Rolnik DL, Zhou W, Estrada-Gutierrez G, Koga K, Francisco RPV, et al. Pre-eclampsia. Nat Rev Dis Primers. 2023;9(1):8.

[4] Zhong Q, Yao C, Zhong W. Causal Relationship Between Inflammation and Preeclampsia: Genetic Evidence from a Mendelian Randomization Study. Twin Res Hum Genet. 2023;26(3):231-5.

[5] Atta S, Mekky R, Ibrahim M, Abdallah MM, Elbaz MAH, Radwan E. Increased Expression of Neprilysin Is Associated with Inflammation in Preeclampsia. Reprod Sci. 2024;31(5):1385-90.

[6] LaMarca B, Cornelius DC, Harmon AC, Amaral LM, Cunningham MW, Faulkner JL, et al. Identifying immune mechanisms mediating the hypertension during preeclampsia. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology. 2016;311(1):R1-R9.

[7] Jasim H. C-Reactive Protein is the Main Factor for Prediction of Fatigue in Preeclampsia Women. Wasit Journal for Pure sciences. 2024;3(4):306-18.

[8] Roes E, Sieben R, Raijmakers M, Peters W, Steegers EJHip. Severe preeclampsia is associated with a positive family history of hypertension and hypercholesterolemia. Hypertension in Pregnancy. 2005;24(3):259-71.

[9] Omar JS, Albarzinji N, Niu M, Taher NH, Aram B, Sulaiman MS, et al. The immune checkpoint pathophysiology of depression and chronic fatigue syndrome due to preeclampsia: focus on sCD80 and sCTLA-4. Acta Neuropsychiatr. 2025;37:e56.

[10] Zhao X, Chen S, Zhao C, Xia F. Maternal Immune System and State of Inflammation Dictate the Fate and Severity of Disease in Preeclampsia. J Immunol Res. 2021;2021:9947884.

[11] de Oliveira LG, Karumanchi A, Sass N. [Preeclampsia: oxidative stress, inflammation and endothelial dysfunction]. Rev Bras Ginecol Obstet. 2010;32(12):609-16.

[12] Zhang H, Dhalla NS. The Role of Pro-Inflammatory Cytokines in the Pathogenesis of Cardiovascular Disease. Int J Mol Sci. 2024;25(2).

[13] Jhansi K, Harsoda JM. Evaluation of maternal cortisol-to-highly sensitive C-reactive protein ratio and glucocorticoid receptor resistance at 11–14 weeks of pregnancy to predict pre-eclampsia. Current Medicine Research and Practice. 2022;12(5).

[14] Akter J, Begum SN, Akter P, Manjuri M, Rehana Z, Salma U. Association of C-reactive Protein in Preeclampsia. Medicine Today. 2024;36(2):67-71.

[15] Strawbridge R, Sartor ML, Scott F, Cleare AJ. Inflammatory proteins are altered in chronic fatigue syndrome-A systematic review and meta-analysis. Neurosci Biobehav Rev. 2019;107:69-83.

[16] Zhou Y, Gan G. The levels of peripheral blood TNF-α, Decorin and neutrophils MAPK1 mRNA levels of patients with preeclampsia and their clinical significance. J Matern Fetal Neonatal Med. 2023;36(1):2183745.

[17] Li Y, Chen WL, Liu L, Gu H. [Expression of peroxisome proliferator-activated receptors, fatty acid binding protein-4 in placenta and their correlations with the prognosis of pre-eclampsia]. Zhonghua Fu Chan Ke Za Zhi. 2017;52(7):443-8.

[18] Hardaway AL, Podgorski I. IL-1β, RAGE and FABP4: targeting the dynamic trio in metabolic inflammation and related pathologies. Future Med Chem. 2013;5(10):1089-108.

[19] Zhang H, Wang R, Wang Z, Wu W, Zhang N, Zhang L, et al. Molecular insight into pentraxin-3: Update advances in innate immunity, inflammation, tissue remodeling, diseases, and drug role. Biomed Pharmacother. 2022;156:113783.

[20] Knoflach M, Kiechl S, Mantovani A, Cuccovillo I, Bottazzi B, Xu Q, et al. Pentraxin-3 as a marker of advanced atherosclerosis results from the Bruneck, ARMY and ARFY Studies. PLoS One. 2012;7(2):e31474.

[21] Tanrıverdi Kılıç G, Yenigül NN, Dinçgez B, Yüce Bilgin E, Kılıç ÜK. The role of pentraxin 3 and cathepsin B levels in pregnancies complicated by preeclampsia. Biomarkers. 2024;29(8):518-27.

[22] Haseeb NM, Mohammed EA, Ibrahem S. Significance of maternal serum pentraxin-3 level in assessment of severity of pre-eclampsia and its effect on neonatal outcome. Medical Journal of Babylon. 2023;20(Supplement 1).

[23] Purwosunu Y, Sekizawa A, Koide K, Farina A, Wibowo N, Wiknjosastro GH, et al. Cell-free mRNA concentrations of plasminogen activator inhibitor-1 and tissue-type plasminogen activator are increased in the plasma of pregnant women with preeclampsia. Clin Chem. 2007;53(3):399-404.

[24] Agersnap I, Nissen PH, Hvas AM. The Role of Plasminogen Activator Inhibitor Type 1 (PAI-1) in Placenta-Mediated Pregnancy Complications: A Systematic Review. Semin Thromb Hemost. 2022;48(5):607-24.

[25] Yildirim M, Dağ Ş, Kurtulgan H, Karakus S. Plazminojen aktivatör inhibitör-1 (PAI-1) 4G/4G polimorfizminin gebelik kayıplarıyla ilişkisi. Cumhuriyet Medical Journal. 2014;36.

[26] Seferovic MD, Gupta MB. Increased Umbilical Cord PAI-1 Levels in Placental Insufficiency Are Associated with Fetal Hypoxia and Angiogenesis. Dis Markers. 2016;2016:7124186.

[27] Godtfredsen AC, Sidelmann JJ, Dolleris BB, Jørgensen JS, Johansen EKJ, Pedersen MFB, et al. Fibrinolytic Changes in Women with Preeclampsia. Clinical and Applied Thrombosis/Hemostasis. 2022;28:10760296221126172.

[28] Lorz C, Benito A, Ucero AC, Santamaría B, Ortiz A. Trail and kidney disease. Front Biosci. 2009;14:3740-9.

[29] Phillips TA, Ni J, Pan G, Ruben SM, Wei YF, Pace JL, et al. TRAIL (Apo-2L) and TRAIL receptors in human placentas: implications for immune privilege. J Immunol. 1999;162(10):6053-9.

[30] Secchiero P, Corallini F, Ceconi C, Parrinello G, Volpato S, Ferrari R, et al. Potential prognostic significance of decreased serum levels of TRAIL after acute myocardial infarction. PloS one. 2009;4(2):e4442.

[31] Cawley KM, Bustamante-Gomez NC, Guha AG, MacLeod RS, Xiong J, Gubrij I, et al. Local Production of Osteoprotegerin by Osteoblasts Suppresses Bone Resorption. Cell Rep. 2020;32(10):108052.

[32] Wang Y, Liu Y, Huang Z, Chen X, Zhang B. The roles of osteoprotegerin in cancer, far beyond a bone player. Cell death discovery. 2022;8(1):252.

[33] Shen P, Gong Y, Wang T, Chen Y, Jia J, Ni S, et al. Expression of osteoprotegerin in placenta and its association with preeclampsia. 2012.

[34] Yang Y, Liu X, Jia J, Bai Y, Dai L, Wang T, et al. Role of osteoprotegerin gene variants in early-onset severe pre-eclampsia. Journal of obstetrics and gynaecology research. 2015;41(3):334-42.

[35] Patel SA, Nilsson MB, Le X, Cascone T, Jain RK, Heymach JV. Molecular Mechanisms and Future Implications of VEGF/VEGFR in Cancer Therapy. Clinical cancer research : an official journal of the American Association for Cancer Research. 2023;29(1):30-9.

[36] Florek K, Mendyka D, Gomułka K. Vascular Endothelial Growth Factor (VEGF) and Its Role in the Cardiovascular System. Biomedicines. 2024;12(5).

[37] Bolatai A, He Y, Wu N. Vascular endothelial growth factor and its receptors regulation in gestational diabetes mellitus and eclampsia. Journal of translational medicine. 2022;20(1):400.

[38] Espinoza J, Vidaeff A, Pettker CM, Simhan H. Gestational hypertension and preeclampsia. Obstetrics and gynecology. 2019;133(1):E1-E25.

[39] Zachrisson O, Regland B, Jahreskog M, Kron M, Gottfries CG. A rating scale for fibromyalgia and chronic fatigue syndrome (the FibroFatigue scale). Journal of Psychosomatic Research. 2002;52(6):501-9.

[40] Al Masoodi WTM, Radhi SW, Al-Hakeim HK, Abdalsada HK. Electrolytes as predictors of fibro fatigue scores in Long-COVID patients. Plos one. 2024;19(8):e0309348.

[41] Logue OC, George EM, Bidwell GL, 3rd. Preeclampsia and the brain: neural control of cardiovascular changes during pregnancy and neurological outcomes of preeclampsia. Clin Sci (Lond). 2016;130(16):1417-34.

[42] Black KD. Stress, symptoms, self-monitoring confidence, well-being, and social support in the progression of preeclampsia/gestational hypertension. Journal of Obstetric, Gynecologic Neonatal Nursing. 2007;36(5):419-29.

[43] Abdel-Wahab Afifi Araby Ali O, Kamal Ali F, Mohamed Salama A, Mansour Abdel Azeem Barakat F. Effect of Progressive Muscle Relaxation Techniques on Physiological Parameters, Psychological Factors and Sleep Quality among Pregnant Women with Preeclampsia. Egyptian Journal of Health Care. 2024;15(2):125-48.

[44] Lee SM, Kwak SH, Koo JN, Oh IH, Kwon JE, Kim BJ, et al. Non-alcoholic fatty liver disease in the first trimester and subsequent development of gestational diabetes mellitus. Diabetologia. 2019;62:238-48.

[45] Wu P, Green M, Myers JE. Hypertensive disorders of pregnancy. BMJ (Clinical research ed). 2023;381.

[46] Shi Y, Wang CC, Wu L, Zhang Y, Xu A, Wang Y. Pathophysiological Insight into Fatty Acid-Binding Protein-4: Multifaced Roles in Reproduction, Pregnancy, and Offspring Health. Int J Mol Sci. 2023;24(16).

[47] Yan JY, Wang XJ. [Expression and significance of adipocyte fatty acid-binding protein in placenta, serum and umbilical cord blood in preeclampsia]. Zhonghua Fu Chan Ke Za Zhi. 2010;45(12):885-90.

[48] Laila Solyman Amer, Mohamed Abdelsalam, Mohamed Ibrahim, Noory MAA. Uterine Artery Doppler and Serum Pentraxin-3 Level in Preeclampsia and Its Correlation to Intrauterine Growth Restriction. The Egyptian Journal of Hospital Medicine. 2025;98(1):828-32.

[49] Elahi S, Rezaeifar M, Osman M, Shahbaz S. Exploring the role of galectin-9 and artemin as biomarkers in long COVID with chronic fatigue syndrome: links to inflammation and cognitive function. Front Immunol. 2024;15:1443363.

[50] Winders S, Lyon DE, Kelly DL, Weaver MT, Yi F, Rezende de Carvalho M, et al. Sleep, Fatigue, and Inflammatory Biomarkers in Older Adults with Chronic Venous Leg Ulcers Receiving Intensive Outpatient Wound Care. Adv Wound Care (New Rochelle). 2024;13(10):508-17.

[51] Møller HI, Persson G, Klok FB, Vojdeman FJ, Lebech M, Hviid TVF. Investigations of leukocyte and inflammatory markers in pregnancies complicated by preeclampsia. Journal of Reproductive Immunology. 2023;160:104163.

[52] Dangat K, Wadhwani N, Randhir K, Poddar A, Gupte S, Wagh G, et al. Longitudinal profile of high-sensitivity C-reactive protein in women with pre-eclampsia. American Journal of Reproductive Immunology. 2023;90(2):e13741.

[53] Tandon V, Hiwale S, Amle D, Nagaria T, Patra PK. Assessment of Serum Vascular Endothelial Growth Factor Levels in Pregnancy-Induced Hypertension Patients. Journal of Pregnancy. 2017;2017(1):3179670.

[54] Pant V, Yadav BK, Sharma J. A cross sectional study to assess the sFlt-1:PlGF ratio in pregnant women with and without preeclampsia. BMC pregnancy and childbirth. 2019;19(1):266.

[55] Khidri FF, Waryah YM, Nigar R, Mughal Z-U-N, Zai JA, Rao AR, et al. Vascular endothelial growth factor/platelet ratio as a potential biomarker for preeclampsia: A study of angiogenic markers in Pakistani patients. Obstetric Medicine. 2024;0(0):1753495X241234961.

[56] Maynard SE, Min J-Y, Merchan J, Lim K-H, Li J, Mondal S, et al. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. The Journal of clinical investigation. 2003;111(5):649-58.

[57] Tsatsaris V, Goffin F, Munaut C, Brichant J-F, Pignon M-R, Noel A, et al. Overexpression of the soluble vascular endothelial growth factor receptor in preeclamptic patients: pathophysiological consequences. The Journal of Clinical Endocrinology Metabolism. 2003;88(11):5555-63.

[58] De Vivo A, Baviera G, Giordano D, Todarello G, Corrado F, D'anna RJAoegS. Endoglin, PlGF and sFlt-1 as markers for predicting pre-eclampsia. Acta Obstetricia et Gynecologica Scandinavica. 2008;87(8):837-42.

[59] Qiao GH, Sun XZ. Increased plasma fatty acid binding protein 4 concentration at the first prenatal visit and its relevance to preeclampsia. Hypertens Res. 2018;41(9):763-9.

[60] Paiboonborirak C, Phupong V. Serum fatty acid binding protein 4 and Doppler of uterine artery ultrasound in the first trimester for the prediction of preeclampsia. Hypertension Research. 2024;47(5):1208-15.

[61] Rampersaud AM, Dunk CE, Lye SJ, Renaud SJ. Palmitic acid induces inflammation in placental trophoblasts and impairs their migration toward smooth muscle cells through plasminogen activator inhibitor-1. Mol Hum Reprod. 2020;26(11):850-65.

[62] Elzein HO, Muddathir AR, Rida M, Rayis DA, Elhassan EM, Adam I. Fibrinolysis parameters in Sudanese women with severe preeclampsia. Hypertens Pregnancy. 2016;35(4):559-64.

[63] Redman CW, Sargent IL. Circulating microparticles in normal pregnancy and pre-eclampsia. Placenta. 2008;29 Suppl A:S73-7.

[64] Zhou C, Long Y, Yang H, Zhu C, Ma Q, Zhang Y. TRAIL Is Decreased Before 20 Weeks Gestation in Women with Hypertensive Disorders of Pregnancy. PloS one. 2015;10(6):e0128425.

[65] Caidahl K, Ueland T, Aukrust P. Osteoprotegerin: a biomarker with many faces. Arterioscler Thromb Vasc Biol. 2010;30(9):1684-6.

[66] Shen P, Gong Y, Wang T, Chen Y, Jia J, Ni S, et al. Expression of osteoprotegerin in placenta and its association with preeclampsia. PLoS One. 2012;7(8):e44340.

[67] Yang Y, Liu X, Jia J, Bai Y, Dai L, Wang T, et al. Role of osteoprotegerin gene variants in early-onset severe pre-eclampsia. J Obstet Gynaecol Res. 2015;41(3):334-42.

[68] Mgbole T. Advanced neural network systems for analysis of blood-based biomarkers in metastatic disease detection. World Journal of Advanced Research and Reviews. 2025;25:662-86.

[69] Raghuwanshi K, Narrey N, Jain BK, Gandhe M, Nagwanshi J. High Sensitive-C Reactive Protein (hs-CRP) as a vital tool for grading of Preeclampsia: A Case Control Study. Frontiers in Health Informatics. 2025;14(1).

[70] Aftab K, Javed S, Mehmod B, Sahar B, Tabassum S, Malik A. Frequency of maternal high serum hs-C reactive protein level in pre-eclampsia patients. The Professional Medical Journal. 2023;30(05):671-5.

[71] Cornelius DC. Preeclampsia: From Inflammation to Immunoregulation. Clinical Medicine Insights: Blood Disorders. 2018;11:1179545X17752325.

[72] Kusuma AANJ, Darmayasa, I. M., Widiyanti, E. S., & Maharta, I. G. B. A. High C-Reactive Protein Serum Levels as a Risk Factor for Preeclampsia. European Journal of Medical and Health Sciences. 2024;6(4):9-14.

[73] Yang C-L, Chang C-YJM, Journal CH. Fatigue during pregnancy: a bibliometric analysis. Maternal Child Health Journal. 2023;27(5):766-73.

[74] Pankiewicz K, Szczerba E, Maciejewski T, Fijałkowska A. Non-obstetric complications in preeclampsia. Menopause Review. 2019;18(2):99-109.

[75] Khodadadi A, Ghadiri A, Ghafourian M, Iranparast S, Najafian M. The TNF-α-308G/A Gene Polymorphism and Serum TNF-α Levels in Women With Preeclampsia. J Family Reprod Health. 2022;16(3):205-11.

[76] Puttaiah A, Kirthan JPA, Sadanandan DM, Somannavar MS. Inflammatory markers and their association with preeclampsia among pregnant women: A systematic review and meta-analysis. Clinical Biochemistry. 2024;129:110778.

[77] Feng BZ, Jianjun; Cai, Yu. Relationship between pentraxin 3 and preeclampsia and its values of evaluating renal function impairment. Acta Medica Mediterranea. 2020;36(4):2485-90.

[78] Zhai J, Li Z, Zhou Y, Yang X. The role of plasminogen activator inhibitor-1 in gynecological and obstetrical diseases: An update review. J Reprod Immunol. 2022;150:103490.

[79] Ye Y, Vattai A, Zhang X, Zhu J, Thaler CJ, Mahner S, et al. Role of Plasminogen Activator Inhibitor Type 1 in Pathologies of Female Reproductive Diseases. Int J Mol Sci. 2017;18(8).

[80] Zhao L, Bracken MB, DeWan AT, Chen S. Association between the SERPINE1 (PAI-1) 4G/5G insertion/deletion promoter polymorphism (rs1799889) and pre-eclampsia: a systematic review and meta-analysis. Molecular Human Reproduction. 2013;19(3):136-43.

Table 1. Demographic and clinical characteristics of PE-FF<25, PE-FF≥25, and healthy control groups.

Parameters	HC	PE-FF<25	PE-FF≥25	df	F	p
Age yrs	31.8 5.40	31.69_5.84	30.4_5.12	2/157	0.960	0.385
Rural/Urban	22/28	29/36	21/24	2	0.075	0.963
Family history No/Yes	49/1^{B,C}	40/25^{A}	29/16 ^{A}	2	22.208	<0.001
Previous abortion No/Yes	38/12^{B,C}	32/33^{A,C}	23/22^{A,B}	2	9.586	0.008
Nullpara No/Yes	35/15	51/14	27/18	2	4.382	0.112
Multipara No/Yes	13/37	16/49	14/31	2	0.599	0.741
SBP mmHg	116.36±4.06^{B,C}	149.34±13.29^{A,C}	162.33±15.98^{A,B}	2/157	184.505	<0.001
DBP mmHg	78.22±2.86^{B,C}	93.52±9.35^{A,C}	98.56±11.23^{A,B}	2/157	75.028	<0.001
Gestational age Wks	30.6±4.87	30±3.152	31±2.70	2/157	1.032	0.359
Parity (#Deliv)	2(1-3)	2(1-3)	2(1-3)	-	KWT	0.684
Cesarean delivery	0(0-0)^{B,C}	1(0-2)^{A}	0(0-2)^{A}	-	KWT	<0.001
Natural vaginal delivery	2(1-3)^{B,C}	1(0-2)^{A}	1(0-2)^{A}	-	KWT	<0.001
Gravidity	3(1-4)	3(2-4)	3(1-4)	-	KWT	0.194
Live Births	2(1-3)	2(1-3)	2(1-3)	-	KWT	0.393
FF-TOTAL	8(6.75-9)^{B,C}	20(16-22)^{A,C}	28(26-32)^{A,B}	-	KWT	<0.001
Age of Onset yrs.	-	27(24-30)	26(22-28)	-	MWUT	0.067
Duration Symptoms Wks.	-	9(6-11)	9(7-11)	-	MWUT	0.449

$^{A, B, C}$: Pairwise comparison, Results are expressed as mean ± standard deviation for normally distributed data. Binomial data were expressed as ratios and analyzed by Chi-squared test, F/χ^2: F- or Chi-square statistic value, *p. probability value. Not normally*

distributed data were expressed as median(Iqs) and compared using Kruskal-Wallis test (KWT), MWUT: Mann-Whitney U test, DBP: diastolic blood pressure, SBP: systolic blood pressure, Nullipara: no live births, Gravidity: number of pregnancies, Multipara: presence of life births, Parity: number of deliveries, Para: number of pregnancies that have reached a viable gestational age (≥ 20 weeks) and resulted in live births or stillbirths, FF: fibro fatigue score.

Table 2. Lipid profile parameters, atherogenic indices, and inflammatory biomarkers of PE-FF<25 and PE-FF≥25 and healthy control groups.

Biomarkers	HC	PE-FF<25	PE-FF≥25	F	p
FBG mM	5.27±0.47^{B,C}	5.55±0.80^{A}	5.59±0.73^{A}	3.207	0.043
Insulin pM	56(50.6-63.06)^{B,C}	74.4(60.59-90.41)^{A}	76.53(64.41-92.3)^{A}	KWT	<0.001
HOMA2%B	88.45(77.33-103.8)	100.9(85.25-117.25)	101(82.35-119.25)	KWT	0.051
HOMA2%S	93.3(84.65-103.15)^{B,C}	71.4(57.55-86.2)^{A}	69.2(57.2-85.2)^{A}	KWT	<0.001
HOMA2IR	1.07(0.97-1.18)^{B,C}	1.4(1.17-1.74)^{A}	1.53(1.29-1.8)^{A}	KWT	<0.001
I/G	10.91(9.44-12.35)^{B,C}	14.24(11.55-16.1)^{A}	13.73(11.48-16.3)^{A}	KWT	<0.001
TRAIL pg/ml	43.4(25.36-51.63)^{B,C}	62.32(48.6-73.73)^{A,C}	73.36(57.92-91.73)^{A,B}	KWT	<0.001
FABP4 pg/ml	46.16(28.4-76.08)^{B,C}	74.64(57.11-105.12)^{A}	85.96(60.95-140.79)^{A}	KWT	<0.001
TNFα pg/ml	35.06(22.06-58.77)^{B,C}	64.31(34.67-88.29)^{A,C}	79.38(70.44-111.82)^{A,B}	KWT	<0.001
PAI-1 ng/ml	2.44(1.13-3.49)^{B,C}	5.42(2.6-8.43)^{A,C}	6.34(5.31-9.12)^{A,B}	KWT	<0.001
PTX3 pg/ml	2.76(1.89-5.31)^{B,C}	5.29(3.01-9.58)^{A}	5.46(3.76-11.36)^{A}	KWT	<0.001
Hs-CRP μg/ml	1.62(0.94-3.4)^{B,C}	2.48(1.79-3.66)^{A,C}	4.05(2.95-5.09)^{A,B}	KWT	<0.001
OPG ng/ml	1.57(1.1-2.72)	1.39(1.07-2.12)^{C}	1.89(1.34-3.37)^{B}	KWT	0.030
VEGF pg/ml	451.84(267.32-718.03)^{C}	504.13(414.53-735.32)	590.71(416.01-958.64)^{A}	KWT	0.017

$^{A, B, C}$: Pairwise comparison, Results are expressed as mean ± standard deviation for normally distributed data. F: F-statistic value, *p. probability value. Not normally distributed data were expressed as median(Interquartiles) and compared using the Kruskal-Wallis test (KWT)*, FBG: fasting blood glucose, I/G: insulin/glucose ratio, TRAIL: TNF-related apoptosis-inducing ligand, Hs-CRP: high-sensitive C-reactive protein, PTX3: pentraxin 3, OPG: Osteoprotegerin, FABP4: fatty acid-binding protein 4, TNFα: tumor necrosis factor-alpha, VEGF: vascular endothelial growth factor, PAI-1: plasminogen activator inhibitor 1, HOMA2(IR): homeostatic model assessment 2 for insulin resistance, HOMA%B: HOMA(beta cell function percentage, and HOMA%S: HOMA(insulin sensitivity percentage).

Table 3. Results of multivariate analysis showing the effect of cofounders on the levels of the measured parameters. Partial η^2: effect size.

Tests	Dependent variables	Explanatory variables	F	p	Partial η^2
Multivariate	All biomarkers (OPG, TRAIL, Hs-CRP, TNFα, FABP4, PAI-1, VEGF, PTX3, HOMA2IR, I/G, Insulin, HOMA2%S, HOMA2%B, and FBG)	Diagnosis	13.473	0.000	0.579
		Previous Abortion	1.753	0.052	0.152
		SBP	1.361	0.180	0.122
		DBP	1.303	0.213	0.117
		Gravidity	1.256	0.243	0.114
		Multipara	1.099	0.364	0.101
		Gestational age	0.836	0.630	0.079
		Age	0.782	0.688	0.074

		Nullipara	0.37	0.981	0.036
		Parity, Cesarean delivery, & Natural delivery	0	1	0
Between-subject effects	**Diagnosis (HC/PE/PE+AT)**	OPG	48.199	<0.001	0.243
		TRAIL	41.666	<0.001	0.217
		Hs-CRP	39.759	<0.001	0.210
		TNFα	30.402	<0.001	0.169
		FABP4	18.700	<0.001	0.111
		PAI-1	16.362	<0.001	0.098
		VEGF	8.128	0.005	0.051
		PTX3	7.668	0.006	0.049
		HOMA2IR	4.978	0.027	0.032
		I/G	2.573	0.111	0.017
		Insulin	2.465	0.119	0.016
		HOMA2%S	2.419	0.122	0.016
		HOMA2%B	1.604	0.207	0.011
		FBG	0.003	0.955	0

Table 4. Results of the partial correlation coefficients (rho) and p-values (in brackets) for the correlation between the FF score and the measured biomarkers after controlling for the characteristics of PE patients (Age, SBP, DBP, Age of Onset, and duration of symptoms)

Control Variables	**Parameter**	**FF-TOTAL**
Age, SBP, DBP, Age of Onset, and duration of symptoms	FBG	0.048(0.550)
	Insulin	0.057(0.482)
	HOMA2%B	-0.005(0.954)
	HOMA2%S	-0.015(0.856)
	HOMA2IR	0.088(0.275)
	I/G	0.023(0.780)
	TRAIL	**0.451(<0.001)**
	FABP4	**0.208(0.009)**
	TNFα	**0.376(<0.001)**
	PAI-1	0.106(0.190)
	PTX3	0.135(0.095)
	Hs-CRP	**0.360(<0.001)**
	OPG	**0.385(<0.001)**
	VEGF	0.124(0.124)

Natural Resources for Human Health
eISSN: 2583-1194

Table 5. Results of neural networks with PE-FF≥25 or PE-FF<25 as output variables and the measured biomarkers as the predictive biomarkers.

	Models	NN#1
Input Layer	Number of units	13
	Rescaling method	Normalized
Hidden layers	Number of hidden layers	2
	Number of units in hidden layers 1/2	4 / 3
	Activation Function	Hyperbolic tangent
Output layer	Dependent variables	PE-FF≥25 vs. PE-FF<25
	Number of units	2
	Activation function	Identity
	Error function	Sum of squares
Training	Sum of squares error term	3.918
	% Incorrect predictions	8.0%
	Prediction (specificity, sensitivity)	92.5%, 91.4%
Testing	Sum of Squares error	0.436
	% Incorrect predictions	0.0%
	Prediction (specificity, sensitivity)	100.0%, 100.0%
	AUC ROC	0.994
Holdout	% Incorrect predictions	9.1%
	Prediction (specificity, sensitivity)	93.8%, 83.7%

AUC ROC: area under the curve of the receiver operating characteristic.

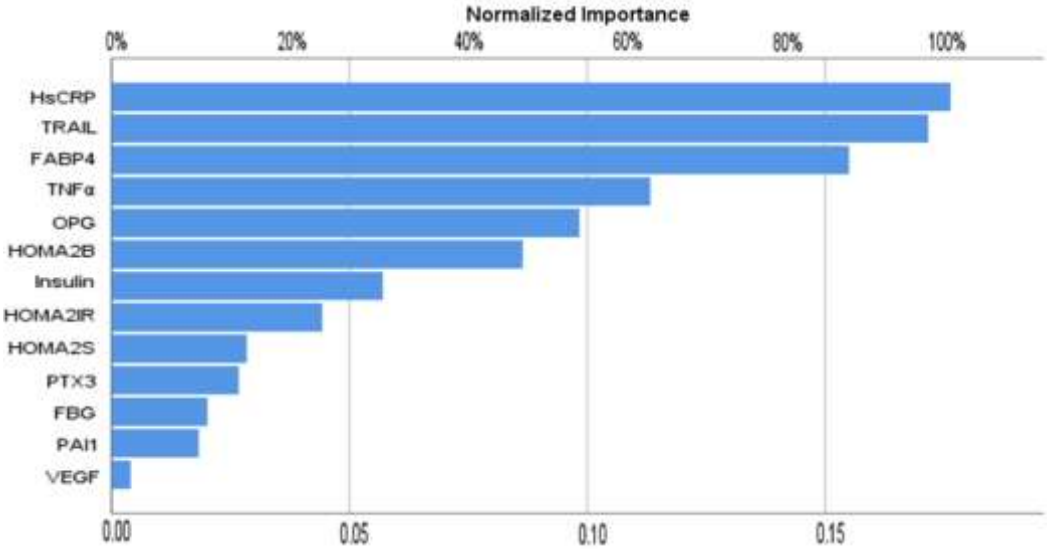

Figure 1. Results of neural network analysis. Importance of the biomarkers for the prediction of severe fatigue in preeclamptic patients (fibrofatigue ≥ 25 versus fibrofatigue < 25).