Research Article

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FIB4 score is increased in severe preeclampsia

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Abstract

Objectives: This study aims to investigate how the fibrosis index based on four factors (FIB-4) is altered in preeclampsia and whether the FIB-4 score differs with respect to the severity of preeclampsia and the presence of fetal and maternal adverse outcomes.

Methods: One hundred and forty-two patients with mild preeclampsia (34.6 %), one hundred and ninety patients who have preeclampsia with severe features (46.2 %), and 79 healthy pregnant controls (19.2 %) were included in the study. Fetal adverse outcomes occurred in 40.1 %, and maternal adverse outcomes only appeared as neurological symptoms in 20.5 % of the preeclampsia patients.

Results: Healthy controls had significantly lower FIB-4 scores than women with mild preeclampsia, and women with mild preeclampsia had significantly lower FIB-4 scores than women who had preeclampsia with severe features (respectively 0.58±0.29 vs. 0.68±0.44 vs. 1.93±4.92, p=0.003). The FIB-4 scores of preeclampsia patients with neurologic symptoms and preeclampsia patients with fetal adverse events were found to be similar to preeclampsia patients who did not have these problems. In ROC curve analysis, FIB-4 scores ≥0.758 indicated the presence of neurologic symptoms in preeclampsia patients, with a sensitivity of 0.66 and a specificity of 0.66 (p=0.004).

Conclusions: To the best of our knowledge, this is the first study to establish the FIB-4 scores of preeclampsia patients and determine if FIB-4 scores change with respect to maternal and fetal adverse outcomes. Our findings suggest that FIB-4 might be used to predict pregnancies destined to be complicated with preeclampsia and preeclampsia patients who are more likely to experience maternal and fetal adverse outcomes.

Keywords: fibrosis index; pregnancy; preeclampsia; severe preeclampsia

Introduction

Preeclampsia is a gestational disease that involves several organ systems and impairs the well-being of pregnant women and their fetuses. Thus, it has been regarded as a main cause of maternal morbidity and mortality [1]. The clinical presentation of preeclampsia varies widely, and it is challenging to predict the women who will develop severe disease. Therefore, the management of preeclampsia has become standardized for all patients and is modified only if there is disease progression [1, 2].

Although the etiology of pre-eclampsia is not yet fully understood, abnormal placentation is thought to lead to placental hypoperfusion, which may sometimes progress to endothelial dysfunction, resulting in preeclampsia, characterised by multi-systemic involvement [2]. Defective arterial placental perfusion results from a failure of trophoblasts to invade the uterine lining. As the pregnancy progresses, this worsens, and the demand for the placenta increases [3]. Nitric oxide, prostaglandins, and endothelin are released from the placental tissue, thereby inducing platelet aggregation, endothelial dysfunction, and arterial hypertension. Fibrin released as a result of endothelial damage creates crosslinked networks in the small blood vessels resulting in microangiopathic hemolytic anaemia. The pathogenesis of liver involvement is thought to be secondary to fibrin deposition within the hepatic sinusoids, which results in sinusoidal obstruction and subsequent hepatic ischaemia, and this combination causes subcapsular hematomas, parenchymal haemorrhage, and ultimately hepatic rupture [4].

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The initial work-up of women with preeclampsia often includes the evaluation of liver function tests [3]. Therefore, serum aminotransferases, lactate dehydrogenase (LDH), bilirubin, albumin, and international normalized prothrombin time ratio are often measured to designate the pregnancies that may be complicated with adverse maternal and fetal outcomes [5]. The identification of pregnancies at high risk for adverse outcomes would help to provide meticulous and cost-effective management, and the identification of pregnancies at low risk for adverse outcomes would assist in avoiding iatrogenic complications [6]. Although some studies have been able to find a strong association between hepatic function tests and adverse outcomes, others have only detected a weak relationship. Similarly, there is no consensus about the power of hepatic function tests in the prediction of the severity of preeclampsia [4, 7, 8].

The Fibrosis Index based on four factors (FIB-4) was initially proposed as an indicator for liver damage in HIV/hepatitis C virus (HCV) co-infection. This index consists of age, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and platelet count [9]. It is known that FIB-4 can be used to classify different stages of liver fibrosis in patients with viral hepatitis and non-alcoholic fatty liver disease [10]. Preeclampsia patients with morbidity have been reported to have significantly higher serum concentrations of AST than those with no morbidity [11]. Peralta et al. also highlighted that serum LDH levels differed significantly according to the severity of preeclampsia [12]. There have also been reported to be significantly increased serum levels of ALT, AST, and LDH in preeclampsia patients who experienced maternal morbidity [13]. Kozic et al. stated that preeclampsia patients with higher serum concentrations of ALT, AST, and LDH and lower serum levels of albumin were at a significantly higher risk for maternal and fetal adverse outcomes [14]. It was also determined that the ALT, AST, and LDH values could all predict adverse maternal outcomes in preeclampsia. The aim of this study was to investigate how the FIB-4 score is altered in preeclampsia and whether this score differs according to the severity of preeclampsia and the presence of maternal and fetal adverse outcomes.

Materials and methods

This study was conducted in the Obstetrics Department of Kahramanmaras Sutcu Imam University Hospital between January 2018 and July 2022. The study design conformed to the Declaration of Helsinki and was approved by the Institutional Review Board and Ethics Committee of the study center (2021/15).

This retrospective study included 332 pregnant women with preeclampsia and 79 healthy women with uncomplicated pregnancies. The diagnosis of preeclampsia was made when hypertension and either proteinuria or hyperuricemia were recorded after 20 weeks of gestation. Hypertension was defined as the measurement of systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg on two occasions at least 4 h apart. Proteinuria refers to the presence of urine protein ≥2+ by dipstick, ≥0.3 g/day by 24 h urine collection, or >30 mg/mmol by spot urinary protein/creatinine ratio. Severe features of preeclampsia included systolic blood pressure ≥160 mmHg and diastolic blood pressure ≥110 mmHg measured on two occasions at least 4 h apart, decreased platelet count, impaired hepatic function tests, renal insufficiency, pulmonary edema, new-onset visual disturbance and/or neurological symptoms. Nervous system manifestations frequently encountered in preeclampsia are headaches unresponsive to medication and not accounted for by alternative diagnoses and hyperreflexia [1]. Therefore, in the present study, patients with those manifestations were evaluated as patients with neurological symptoms.

The study exclusion criteria were defined as pregnancy <24 weeks, multiple pregnancies, pregnant women in active labor, or pregnant women lost to follow-up. Women were also excluded if any adverse maternal outcome occurred before the determination of biochemical parameters and the emergence of eligibility criteria.

Data related to maternal age, body mass index (BMI), gravidity, parity, smoking, chronic diseases, and previous pregnancies were retrieved from the medical records. BMI (kg/m^2) was calculated as body weight (kg) divided by the square of body height (m^2). Gestational age at diagnosis and delivery, ultrasonography findings, delivery type, birth weight, and Apgar scores were also recorded.

On admission, all participants underwent obstetric ultrasonography using a device with 3.5 and 5 mHz convex probes (Voluson E8, GE Healthcare, Buckinghamshire, UK). Then, venous blood samples were drawn from all patients with standardized phlebotomy. Platelet count was determined using an automated commercial counter (Coulter counter, Max Instruments Laboratory, Milan, Italy). Serum creatinine, ALT, and AST concentrations were measured photometrically on a Roche Cobas c702 device. Serum thyroid-stimulating hormone (TSH) levels were examined with the electrochemiluminescence (ECLIA) method on a Roche Cobas e602 device. The intra-assay and inter-assay coefficients of variation were respectively 7.8 and 10.0 % for TSH measurements. The laboratory parameters of the control group, including ALT, AST, and platelet count, were retracted from the routine pregnancy follow-up blood tests obtained in the third trimester of pregnancy. The FIB-4 score was calculated using the following formula:

$$\text{FIB} - 4 = \text{Age (years)} \times \text{AST}\left(\text{U/L}\right)/\text{Platelet count}\left(\times 10^9/\text{L}\right) \times \text{ALT}\left(\text{U/L}\right)^{1/2}$$

Maternal adverse outcomes were recorded for seven days after delivery. These adverse outcomes were classified through the Delphi consensus, which indicated maternal mortality or the presence of at least one serious morbidity involving the central nervous system, heart, lungs, liver, kidneys, and/or hematological system [15, 16].

Fetal adverse outcomes were defined as intrauterine demise, intrauterine growth restriction (IUGR), and need for neonatal intensive care. IUGR was defined as an estimated fetal weight ≤fifth percentile since early onset preeclampsia might hinder normal fetal growth.

Statistical analysis

The data obtained were analyzed statistically using the Statistical Package for Social Sciences version 22.0 software (SPSS IBM, Armonk,

NY, USA). Continuous variables were expressed as median or mean±standard deviation (range: minimum–maximum) values, and categorical variables as numbers and percentages. The conformity of data to normal distribution was tested using the Kolmogorov–Smirnov test. The Mann–Whitney U test and the Kruskal Wallis test were used in the comparisons. The ROC curve was operated for the FIB-4 index. Using the cut-off value obtained from the ROC analysis of the FIB-4 index, logistic regression analysis was performed to determine the effect on the probability of occurrence of neurologic symptoms and adverse fetal events.

A two-tailed p-value <0.05 was accepted as statistically significant.

Results

Evaluation was made of 142 (34.6 %) patients with mild preeclampsia, 190 (46.2 %) patients with severe preeclampsia, and 79 (19.2 %) healthy women with uncomplicated pregnancy. The healthy control group subjects with uncomplicated pregnancy were determined to have significantly lower FIB-4 scores than women with mild preeclampsia, and the women with mild preeclampsia had significantly lower FIB-4 scores than those with severe preeclampsia (0.58±0.29 vs. 0.68±0.44 vs. 1.93±4.92, respectively, p=0.001) (Table 1).

The patients who had preeclampsia with severe features had significantly lower gestational age at delivery, birth weight, and Apgar scores than the patients with mild preeclampsia and the healthy control group. Caesarean section delivery and perinatal complications were significantly more frequent in the severe preeclampsia group (p<0.05 for all) (Table 2).

Maternal adverse outcomes only appeared as neurological symptoms, which affected 68 patients with preeclampsia (20.5 %). There was neither maternal mortality nor any morbidity related to the cardiovascular system, liver, kidneys, and/or hematological system in any patient. The FIB-4 scores of the preeclampsia patients with neurological symptoms were statistically similar to those of the preeclampsia patients without neurological symptoms (1.52±2.18 vs. 1.36±4.09, p=0.758) (Table 3). The frequency of caesarean section delivery was significantly more frequent, and first-minute Apgar scores were significantly higher in preeclampsia patients with neurological symptoms (p=0.031 and p=0.046, respectively) (Table 4).

Fetal adverse outcomes occurred in 133 patients with preeclampsia (40.1 %). These adverse outcomes included intrauterine demise in nine patients (6.8 %), IUGR in 56

Table 1: Demographic and clinical characteristics of preeclampsia patients and controls.

	Control group (n=79)	Mild preeclampsia (n=142)	Preeclampsia with severe features (n=190)	p-Value
Age, years	28.9±5.7	29.6±7.0	30.4±5.7	0.181
Gravidity	2.8±1.4	3.1±2.1	3.3±1.9	0.288
Parity	1.4±1.2	1.7±0.6	1.8±1.5	0.299
Miscarriages	0.7±0.4	0.8±0.4	0.8±0.5	0.504
Body mass index, kg/m^2	28.20±1.72	28.64±3.81	28.62±4.26	0.851
Maternal smoking[e]	0 (0.0 %)	12 (8.5 %)	23 (12.1 %)	0.093
Chronic hypertension[e]	0 (0.0 %)	22 (15.5 %)	11 (50.0 %)	0.563
Gestational HT in the previous[e]	0 (0.0 %)	2 (1.4 %)	9 (4.7 %)	0.148
Preeclampsia in a previous pregnancy[e]	0 (0.0 %)	11 (7.7 %)	22 (11.6 %)	0.136
In vitro fertilization pregnancy[e]	0 (0.0 %)	8 (5.6 %)	11 (5.8 %)	0.403
Gestational age at diagnosis, weeks	–	34.9±3.0	33.4±3.2	0.001[a,b]
Systolic blood pressure, mmHg	115.8±8.4	148.6±9.2	164.9±12.5	0.001[a,b,c,d]
Diastolic blood pressure, mmHg	68.2±7.2	91.1±8.2	102.7±10.6	0.001[a,b,c,d]
Oligohydramnios[e]	0 (0.0 %)	24 (16.9 %)	24 (12.6 %)	0.037[a,c]
Polyhydramnios[e]	0 (0.0 %)	1 (0.7 %)	2 (1.1 %)	0.150
Neurological symptom[e]	0 (0.0 %)	0 (0.0 %)	68 (35.8 %)	0.001[a,b,c,d]
Hemoglobin, g/dL	11.4±1.3	11.6±1.5	12.0±1.8	0.007[a,d]
Platelet count, ×10^3/mm^3	231±76	239±77	201±90	0.001[a,b,d]
Alanine aminotransaminase, U/L	12.8±4.7	20.5±14.1	117.2±54.2	0.001[a,b,c,d]
Aspartate aminotransaminase, U/L	15.2±6.0	21.2±11.9	120.9±58.9	0.001[a,b,c,d]
Creatinine, mg/dL	0.51±0.11	0.59±0.22	0.65±0.31	0.001[a,c,d]
Proteinuria, mg/L	6.3±5.0	1,958.1±1,149.2	2,287.1±1,280.9	0.007[a,c,d]
FIB-4 score	0.58±0.29	0.68±0.44	1.93±4.92	0.001[a,b,c,d]

[a]p<0.05 was accepted to be statistically significant. [b]There is statistical significance between mild preeclampsia and preeclampsia with severe features. [c]There is statistical significance between mild preeclampsia and the control group. [d]There is statistical significance between the control group and preeclampsia with severe features. [e]Values are expressed as numbers (%). All of the remaining variables are expressed as mean±SD.

Table 2: Perinatal characteristics of preeclampsia patients and controls.

	Control group (n=79)	Mild preeclampsia (n=142)	Preeclampsia with severe features (n=190)	p-Value
Gestational age at delivery, weeks	38.5±0.5	35.6±2.8	34.0±3.1	0.001[a,b,c,d]
Vaginal delivery[e]	28 (93.3 %)	22 (15.5 %)	11 (5.8 %)	0.001[a,b,c,d]
Cesarean delivery[e]	2 (6.7 %)	120 (84.5 %)	179 (94.2 %)	0.001[a,b,c,d]
Birth weight, grams	3,284±536	2,538±636	2,123±710	0.001[a,b,c,d]
First-minute Apgar score	7.8±0.7	7.8±1.4	7.2±2.0	0.001[a,b,d]
Fifth-minute Apgar score	9.0±0.8	9.1±1.4	8.3±2.1	0.001[a,b,d]
Fetal adverse outcomes[e]	0 (0.0 %)	42 (29.6 %)	91 (47.9 %)	0.001[a,b,c,d]
Intrauterine demise	0 (0.0 %)	1 (2.4 %)	8 (8.8 %)	0.232
Intrauterine growth restriction	0 (0.0 %)	20 (47.6 %)	36 (39.6 %)	0.280
Need for neonatal intensive unit	0 (0.0 %)	21 (50.0 %)	47 (51.6 %)	0.200

[a]p<0.05 was accepted to be statistically significant. [b]There is statistical significance between mild preeclampsia and preeclampsia with severe features. [c]There is statistical significance between mild preeclampsia and the control group. [d]There is statistical significance between the control group and preeclampsia with severe features. [e]Values are expressed as numbers (%). All of the remaining variables are expressed as mean±SD.

Table 3: Demographic and clinical characteristics of preeclampsia patients with respect to neurological symptoms.

	Neurological symptoms (n=68)	No neurological symptoms (n=264)	p-Value
Gravidity	3.6±2.2	3.1±2.0	0.123
Parity	2.0±1.6	1.7±1.6	0.194
Miscarriages	0.9±0.6	0.8±0.5	0.209
Body mass index, kg/m^2	28.43±4.20	28.68±4.04	0.646
Maternal smoking[a]	9 (13.2 %)	26 (9.8 %)	0.417
Chronic hypertension[a]	2 (2.9 %)	22 (8.3 %)	0.043[b]
Preeclampsia in a previous pregnancy[a]	6 (8.8 %)	27 (10.2 %)	0.150
Gestational hypertension in previous pregnancy[a]	4 (5.9 %)	7 (2.7 %)	0.124
In vitro fertilization pregnancy[a]	4 (5.9 %)	15 (5.7 %)	0.949
Mild preeclampsia[a]	13 (19.1 %)	129 (48.9 %)	0.001[b]
Severe preeclampsia[a]	55 (80.9 %)	135 (51.1 %)	0.001[b]
Gestational age at diagnosis, weeks	33.3±2.9	34.2±3.2	0.034[b]
Systolic blood pressure, mmHg	160.4±15.2	157.3±13.4	0.105
Diastolic blood pressure, mmHg	98.4±10.5	97.6±11.4	0.573
Oligohydramnios[a]	0 (0.0 %)	48 (18.2 %)	0.001[b]
Polyhydramnios[a]	0 (0.0 %)	3 (1.1 %)	0.001[b]
Umbilical artery pulsatility index	2.94±0.69	2.99±0.88	0.645
Hemoglobin, g/dL	11.8±1.4	11.9±1.7	0.848
Platelet count, $\times 10^3$/mm^3	196.897±80.494	221.837±88.081	0.035[b]
Alanine aminotransaminase, U/L	84.3±43.3	92.3±38.9	0.721
Aspartate aminotransaminase, U/L	71.3±44.4	98.6±42.4	0.876
Creatinine, mg/dL	0.67±0.25	0.61±0.28	0.134
Proteinuria, mg/L	2,227.0±1,438.5	2,131.1±1,169.5	0.372
FIB-4 score	1.52±2.18	1.36±4.09	0.758

[a]Values are expressed as numbers (%). All of the remaining variables are expressed as mean±SD [b]p<0.05 was accepted to be statistically significant.

patients (42.1 %), and the need for the neonatal intensive care unit in 68 patients (51.1 %). The FIB-4 scores of the preeclampsia patients with fetal adverse outcomes were higher than those of the preeclampsia patients without fetal adverse outcomes, but this difference was statistically insignificant (1.74±5.59 vs. 1.70±1.17, p=0.252) (Table 5).

The ROC curve was drawn for the FIB-4 index. High values indicated the presence of neurologic symptoms in preeclampsia patients, with a cut-off point of 0.758, sensitivity of 0.66, and specificity of 0.66. The area under the curve (AUC) was found to be 0.615 (confidence interval, CI 0.538–0.691, p=0.004) for the FIB-4 index (Figure 1). There was no statistical significance in ROC analysis of the FIB 4 index for fetal adverse outcomes.

Logistic regression analysis was performed by taking the cut-off value of 0.758 obtained in the ROC analysis for the

Table 4: Perinatal characteristics of preeclampsia patients with respect to neurological symptoms.

	Neurological symptoms (n=68)	No neurological symptoms (n=264)	p-Value
Gestational age at delivery, weeks	34.2±2.8	34.8±3.1	0.174
Vaginal delivery[a]	2 (2.9 %)	31 (11.7 %)	0.031[b]
Cesarean delivery[a]	66 (97.1 %)	233 (88.3 %)	0.031[b]
Birth weight, grams	2,168.9±658.0	2,334.1±719.0	0.087
First-minute Apgar score	7.8±1.1	7.4±1.9	0.046[b]
Fifth-minute Apgar score	8.9±1.0	8.6±2.0	0.133
Fetal adverse outcomes[a]	24 (35.3 %)	109 (41.3 %)	0.368
Intrauterine demise	0 (0.0 %)	9 (3.4 %)	0.238
Intrauterine growth restriction	9 (13.2 %)	47 (17.8 %)	0.847
Need for neonatal intensive unit	15 (22.1 %)	53 (20.1 %)	0.109

[a]Values are expressed as numbers (%). All of the remaining variables were expressed as mean±SD. [b]p<0.05 was accepted to be statistically significant.

Table 5: Characteristics of preeclampsia patients with respect to fetal adverse outcomes.

	Fetal adverse outcomes (n=133)	No fetal adverse outcomes (n=199)	p-Value
Gravidity	3.4±1.9	3.1±2.1	0.143
Parity	1.9±1.6	1.7±1.6	0.148
Miscarriages	0.8±0.6	0.8±0.4	0.117
Body mass index, kg/m^2	28.72±3.99	28.57±4.12	0.742
Maternal smoking[a]	12 (9.0 %)	23 (11.6 %)	0.461
Chronic hypertension[a]	9 (6.8 %)	15 (7.5 %)	0.537
Preeclampsia in a previous pregnancy[a]	10 (7.7 %)	23 (11.6 %)	0.148
Gestational hypertension in previous pregnancy[a]	3 (2.3 %)	8 (4.0 %)	0.462
In vitro fertilization pregnancy[a]	6 (4.5 %)	13 (6.5 %)	0.437
Gestational age at diagnosis, weeks	32.0±3.2	35.4±2.4	0.001[b]
Systolic blood pressure, mmHg	159.0±14.7	157.2±13.2	0.248
Diastolic blood pressure, mmHg	97.3±12.5	98.0±10.2	0.585
Oligohydramnios[a]	21 (15.8 %)	27 (13.6 %)	0.534
Polyhydramnios[a]	2 (1.5 %)	1 (0.5 %)	0.540
Umbilical artery pulsatility index	3.14±0.86	2.87±0.82	0.004[b]
Neurological symptom[a]	24 (18.0 %)	44 (22.1 %)	0.368
Hemoglobin, g/dL	12.0±1.7	11.7±1.7	0.161
Platelet count, ×10^3/mm^3	213.526±91.272	218.869±84.275	0.584
Alanine aminotransaminase, U/L	129.5±54.8	47.8±29.7	0.034[b]
Aspartate aminotransaminase, U/L	121.7±53.3	68.1±35.8	0.133
Creatinine, mg/dL	0.65±0.34	0.61±0.23	0.206
Proteinuria, mg/L	2,394.7±1,407.1	1,967.2±1,102.6	0.207
FIB-4 score	1.74±5.59	1.70±1.17	0.252
Gestational age at delivery, weeks	32.7±3.2	36.0±2.1	0.001[b]
Vaginal delivery[a]	15 (11.3 %)	18 (9.0 %)	0.505
Cesarean delivery[a]	118 (88.7 %)	181 (91.0 %)	0.505
Birth weight, grams	1,778.0±517.2	2,649.3±597.2	0.001[b]
First-minute Apgar score	6.8±2.3	7.9±1.2	0.001[b]
Fifth-minute Apgar score	7.9±2.5	9.1±1.0	0.001[b]

[a]Values are expressed as numbers (%). All of the remaining variables were expressed as mean±SD. [b]p<0.05 was accepted to be statistically significant.

FIB-4 index. The odds ratio was found to be 0.463 in terms of neurological symptom development in patients with a FIB4 score lower than 0.758 (p=0.006, 95 % CI: 0.267–0.802). In the logistic regression analysis, no significant relationship was found between the FIB 4 index and fetal adverse events (p=0.069).

Discussion

Preeclampsia is a systemic disease characterized by increased systemic vascular resistance and platelet aggregation, along with impaired coagulation and endothelial functions [17]. Liver involvement has been recognized in

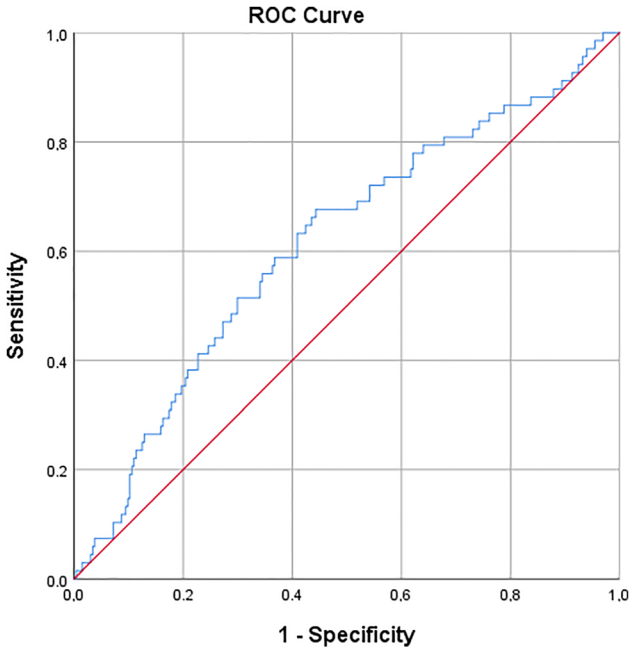

Figure 1: ROC curve analysis of FIB-4 index in determining neurologic adverse outcomes in preeclampsia patients. The area under the curve (AUC): 0.615 (confidence intervals, CI 0.538–0.691, p=0.004).

approximately 15 % of preeclampsia-related deaths. Preeclampsia-related hepatic involvement usually presents with subcapsular hematoma (leading to a rupture in some cases), diffuse infarction, and necrosis [18].

Liver involvement in preeclampsia is associated with endothelial dysfunction, which triggers the release of vasoactive mediators such as fibronectin, thrombomodulin, endothelin-l, and thromboxane. These mediators cause vasoconstriction and thereby impair hepatic microcirculation [4, 17]. Another participating factor is the antagonism of vascular endothelial growth factor by soluble fms-like tyrosine kinase-1, which decreases the expression of endothelial nitric oxide synthase and induces vasoconstriction [1, 18]. The impairment of hepatic microcirculation will ultimately result in hypoxia, degeneration of hepatocytes, and necrosis. Therefore, it would be natural to expect a significant change in serum transaminase levels in preeclampsia patients [1, 19].

In clinical practice, hepatic dysfunction in preeclampsia is defined as a >2-fold increase in the upper limits of aminotransferases accompanied by severe pain in the right upper abdomen and/or epigastric tenderness [20]. It has been claimed that the increase in aminotransferases merely reflects a mild disturbance of hepatic functions, and this increase is not correlated with either hypertension or proteinuria [21]. Similarly, Peralta et al. failed to detect any significant differences between serum aminotransferase levels of healthy control subjects and preeclampsia patients [12]. In contrast, it has been declared that elevated aminotransferases during the first half of pregnancy are significantly predictive of severe preeclampsia emerging in the second half [21]. Therefore, platelet count and measurement of liver enzymes might have significant prognostic value for the prediction of preeclampsia [19]. In parallel, preeclampsia with severe features usually leads to an increase in serum LDH levels and alteration in coagulation tests [1, 22].

Taking these findings into account, Martin et al. investigated the use of platelet count and serum LDH levels as indicators for severe preeclampsia. They introduced the Mississippi triple-class system for categorizing affected pregnancies and predicting the outcomes. According to this system, postpartum recovery duration is associated with platelet count and serum LDH level [23]. Nine years later, the same authors developed a risk assessment model based on ALT, AST, LDH, uric acid, creatinine, and proteinuria values that were determined as soon as the diagnosis of severe preeclampsia or HELLP was made. It was suggested that this model could be used as a complementary tool to the Mississippi triple-class system. The measurement of ALT, AST, and LDH can be used to identify pregnancies with a low, moderate, or high risk for maternal morbidity [13]. The full preeclampsia integrated estimate of risk score (PIERS) was later introduced to identify pregnant women at risk of adverse outcomes. This scoring system consists of gestational age at diagnosis, the presence of chest pain and dyspnea, oxygen saturation, platelet count, serum creatinine, and AST levels [15, 24].

Wolf et al. were the first to use Fibroscan and directly observed the marked increase in hepatic stiffness, namely, hepatic fibrosis in preeclampsia patients [25]. In fact, liver stiffness significantly increases in the majority of healthy women during the third trimester of pregnancy and rapidly resolves after delivery. Moreover, an increase in liver stiffness above 7.6 kPa has been identified as an independent predictive factor for preeclampsia [26]. It has been reported that pathophysiological abnormalities such as generalized vasospasm, vascular endothelial dysfunction, abnormal lipid metabolism, and insulin resistance could have an effect on the liver and result in partially elevated liver enzymes before preeclampsia develops [4]. During the first 20 weeks of pregnancy, an increase in AST and ALT levels has been shown to be significantly associated with a greater risk of severe preeclampsia developing during the second half of the pregnancy. In addition, it has been reported that several laboratory tests, together with several standard biochemical and hematological parameters, such as liver enzymes, could have significant prognostic value in the prediction of preeclampsia, albeit in the third trimester [4]. However, it is

difficult in practice to estimate morbidity for preeclampsia by considering many different parameters, such as ALT, AST, LDH, platelet count, etc., simultaneously. Therefore, since the FIB-4 index is an index that uses more than one parameter, it would be convenient to use the FIB-4 index to predict adverse outcomes in preeclampsia. FIB-4 has been determined to be an accurate and effective means of distinguishing different stages of hepatic fibrosis in patients with viral hepatitis and non-alcoholic fatty liver disease [10]. The FIB-4 score is also a significant predictor of mortality, mainly from cardiovascular diseases, followed by malignancies other than hepatic tumors, liver diseases, and diabetes mellitus [27, 28]. As FIB-4 is based on age, platelet count, and serum transaminase levels, it can be presumed that this score would be altered in preeclampsia, and it can be valuable for the prediction of adverse maternal and fetal outcomes and for the early prediction of pregnancies, which are at risk of developing preeclampsia in the future.

To the best of our knowledge, this is the first study to have established the FIB-4 scores of preeclampsia patients and determined the change in FIB-4 scores with respect to maternal and fetal adverse outcomes. The study results demonstrated that the patients who had preeclampsia with severe features had significantly higher FIB-4 scores than patients with mild preeclampsia and the healthy control group. Although the FIB-4 scores of the preeclampsia patients with fetal adverse outcomes were higher, this difference was not statistically significant. Moreover, the FIB-4 scores did not differ significantly in preeclampsia patients with neurological symptoms. The ROC analysis of the present study revealed that high FIB4 scores determine the presence of neurologic symptoms. Although it has limitations due to moderate sensitivity and specificity values, this finding is still a valuable finding in clinical practice as it emphasizes the questioning of the presence of neurological symptoms in patients with high FIB-4 scores and prevents these symptoms from being overlooked.

Additionally, the results of logistic regression analysis showed that in preeclampsia patients with low FIB-4 scores (<0.758), the probability of developing neurological symptoms would be approximately 54 % less.

In conclusion, these findings suggest that FIB-4 might be used to predict pregnancies that are destined to be complicated with preeclampsia and preeclampsia patients who are more likely to experience maternal and fetal adverse outcomes. However, these findings should be interpreted with caution as their power is limited by a lack of longitudinal findings and the retrospective design of the study. Further research is warranted to clarify the role of FIB-4 in predicting the severity of preeclampsia and adverse maternal and fetal outcomes.

Research ethics: The research complied with all the relevant national regulations, institutional policies and in accordance with the tenets of Helsinki Decleration and the study was approved by the Institutional Ethics Committee Approval number: # 08/2019.

Informed consent: Informed consent was obtained from all individuals included in this study.

Author contributions: Substantial contributions to the conception or design of the work, acquisition of data: Alev Özer. Analysis, and interpretation of data for the work: Serdar Özer. Drafting the work or revising it critically for important intellectual content: Hakan Güneş, Alev Özer. Final approval of the version to be published: Hakan Güneş. All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

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