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Liver fibrosis markers as predictors of adverse outcomes in pregnancy-related hypertensive disorders

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Abstract

Objectives: This study aimed to compare noninvasive liver fibrosis markers, including the Aspartate Aminotransferase Platelet Ratio Index (APRI) and FIB-4, between patients with hypertensive disorders of pregnancy (HDP) and healthy controls and to investigate the association between these markers and adverse maternal and perinatal outcomes.
Methods: In this retrospective case-control study, 205 patients with HDP and 192 normotensive controls were included for evaluation. Demographic data, laboratory findings, and maternal and perinatal outcomes were compared. FIB-4 and APRI scores were calculated using second-trimester AST, ALT, and platelet levels. ROC curve analysis was used to assess the predictive accuracy of these indices for HELLP syndrome and other complications. Linear regression analysis was applied to evaluate the parameters associated with the FIB-4 score.
Results: FIB-4 and APRI scores were significantly higher in patients with HDP compared to controls ($p<0.05$). Among patients with severe preeclampsia and HELLP syndrome, fibrosis scores were markedly elevated. FIB-4 and APRI showed excellent diagnostic performance for HELLP syndrome (AUC: 0.976 and 0.992, respectively), with optimal cutoffs of 1.52 and 0.7. However, their predictive role for general adverse maternal and perinatal outcomes was limited. In multivariate regression, systolic blood pressure, maternal age, and adverse maternal outcomes were independent predictors of increased FIB-4 scores ($p<0.05$).
Conclusions: FIB-4 and APRI may be considered simple, noninvasive indices that could contribute to early risk stratification for HELLP syndrome among patients with HDP. Although their predictive capacity remains to be validated in larger prospective studies, they may offer preliminary insights into hepatic dysfunction during pregnancy.

Keywords: hypertensive disorders of pregnancy; preeclampsia; HELLP syndrome; fibrosis-4 index; APRI; pregnancy complications

Introduction

Hypertensive diseases complicate up to 10 % of pregnancies, and the prevalence of hypertension is rising owing to changes in maternal demography [1]. The hypertensive diseases of pregnancy (HDP), including chronic hypertension, gestational hypertension, preeclampsia with or without severe symptoms, eclampsia, and HELLP syndrome, remain significantly linked to unfavorable mother and fetal outcomes throughout [2]. Preeclampsia, with or without severe symptoms, is characterized by systemic vascular dysfunction and endothelial damage, representing discrete medical diseases with diverse prognoses and clinical outcomes. Nevertheless, they often progress and may lead to significant issues that may be life-threatening, including cerebral edema, stroke, convulsions, pulmonary edema, HELLP syndrome, disseminated intravascular coagulopathy (DIC), and liver rupture, as well as conditions for the fetus such as prematurity, low birth weight, and intensive care unit admission (NICU) [3, 4].

Proper prenatal care, including preeclampsia risk assessment, aspirin prophylaxis, and meticulous blood pressure monitoring, along with antenatal interventions such as antihypertensive therapy and magnesium prophylaxis, as well as aware fetal monitoring, are crucial for mitigating morbidity and mortality in patients with hypertension during pregnancy. Furthermore, reliable and

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clinically accurate markers may serve as predictors for estimating preeclampsia and associated disorders [5].

Hepatic involvement is one of the key conditions that lead to the most significant clinical findings in preeclampsia. HELLP syndrome is a well-known complication of preeclampsia, in which spasms of the intrahepatic vasculature cause elevated liver enzyme levels and a marked decrease in platelets, which can lead to maternal death. Previous studies suggest that liver enzymes may predict the onset of preeclampsia and aid in its early detection [6]. In this context, mid-trimester examination of noninvasive liver fibrosis indices such as the Aspartate Aminotransferase Platelet Ratio Index (APRI) and fibrosis 4 (FIB-4) indices, which are calculated using maternal age, liver enzymes, and platelet counts, may provide insights into hepatic dysfunction and help identify patients at increased risk for HDP [7].

The aims of this study are i) to compare mid-trimester noninvasive liver fibrosis indices, including APRI and FIB-4 indices, between patients with HDP and healthy controls and ii) to investigate the association between these indices and adverse maternal and perinatal outcomes in patients with HDP.

Materials and methods

Study population

This retrospective case-control study involved 205 patients diagnosed with HDP, including gestational hypertension, preeclampsia, and eclampsia, and 192 healthy comparative control groups. Control patients were selected from a convenience sample of normotensive pregnant women who were routinely followed at our institution during the same study period as the HDP group. The study was approved by the Ethics Committee of the Zeynep Kamil Women and Children Diseases Training and Research Hospital (date and number: February 5, 2025, 19). The study was conducted according to the Declaration of Helsinki.

Patients who were diagnosed with hypertension during pregnancy but had no prior history of chronic hypertension were included in this study during routine follow-up from January 2020 to December 2024. We divide HDP into four groups: preeclampsia, gestational hypertension, preeclampsia superimposed on chronic hypertension, and chronic hypertension [8]. In the HDP group, we included the preeclampsia and gestational hypertension groups. We excluded patients with chronic hypertension due to their disease duration. Hypertension was defined in pregnant women as the clinical maternal systolic blood pressure being 140 mm Hg or more and/or the diastolic blood pressure being 90 mmHg or more, measured at least twice with a minimum interval of 4 h. Gestational hypertension was defined as SBP≥140 mm Hg or DBP≥90 mm Hg at or after 20 weeks of amenorrhea. Preeclampsia was defined as new-onset hypertension (≥140/90 mmHg) after 20 weeks of gestation, accompanied by proteinuria (≥300 mg/24 h) and/or evidence of systemic involvement, such as thrombocytopenia, elevated liver enzymes, renal insufficiency, pulmonary edema, or cerebral/visual disturbances [9]. Eclampsia was defined as the occurrence of new-onset generalized tonic-clonic seizures in a woman with preeclampsia, in the absence of other neurological conditions [10]. HELLP syndrome was described as a severe form of preeclampsia characterized by hemolysis, elevated liver enzymes, and low platelet count, typically occurring in the third trimester or postpartum period [11]. Exclusion criteria included women with twin pregnancies and comorbidities such as chronic hypertension, viral hepatitis, gestational diabetes mellitus, coagulopathy, elevated liver enzymes, low platelet count, and drug-induced liver injury.

Fetal and maternal parameters

The data of pregnant women diagnosed with HDP and healthy controls were extracted from the hospital database. The study included maternal age, body mass index (BMI), gravida, parity, gestational age at the time of diagnosis, and systolic and diastolic blood pressure. Additionally, fetal and neonatal outcomes were assessed, including fetal growth restriction (FGR), oligohydramnios, birth weight, gestational age at birth, neonatal cord blood pH, Apgar scores at 1 min and 5 min, and NICU admission. Fetal growth restriction was traditionally defined by an ultrasound estimate of fetal weight below the 10th percentile for gestational age [12]. Prematurity was defined as birth before 37 completed weeks of gestation [13]. Low birth weight refers to infants whose birth weight is less than 2,500 g at birth, regardless of gestational age [14].

The composite adverse perinatal outcome was defined as neonatal death, NICU admission, low birth weight, prematurity, or<7 APGAR at 5 min.

Composite adverse maternal outcomes encompassed the occurrence of any severe maternal complication, including eclampsia, HELLP syndrome, placental abruption, or DIC.

FIB-4 index and APRI

The Fibrosis-4 and APRI scores are both noninvasive biomarkers effective in predicting fibrosis in hepatic disorders. The alanine aminotransferase (ALT), aspartate aminotransferase (AST), and platelet levels of the patients during the mid-trimester (18–24 weeks) before the diagnosis of any hypertensive disorders or related adverse outcomes were assessed to compute the FIB-4 and APRI scores. Laboratory evaluations including complete blood count and liver enzyme levels are commonly performed during the second trimester as part of institutional practice. The FIB-4 score was calculated using the following formula (Age × AST [U/L])/(Platelet count [10^9/L] × $\sqrt{}$ALT [U/L]) [15]. The APRI (AST to Platelet Ratio Index) score follows the formula (AST level/Upper Limit of Normal AST) × 100 ÷ Platelet count [10^9/L] [15].

Statistical analysis

Statistical analysis was conducted using the Statistical Package for the Social Sciences software (SPSS v22.00, Armonk, IBM Corp). Descriptive data were expressed as mean and standard deviation. The normality of the distribution of the variables was evaluated using the Kolmogorov-Smirnov test. Chi-square tests (Fisher's exact test if expected counts were below five) were used for categorical data. The Mann–Whitney U test was used to compare two groups. The Kruskal–Wallis test was used to compare two or more groups when the normality assumption was not met, and the Bonferroni correction was applied for multiple comparisons. Receiver Operating Characteristic (ROC) analysis was conducted to evaluate the predictive ability of FIB-4 and APRI scores for HELLP syndrome and adverse maternal and perinatal outcomes. The area under the curve (AUC) was calculated to evaluate the discriminative power of these indices. Optimal cutoff values were determined using the Youden index. Linear regression analysis was applied to assess the parameters associated with the FIB-4 score. In statistical analyses, a significance level of $p<0.05$ was considered statistically significant.

Results

The mean age of the 397 patients included in the study was 30.1 (5.7) years in the HDP group (n=205) and 28.5 (5.6) years in the control group (n=192) (Table 1). In the HDP (n=205), the mean systolic blood pressure was 150 (SD: 12.6), and the mean diastolic blood pressure was 92.8 (9.3). One hundred two patients received a single antihypertensive treatment with either alpha-methyldopa, nifedipine, or amlodipine, while 56 patients received a combination of these treatments.

Table 1: Evaluation of maternal characteristics and fibrosis scores in hypertensive disorders of pregnancy vs. control group.

	Hypertensive disorders of pregnancy (n=205)	Control (n=192)	p-Value
Demographic			
Maternal age, years	30.1 (5.7)	28.5 (5.6)	**0.005**
BMI, kg/m^2	31.2 (5.9)	28 (3.8)	<**0.001**
Gravida	2.4 (1.6)	2.1 (1.4)	0.96
Parity	1.7 (1.1)	1.7 (0.9)	0.35
Outcomes			
Gestational age at birth	36 (3.1)	37.8 (2.1)	<**0.001**
Mode of delivery: C/S, n (%)	149 (72.7 %)	101 (52.6 %)	<**0.001**
Fetal birth weight	2,622.9 (858.3)	2,982.2 (543.9)	<**0.001**
APGAR 1 min	6.78 (1.2)	7.2 (0.8)	<**0.001**
APGAR 5 min	8.1 (0.9)	8.4 (0.6)	<**0.001**
pH	7.2 (0.1)	7.3 (0.1)	**0.01**
NICU	99 (48.3 %)	47 (24.5 %)	<**0.001**
Neonatal death	2 (1 %)	0	0.17
Laboratory findings			
ALT, U/L	13.4 (14.2)	9.8 (4.9)	**0.02**
AST, U/L	21 (14.2)	16.9 [31]	**0.03**
PLT, 10^9/L	224.2 (81.6)	232.8 (66.4)	**0.14**
APRI	0.3 (0.5)	0.2 (0.1)	**0.02**
FIB-4	0.9 (0.6)	0.7 (0.2)	**0.002**

Data are presented as mean (SD) or n (%). Bold value indicates statistical significance. BMI, body mass index; C/S, cesarean section; NICU, Nneonatal intensive care unit; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PLT, platelet count; APRI, aspartate transaminase-to-platelet ratio index, FIB-4, fibrosis-4 index.

In terms of FIB-4, APRI scores, and their parameters, ALT, AST, FIB-4, and APRI levels were significantly higher, and platelet levels were lower in patients with HDP than in controls ($p<0.05$) (Table 1). Gestational age, birth weight, APGAR scores at 1st and 5th minutes, and pH values were lower in patients with HDP compared to controls. Additionally, the cesarean section rate and NICU stay were significantly higher in these patients ($p<0.05$). In the HDP group, there were two cases of neonatal mortality (Table 1). In two patients who died neonatally, the placenta was detached, one at 26 weeks (540 g) and the other at 31 weeks (833 g).

Maternal and neonatal outcomes according to the severity of hypertensive disorders of pregnancy

Adverse maternal and neonatal outcomes significantly increased with the severity of hypertensive disorders. While

Table 2: Comparison of outcomes and fibrosis indices across hypertensive disorders of pregnancy.

	Gestational HT (n=36)	Preeclampsia without severe features (n=139)	Preeclampsia with severe features (n=30)	p-Value
Maternal outcomes				
24-h urine protein	0	673 (776)	1,747 (1,671)	<**0.001**
Systolic blood pressure	145 (7.7)	148 (10.2)	165 (16.7)	<**0.001**
Diastolic blood pressure	88.2 (7.8)	92.7 (8.6)	98.7 (11.4)	<**0.001**
HELLP syndrome	0	0	6 (20 %)	<**0.001**
Eclampsia	0	0	1 (33 %)	0.05
Placental abruption	0	6 (4.3 %)	5 (16.7 %)	**0.007**
DIC	0	0	1 (3.3 %)	0.05
Composite outcomes: Adverse maternal outcome	0	6 (4.3 %)	11 (36.7 %)	<**0.001**
Neonatal outcomes				
Gestational age at birth	37.6 (1.9)	36.2 (2.8)	33.5 (3.4)	<**0.001**
Premature (<37 week)	5 (13.9 %)	49 (35.35)	24 (80 %)	<**0.001**
Fetal birth weight	2,959 (630)	2,678 (850)	1,962 (810)	<**0.001**
Low birth weight (<2,500 gr)	6 (16.7 %)	45 (32.4 %)	22 (73.35)	<**0.001**
APGAR 1 min	7.1 (1.01)	6.78 (1.16)	6.3 (1.44)	**0.005**
APGAR 5 min	8.4 (0.7)	8.1 (0.9)	7.6 (1.2)	**0.003**
pH	7.3 (0.1)	7.2 (0.1)	7.2 (0.1)	0.57
NICU	10 (27.8 %)	67 (48.2 %)	22 (73.3 %)	**0.001**
Neonatal death	0	1 (0.7 %)	1 (3.3 %)	0.33
Composite outcomes: Adverse neonatal outcomes	14 (38.9 %)	82 (59 %)	28 (93.3 %)	<**0.001**
Fibrosis indices				
APRI	0.3 (0.2)	0.3 (0.1)	0.9 (1.1)	<**0.001**
FIB-4	0.7 (0.4)	0.8 (0.4)	1.8 (1.2)	<**0.001**

Data are presented as mean (SD) or n (%). Bold value indicates statistical significance. HELLP, hemolysis elevated liver enzymes, and low platelet count; DIC, disseminated intravascular coagulation; NICU, neonatal intensive care unit; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PLT, platelet count; APRI, aspartate transaminase-to-platelet ratio index, FIB-4, fibrosis-4 index.

no maternal complications occurred in the gestational hypertension group, the incidence of adverse maternal outcomes was 36.7 % in patients with severe preeclampsia (p<0.001). Severe preeclampsia was also associated with higher rates of HELLP syndrome, placental abruption, and NICU admissions. Neonatal outcomes, including gestational age at delivery, birth weight, and Apgar scores at 1 and 5 min, significantly declined with increasing severity of hypertensive disorders. APRI and FIB-4 scores were significantly higher in the severe preeclampsia group (p<0.001) (Table 2).

Assessment of adverse maternal and neonatal outcomes in patients with hypertensive disorders of pregnancy based on FIB-4 and APRI indices

In the analysis of liver fibrosis indices, both FIB-4 and APRI scores were significantly higher in patients with HELLP syndrome compared to those without (both p<0.001). No significant differences in FIB-4 or APRI were observed regarding overall adverse maternal outcomes or placental abruption (p>0.05). In terms of neonatal outcomes, both FIB-4 and APRI scores were significantly higher in patients with low birth weight (both p=0.01). Additionally, FIB-4 was significantly associated with preterm birth (p=0.02), whereas APRI demonstrated a borderline association (p=0.09) (Table 3).

Multivariable linear regression analysis of factors associated with FIB-4

A multivariate linear regression analysis was conducted to examine the clinical factors affecting liver fibrosis in hypertensive disorders of pregnancy, using the FIB-4 index as the dependent variable. The model included maternal and clinical variables, including systolic and diastolic blood pressure, maternal age, BMI, presence of adverse maternal and perinatal outcomes, and proteinuria levels. In this multiple linear regression model, systolic blood pressure (β=0.0087, p=0.039), maternal age

Table 3: Adverse maternal and neonatal outcomes in patients with hypertensive disorders of pregnancy according to FIB-4 and APRI indices.

	FIB-4	p-Value	APRI	p-Value
Adverse maternal outcome				
Yes	1.7 (1.4)	0.21	1.1 (1.5)	0.27
No	0.9 (0.5)		1.2 0.3 (0.2)	
HELLP syndrome				
Yes	3.1 (1.1)	**<0.001**	2.6 (1.7)	**<0.001**
No	0.9 (0.5)		0.3 (0.2)	
Placental abruption				
Yes	0.9 (0.8)	0.15	0.3 (0.5)	0.08
No	0.9 (0.6)		0.3 (0.5)	
Adverse neonatal outcomes				
Yes	1.1 (0.7)	0.16	0.4 (0.6)	0.11
No	1.2 (0.5)		0.2 (0.1)	
Premature (<37 week)				
Yes	1.3 (0.9)	**0.02**	0.5 (0.7)	0.09
No	1.4 0.8 (0.4)		0.2 (0.1)	
Low birth weight (<2,500 g)				
Yes	1.2 (0.9)	**0.01**	0.5 (0.7)	**0.01**
No	0.8 (0.5)		0.2 (0.3)	
NICU admission				
Yes	1.03 (0.8)	0.66	0.4 (0.7)	0.41
No	0.8 (0.5)		0.3 (0.2)	
Neonatal mortality				
Yes	0.4 (0.01)	0.06	1.1 (0.05)	0.08
No	0.9 (0.6)		0.4 (0.5)	

Data are presented as n (%). Bold value indicates statistical significance. HELLP, hemolysis elevated liver enzymes, and low platelet count; NICU, neonatal intensive care unit; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PLT, platelet count; APRI, aspartate transaminase-to-platelet ratio index, FIB-4, fibrosis-4 index.

(β=0.0312, p<0.001), and adverse maternal outcomes (β=0.5963, p<0.001) were identified as significant independent predictors of the FIB-4 score. Other variables, including diastolic blood pressure, BMI, proteinuria, and adverse perinatal outcomes, did not show a significant association with FIB-4 (p>0.05).

Diagnostic performance of FIB-4 and APRI scores in predicting HELLP syndrome and perinatal outcomes

ROC curve analysis demonstrated excellent diagnostic performance of the FIB-4 and APRI scores in predicting HELLP syndrome. The optimal cutoff value for FIB-4 was 1.5279, with an AUC of 0.976 (95 % CI 0.944-1.000), yielding a sensitivity of 100 % and a specificity of 89.95 %. Similarly, the optimal cutoff value for APRI was 0.795, with an AUC of 0.992 (95 % CI 0.975-1.000), a sensitivity of 100 %, and a specificity of 94.97 % (Figure 1).

In contrast, the diagnostic performance of both scores for adverse maternal outcomes was limited. For the FIB-4, the AUC was 0.408 (95 % CI 0.408-0.776), with a cutoff of 0.4119, a sensitivity of 87.77 %, and a specificity of 23.53 %. APRI yielded an AUC of 0.420 (95 % CI 0.393-0.766), with a cutoff of 0.2177, a sensitivity of 59.04 %, and a specificity of 52.94 %.

Similarly, in predicting adverse perinatal outcomes, both scores exhibited poor discriminatory performance. FIB-4 showed an AUC of 0.557 (cutoff: 0.99, sensitivity: 38.71 %, specificity: 77.78 %, 95 % Cl 0.479-0.636), and APRI had an AUC of 0.565 (cutoff: 0.2726, sensitivity: 45.16 %, specificity: 64.20 %, 95 % Cl 0.486-0.644).

Discussion

This study examined the potential clinical relevance of noninvasive fibrosis-related indices, including FIB-4 and

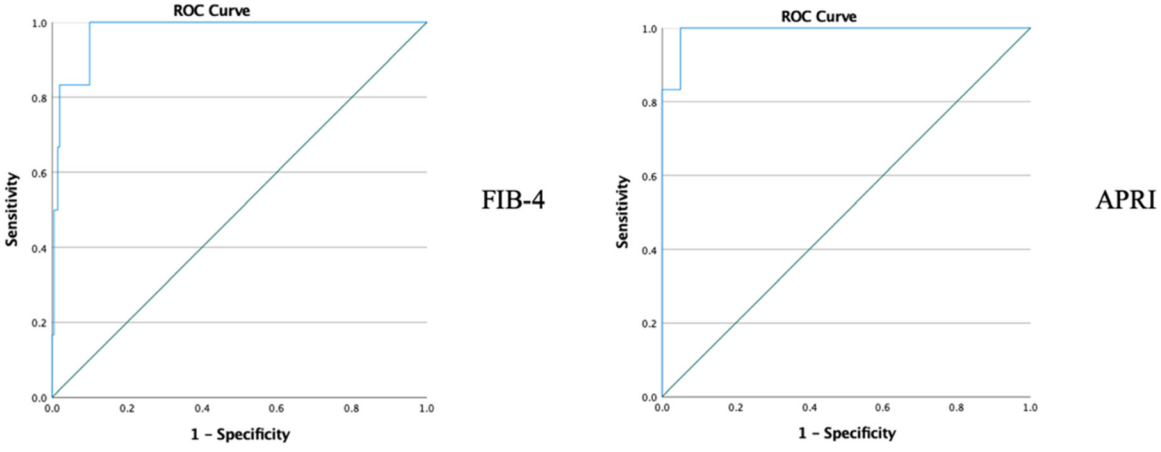

Figure 1: Receiver operating characteristic (ROC) curves for FIB-4 and APRI scores in predicting HELLP syndrome among patients with hypertensive disorders of pregnancy.

APRI, in relation to HDP, with a particular focus on their association with maternal and perinatal outcomes. Our results showed that both indices were markedly increased in patients with HDP compared to normotensive controls, with the most elevated values noted in instances of severe preeclampsia and HELLP syndrome. Both FIB-4 and APRI scores have shown high sensitivity and specificity in predicting HELLP syndrome. While these scores are not specific markers of fibrosis in pregnancy, they may reflect underlying hepatic dysfunction or systemic vascular involvement. Additionally, systolic blood pressure, advanced maternal age, and the presence of adverse maternal outcomes were independent predictors of higher FIB-4 scores.

Hypertension is the most common medical disorder occurring during pregnancy, complicating 5–10 % of all pregnancies [16]. Since it is one of the leading causes of maternal morbidity and mortality, early diagnosis and appropriate management are critical. Therefore, reliable clinical tools and biomarkers for the early detection and risk stratification of patients with HDP remain a significant research priority [17, 18]. In patients with preeclampsia, signs of hepatic dysfunction include abdominal pain, increased transaminase levels, coagulopathy, and, in extreme cases, subcapsular hemorrhage or hepatic rupture. These results may present clinically with varying degrees of severity, ranging from moderate to severe. In addition to clinical findings, histopathological changes, such as periportal and sinusoidal fibrin accumulation, as well as microvesicular fat accumulation, are also observed in these patients [3, 4]. In a study investigating liver involvement in the postpartum period of preeclamptic patients using FibroScan, a noninvasive ultrasound-based method that measures liver stiffness as a surrogate for fibrosis, higher liver stiffness values were found in the preeclamptic group. This observed increase in liver stiffness among hypertensive patients may reflect underlying hepatic fibrosis. Additionally, increased liver stiffness was also correlated with elevated liver enzyme levels [19]. Similarly, Serra et al. showed values of liver stiffness parameters were higher and significantly associated with a diagnosis of gestational hypertensive disorder [20]. Liver fibrosis is traditionally assessed using invasive methods, such as liver biopsy, or noninvasive imaging techniques, like elastography. However, recently, serum-based indices such as FIB-4 have gained attention for their good diagnostic accuracy and validated discriminative capacity [21]. The American Association for the Study of Liver Diseases recommends it as a reliable and noninvasive approach for identifying people at risk of fibrosis [22]. In contrast to previous studies that assessed liver involvement in pregnancy using elastography or biopsy, our study demonstrated significantly higher FIB-4 and APRI scores in patients with HDP, indicating liver fibrosis non-invasively through these indices. While these indices are not direct measures of histological fibrosis, they may reflect early or subclinical hepatic changes, offering a hypothesis-generating tool for identifying hepatic involvement during pregnancy, though not yet ready for use in routine clinical decision-making.

In HELLP syndrome, hepatic injury is considered multifactorial, involving thrombotic microangiopathy, inflammatory response, and Fas Ligand from the placenta, which collectively impair portal blood flow and directly damage hepatocytes. Histopathological analyses revealed periportal necrosis, fibrin deposition, and sinusoidal blockage, all indicative of microvascular damage and hepatic dysfunction. This mechanistic overlap supports the increase in hepatic fibrosis indices in HELLP and highlights the liver's pivotal role in the pathophysiology of this syndrome [23]. Ammon et al. showed that elevated liver stiffness was identified as an independent predictor of preeclampsia [24]. Similarly, one of the most notable findings of our study was the high AUC values observed for both FIB-4 (0.976) and APRI (0.992) in distinguishing patients with HELLP syndrome. A FIB-4 threshold of 1.52 and an APRI of 0.7 demonstrated promising discriminatory capacity. However, given the limited number of HELLP cases (n=6), these results should be interpreted with caution. While our findings highlight the potential utility of these indices in early risk stratification among patients with HDP at mid-gestation, larger prospective studies are needed to validate these thresholds and confirm their clinical applicability. However, we acknowledge that these scores do not currently warrant any antenatal intervention based solely on elevated values, and their role remains exploratory rather than actionable.

In addition to their high predictive value in HELLP syndrome, the diagnostic performance of these scores in predicting adverse maternal and perinatal outcomes is limited. These findings suggest that while FIB-4 and APRI may reflect liver-related complications, they may not be sensitive enough to capture the broader multisystem involvement that characterizes severe maternal and fetal outcomes. It has also been shown that many factors can affect adverse maternal and neonatal outcomes in these patients, and in our study, no significant association was observed between FIB-4/APRI and general adverse maternal outcomes [25]. Importantly, our multivariate regression analysis identified systolic blood pressure, maternal age, and adverse maternal outcomes as independent predictors of FIB-4 levels. In accordance with our results, Sato et al. demonstrated a relationship between systolic blood pressure and FIB-4 levels [26], and Sugiyama et al. have also shown, as expected, that FIB-4 increases with age [27]. In

terms of maternal outcomes, there are different findings. A research study assessing the FIB-4 score in severe preeclampsia revealed no correlation between unfavorable maternal outcomes and FIB-4 scores; however, neurological involvement was considered an adverse maternal outcome in this study [28]. Our study adds to the existing literature by evaluating these associations in a broader obstetric population and highlights the potential value of FIB-4 not only as a fibrosis marker but also as a hepatic indicator influenced by maternal characteristics in hypertensive pregnancies.

The follow-up of these patients in the postpartum period and the long term is also essential. Although our study was limited to the antenatal period, these findings underscore the importance of continued monitoring beyond delivery. While liver dysfunction in preeclampsia and HELLP syndrome is typically considered a temporary prenatal complication, recent evidence suggests long-term liver effects. A population-based cohort study by Auger et al. reported an increased risk of chronic liver disease among women with a history of preeclampsia. Although the mechanisms have not yet been elucidated, this observation underscores the importance of long-term follow-up in this population [29]. Although our findings are limited to the midgestation period, they support the need for prospective studies evaluating postpartum liver outcomes in patients with HDP. Future studies focusing on postpartum hepatic changes in this population would provide valuable insights. In a study assessing the prevalence of elevated liver stiffness and steatosis with elastography, the postpartum period showed that patients with preeclampsia, type 2 diabetes, and elevated ALT were more likely to have elevated postpartum liver stiffness [30]. In another study, liver fibrosis is evaluated in 537 pregnant women during pregnancy and in 41 women again 24 weeks postpartum. They show that liver fibrosis increases during pregnancy but decreases in all patients 24 weeks later. As a result, they state that the increasing fibrosis during pregnancy is due to mechanical and pressure-related mechanisms rather than inflammatory or apoptotic mechanisms [24].

This study is one of the first to comprehensively evaluate the utility of FIB-4 and APRI in the HDP cohort. Previous studies have evaluated transaminase levels separately; our research extends this by incorporating previously used noninvasive scores that are commonly applied to estimate liver fibrosis. The study's retrospective design, single-center nature, and relatively small number of HELLP cases are its most significant limitations. Additionally, liver fibrosis was evaluated non-invasively and was not confirmed by imaging or histological methods. Control subjects were selected from a convenience sample of normotensive pregnant women, which may introduce selection bias. With future prospective studies, longitudinal monitoring of these indices throughout pregnancy could further clarify their temporal association with disease progression in HDP.

In conclusion, our findings suggest that FIB-4 and APRI may serve as rapid, cost-effective, and noninvasive indices that show promise in research settings for early identification of hepatic involvement in HDP, though their routine clinical application remains premature at this stage. While a FIB-4 threshold of 1.52 and an APRI value of 0.7 showed discriminatory capacity for HELLP syndrome in our cohort, these cutoff values should be interpreted with caution and validated in larger, prospective studies before clinical implementation.

Research ethics: The study was approved by the Ethics Committee of Zeynep Kamil Women and Children Diseases Training and Research Hospital (date and number: 05.02.2025/19) and performed in compliance with the Declaration of Helsinki.

Informed consent: Not applicable.

Author contributions: MG, ÜT, OD, SY and BC contributed to the conception and design of the study. MG, MEÖ, ÜT, and SY were responsible for data collection and clinical coordination. MG, BC, SY and MEÖ conducted the statistical analysis and contributed to data interpretation. MG, BC, and OD drafted the initial version of the manuscript. MEÖ, OD and ÜT provided critical revisions and supervised the overall project. All authors reviewed and approved the final version of the manuscript and agreed to be accountable for all aspects of the work. All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

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Data availability: The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

References

1. Timpka S, Markovitz A, Schyman T, Mogren I, Fraser A, Franks PW, et al. Midlife development of type 2 diabetes and hypertension in women by history of hypertensive disorders of pregnancy. Cardiovasc Diabetol 2018;17:124.
2. Cífková R. Hypertension in pregnancy: a diagnostic and therapeutic overview. High Blood Pres Cardiovasc Prev 2023;30:289–303.
3. Yang Y, Le Ray I, Zhu J, Zhang J, Hua J, Reilly M. Preeclampsia prevalence, risk factors, and pregnancy outcomes in Sweden and China. JAMA Netw Open 2021;4:e218401.

4. Alese MO, Moodley J, Naicker T. Preeclampsia and HELLP syndrome, the role of the liver. J Matern Fetal Neonatal Med 2021;34:117–23.
5. 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 Publ Health 2023;20. https://doi.org/10.3390/ijerph20042994.
6. Naruse K. Liver biomarkers and preeclampsia: an easy-accessible prediction method of the disease. Hypertens Res 2024;47:2610–1.
7. Vanlı Tonyalı N, Karabay G, Aktemur G, Tokgöz Çakır B, Şeyhanlı Z, Çetin S, et al. Evaluation of APRI and FIB-4 indices in early and late-onset preeclampsia. Eur Res J 2025;11:363–70.
8. Magee LA, Brown MA, Hall DR, Gupte S, Hennessy A, Karumanchi SA, et al. The 2021 International Society for the Study of Hypertension in Pregnancy classification, diagnosis & management recommendations for international practice. Pregnancy Hypertens 2022;27:148–69.
9. Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin. Number 222. Obstet Gynecol 2020;135:e237–60.
10. Sibai BM. Diagnosis, prevention, and management of eclampsia. Obstet Gynecol 2005;105:402–10.
11. Sibai BM. Diagnosis, controversies, and management of the syndrome of hemolysis, elevated liver enzymes, and low platelet count. Obstet Gynecol 2004;103:981–91.
12. Lees CC, Stampalija T, Baschat A, da Silva Costa F, Ferrazzi E, Figueras F, et al. ISUOG Practice Guidelines: diagnosis and management of small-for-gestational-age fetus and fetal growth restriction. Ultrasound Obstet Gynecol 2020;56:298–312.
13. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller AB, Narwal R, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet 2012;379:2162–72.
14. K CA, Basel PL, Singh S. Low birth weight and its associated risk factors: health facility-based case-control study. PLoS One 2020;15:e0234907.
15. Lai JC, Liang LY, Wong GL. Noninvasive tests for liver fibrosis in 2024: are there different scales for different diseases? Gastroenterol Rep (Oxf) 2024;12:goae024.
16. Hutcheon JA, Lisonkova S, Joseph KS. Epidemiology of preeclampsia and the other hypertensive disorders of pregnancy. Best Pract Res Clin Obstet Gynaecol 2011;25:391–403.
17. Metoki H, Iwama N, Hamada H, Satoh M, Murakami T, Ishikuro M, et al. Hypertensive disorders of pregnancy: definition, management, and out-of-office blood pressure measurement. Hypertens Res 2022;45:1298–309.
18. Khedagi AM, Bello NA. Hypertensive disorders of pregnancy. Cardiol Clin 2021;39:77–90.
19. Frank Wolf M, Peleg D, Kariv Silberstein N, Assy N, Djibre A, Ben-Shachar I. Correlation between changes in liver stiffness and preeclampsia as shown by transient elastography. Hypertens Pregnancy 2016;35:536–41.
20. Serra C, Dajti E, De Molo C, Montaguti E, Porro A, Seidenari A, et al. Utility of Doppler-ultrasound and liver elastography in the evaluation of patients with suspected pregnancy-related liver disease. J Clin Med 2023;12. https://doi.org/10.3390/jcm12041653.
21. Imajo K, Kessoku T, Honda Y, Tomeno W, Ogawa Y, Mawatari H, et al. Magnetic resonance imaging more accurately classifies steatosis and fibrosis in patients with nonalcoholic fatty liver disease than transient elastography. Gastroenterology 2016;150:626–37.e7.
22. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2018;67:328–57.
23. Abildgaard U, Heimdal K. Pathogenesis of the syndrome of hemolysis, elevated liver enzymes, and low platelet count (HELLP): a review. Eur J Obstet Gynecol Reprod Biol 2013;166:117–23.
24. Ammon FJ, Kohlhaas A, Elshaarawy O, Mueller J, Bruckner T, Sohn C, et al. Liver stiffness reversibly increases during pregnancy and independently predicts preeclampsia. World J Gastroenterol 2018;24:4393–402.
25. Li X, Zhang W, Lin J, Liu H, Yang Z, Teng Y, et al. Risk factors for adverse maternal and perinatal outcomes in women with preeclampsia: analysis of 1396 cases. J Clin Hypertens 2018;20:1049–57.
26. Sato S, Kawai H, Sato S, Iwasaki H, Omori M, Kita Y, et al. Hypertension and diabetes mellitus are associated with high FIB-4 index in a health checkup examination cohort without known liver disease. BMC Gastroenterol 2022;22:478.
27. Sugiyama A, Kurisu A, E B, Ouoba S, Ko K, Rakhimov A, et al. Distribution of FIB-4 index in the general population: analysis of 75,666 residents who underwent health checkups. BMC Gastroenterol 2022;22:241.
28. Özer S, Güneş H, Özer A. FIB4 score is increased in severe preeclampsia. Turk J Biochem 2024;49:56–63.
29. Auger N, Jutras G, Paradis G, Ayoub A, Lewin A, Maniraho A, et al. Long-term risk of chronic liver disease after pre-eclampsia. Int J Epidemiol 2025;54:dyaf072.
30. Hussain FN, Rosenbluth E, Feldman KM, Strauss TS, Schneider E, Schmidt-Beauchat E, et al. Transient elastography and controlled attenuation parameter to evaluate hepatic steatosis and liver stiffness in postpartum patients. J Matern Fetal Neonatal Med 2023;36:2190838.