Ann Med Res

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Impact of neutrophil-to-lymphocyte ratio (NLR), derived neutrophil-to-lymphocyte ratio (dNLR), systemic inflammation index (SII), systemic inflammation response index (SIR-I), and aspartate transaminase/platelet ratio (APRI) in predicting pregnancy outcomes of inflammatory bowel disease

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ARTICLE INFO

Keywords:
Inflammatory bowel disease
Pregnancy
Systemic inflammation index

Received: Jun 26, 2023
Accepted: Sep 11, 2023
Available Online: 27.09.2023

DOI:
10.5455/annalsmedres.2023.06.148

Abstract

Aim: We aimed to investigate the effect of systemic inflammation indices in predicting pregnancy outcomes of inflammatory bowel disease (IBD).

Materials and Methods: Pregnant women with Crohn's disease (CD) and Ulcerative colitis (UC) were identified from hospital medical records. Demographic features, disease type, duration and activity, and obstetric outcomes such as gestational age, mode of delivery, birth weight, Apgar scores at the first and fifth minutes after birth, and neonatal intensive care unit admission were assessed. Laboratory tests were conducted in the first trimester, including complete blood count and liver function. Neutrophil/lymphocyte ratio (NLR), derived neutrophil/lymphocyte ratio (dNLR), systemic inflammation index (SII), systemic inflammation response index (SIR-I), and aspartate transaminase/platelet ratio (APRI) were measured.

Results: The study involved 48 pregnant women, 26 diagnosed with UC and 22 with CD. At least one attack occurred in 31.3% of all patients during pregnancy. For predicting attacks during pregnancy, the optimal cutoff values of dNLR, NLR, SII, SIR-I, and APRI were 2.12 (86.7% sensitivity, 82.8% specificity), 2.89 (86.7% sensitivity, 81.8% specificity), 850.7 109/L (66.7% sensitivity, 63.6% specificity), 1.06 109/L (66.7% sensitivity, 72.7% specificity), 0.051 (80% sensitivity, 75.8% specificity), respectively. A cut-off value of 0.07 for APRI (71.4% sensitivity and 73.2% specificity) was calculated to predict low birth weight.

Conclusion: NLR, dNLR, SII, SIR-I, and APRI might help predict attacks in pregnant women with IBD. In addition, APRI may be utilized to predict low birth weight in pregnant women with IBD.

Introduction

Inflammatory bowel disease (IBD) is a chronic condition that consists mainly of ulcerative colitis (UC) and Crohn's disease (CD). UC is characterized by diffuse mucosal inflammation limited to the colon, whereas CD affects any part of the gastrointestinal tract. Both diseases mainly affect women of reproductive age, with most patients diagnosed before the age of 40 [1]. The incidence in pregnant women is about 1 in 200 [2]. The course of IBD during pregnancy is unpredictable, with periods of exacerbation and remission occurring throughout pregnancy. Successful outcomes are achieved when the disease is in remission at conception and is controlled during pregnancy [3].

Pregnant women with IBD have an increased risk for several pregnancy complications [4]. Studies have shown that IBD has been related to adverse pregnancy outcomes such as spontaneous abortion, stillbirth, preterm birth, intrauterine growth restriction, and low birth weight [5, 6]. Disease exacerbation is observed in 20-35% of the patients and is the main predictor of obstetric complications [7]. Reassuringly, women who become pregnant during remission and who remain pregnant tend to have a course of disease similar to that of non-pregnant women [8]. Thus, the importance of maintaining remission throughout preg-

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nancy from conception is underscored by the potential for adverse effects.

Extraintestinal manifestations, such as involvement of the hepatopancreatobiliary system, are also common in UC and CD. Depending on the activity of the disease, inflammation in the gastrointestinal tract leads to these extraintestinal involvements [9]. Several laboratory markers have been used to detect inflammatory activity in both UC and CD. However, clinical indices have not been validated for pregnancy. Inflammation markers that are elevated in patients with IBD may increase during pregnancy due to physiological adaptation. Therefore, they may not reflect the true disease activity. Researchers in various fields of medicine are focusing on blood cell indices. Peripheral blood cells have multiple functions, including immune regulation, cytokine excretion, and cell regeneration, and may reflect altered immune responses in systemic diseases [10, 11]. Recently, neutrophil-to-lymphocyte ratio (NLR), derived neutrophil-to-lymphocyte ratio (dNLR), systemic inflammation index (SII), and systemic inflammation response index (SIR-I) are novel inflammatory markers that have prognostic significance in various inflammatory and infectious diseases due to their mixture of cell types [12, 13]. Aspartate transaminase to platelet ratio index (APRI) is another marker used to predict pregnancy outcome in hepatobiliary system diseases [14]. Although some studies have investigated complete blood cell count indices, their usefulness in predicting the prognosis of pregnant women with IBD has not yet been clarified. Further investigation of this topic is imperative to obtain more reliable outcomes. Therefore, the aim of this study to evaluate NLR, dNLR, SII, SIR-I, and APRI in predicting pregnancy outcomes in inflammatory bowel disease.

Materials and Methods

Data collection

The study population included pregnant women with IBD admitted to the Perinatology Clinic of Ankara City Hospital between September 2019 and January 2023. Pregnant women with IBD (CD and UC) were identified from hospital records by the disease codes defined in the electronic record system. The The Ministry of Health of the Republic of Turkey Ankara City Hospital Clinical Research Ethics Committee approved the study protocol (E2-22-2588).

The data were obtained from perinatology, gastroenterology, and emergency department visits' medical records. Fifty-six pregnant women diagnosed with IBD were admitted to the hospital, and six discontinued follow-ups. Two pregnant women had spontaneous abortions in the first trimester, so they were not included in the further evaluation (Figure 1). Demographic features, disease type, duration and activity, and birth outcomes were assessed. An increased frequency in symptoms was set as having an attack during pregnancy. The gestational age of the patients was based on the last menstrual period or crown-rump length, measured in the first trimester. The study also excluded pregnant women who had fetuses with suspected or confirmed chromosomal and morphological abnormalities. None of the pregnant women in the study group had a history of liver-related disorders such as chronic viral hepatitis or primary sclerosing cholangitis. Obstetric

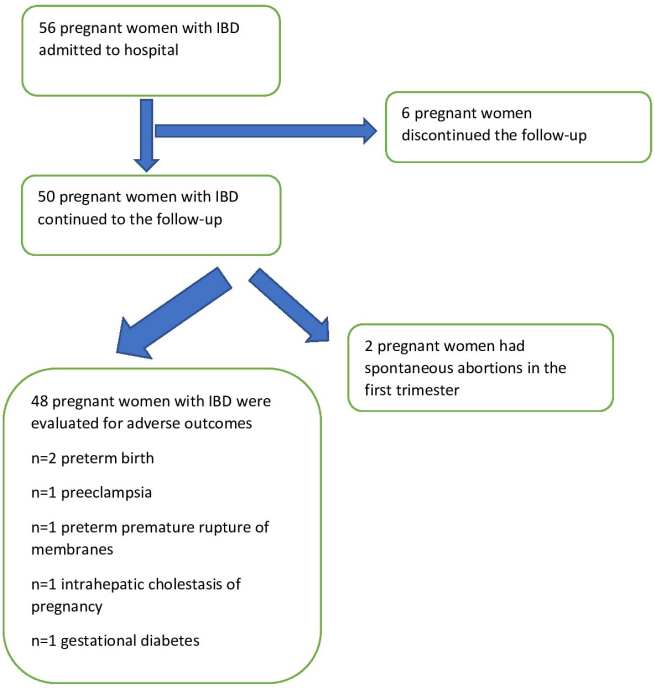

Figure 1. Flow diagram for the pregnant women in the study population.

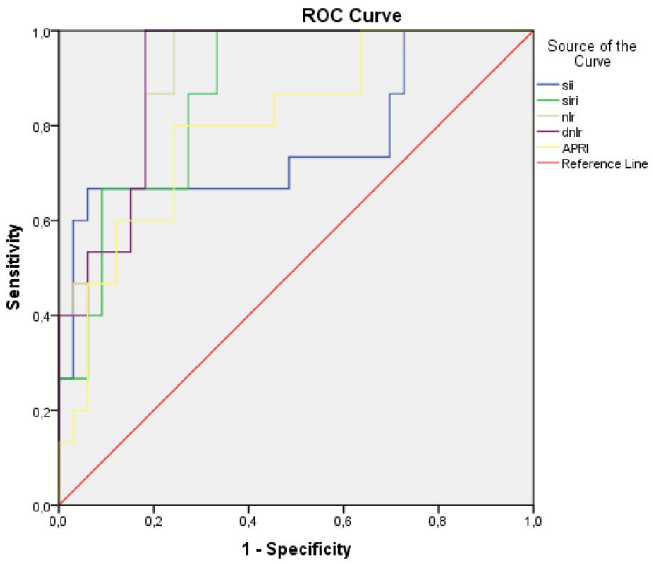

Figure 2. Receiver operating characteristic (ROC) curve of the inflammation indices for attack during pregnancy.

outcomes included the gestational age, mode of delivery, birth weight, Apgar scores at the first and fifth minutes after birth, and neonatal intensive care unit admission. Low birth weight (LBW) was defined as < 2.500 g.

We evaluated the laboratory parameters of the patients in the first trimester when they applied to the hospital on the first visit. Complete blood count parameters, including white blood cell count, hemoglobin, lymphocytes, neutrophils, monocytes, platelets, and eosinophils, were recorded. Renal and liver function tests and coagulation profiles were collected during this prenatal visit. We checked by the system that there was no sign of attack in

the patients when laboratory tests were performed. For all participants, the formulas were calculated as the following: NLR (neutrophil / lymphocyte), dNLR (neutrophil / (white blood cells - neutrophils)), SII ((neutrophils x platelets) / lymphocytes), SIR-I ((neutrophils x monocytes) / lymphocytes), and APRI (aspartate transaminase / platelet).

Statistical analysis

All statistical analyses were conducted using the Statistical Package for Social Sciences software version 17.0 (SPSS Inc, Chicago, IL). The data was tested for normal distribution using the Shapiro-Wilk test. Descriptive parameters for normal distribution were presented as mean ± standard deviation (SD), while non-normal distribution was expressed as median (interquartile ranges (IQRs). The Mann-Whitney U test was used to detect the non-normally distributed variables. Due to normal distribution, age, gravidity, disease duration, birth weight, and all laboratory parameters were presented as mean ± SD. Receiver operating characteristic (ROC) curves were used to estimate the performances of NLR, dNLR, SII, SIR-I, and APRI values in predicting attack during pregnancy and APRI value for predicting low birth weight. Mann–Whitney U test was performed to compare the median values of APRI among the low and average birth weight groups. Youden index was used to the ROC curve to determine the best cut-off values. A two-tailed P value < 0.05 was considered statistically significant.

Results

Clinical characteristics, laboratory test results, NLR, dNLR, SII, SIR-I, and APRI calculated from blood parameters, and obstetric outcomes are shown in Table 1. The study population consisted of 26 pregnant women with UC and 22 pregnant women with CD. 31.3% of all patients had at least one attack during pregnancy. Birth week, mode of delivery, birth weight, Apgar scores, and

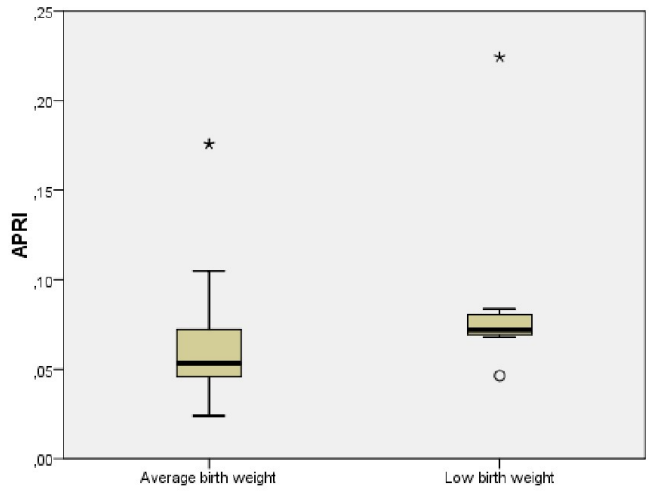

Figure 3. Box plot for comparison of aspartate transaminase-to-platelet ratio (APRI) in low birth weight and average birth weight groups.

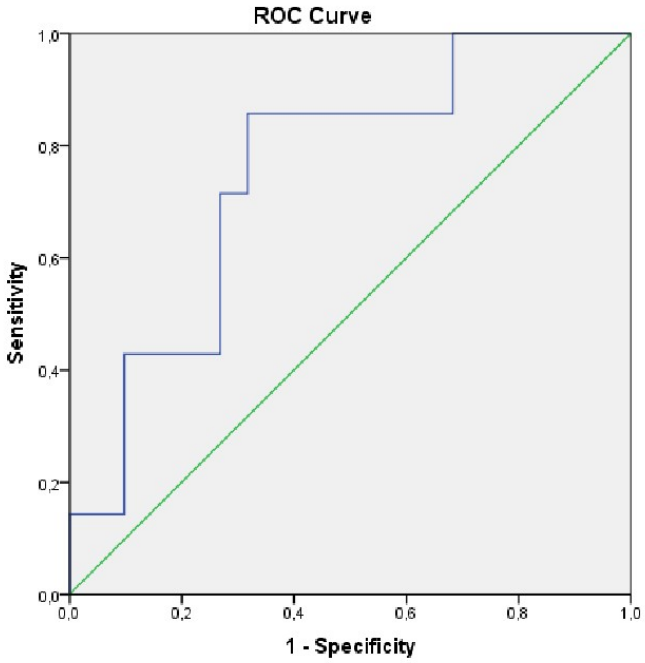

Figure 4. Receiver operating characteristic (ROC) curve analysis for the performance of aspartate transaminase-to-platelet ratio (APRI) in predicting low birth weight.

NICU admission were presented as obstetric outcomes. The mean ± SD of gestational age at delivery was 37 ± 2 weeks. Cesarean delivery was performed in 52.1% of the patients. Only four newborns were admitted to the NICU. Five pregnant women had obstetric complications, including spontaneous preterm birth (n=2), preterm premature rupture of membranes (n=1), intrahepatic cholestasis of pregnancy (n=1), and gestational diabetes mellitus (n=1). There were 7 (14.6%) newborns defined as low birth weight. Fifteen of the patients were not using any medications. The drugs used by the patients were as follows: mesalazine (n=23), infliximab (n=2), infliximab and mesalazine (n=3), trastuzumab (n=2), adalimumab (n=1), azathioprine and mesalazine (n=2).

Table 2 compares the laboratory parameters between UC and CD groups and the results of those with and without attack. There were no significant differences in dNLR, NLR, SII, SIR-I, and APRI values between the UC and CD groups, nor between those with and without a history of attacks.

ROC curve analysis to assess the performance of dNLR, NLR, SII, SIR-I, and APRI values in predicting attacks during pregnancy are shown in Table 3 and Figure 2. The optimal cutoff values of dNLR, NLR, SII, SIR-I, and APRI were 2.12 (86.7% sensitivity, 82.8% specificity), 2.89 (86.7% sensitivity, 81.8% specificity), 850.7 109/L (66.7% sensitivity, 63.6% specificity), 1.06 109/L (66.7% sensitivity, 72.7% specificity), 0.051 (80% sensitivity, 75.8% specificity), respectively. The comparison of the APRI values of those with LBW and ABW is shown in Table 4 and Figure 3. Except for APRI, other indices did not have significant value in predicting low birth weight. A cut-off value of 0.07 for APRI (71.4% sensitivity and 73.2% speci-

Table 1. Clinical features and laboratory results of the participants.

Age (years)	28.3±5.4
Gravidity	2.6±1.4
Parity	1 (0-2)
Abortus	1 (0-2)
Ulcerative colitis	26 (54.2%)
Crohn's disease	22 (45.8%)
Duration of disease (years)	7.1±4.3
Attack during pregnancy	15 (31.3%)
White blood cell (x10^9/L)	8.2±2.2
Neutrophils (x10^9/L)	5.7±1.9
Lymphocytes (x10^9/L)	1.9±0.7
Platelets (x10^9/L)	286.2±72.1
Monocytes (x10^9/L)	0.40±0.15
AST (IU/L)	18±8.7
NLR	3.47±1.66
dNLR	2.52±1.1
SII (x10^9/L)	983.7±531.5
SIRI (x10^9/L)	1.41±0.82
APRI	0.07±0.03
Cesarean delivery	25 (52.1%)
Gestational age at birth	37±2
Birth weight (grams)	3031±618
Low birth weight	7 (14.6%)
Apgar score at 1 minute	7 (6-8)
Apgar score at 5 minutes	8 (7-9)
NICU	4 (8.3%)

†Values are presented as mean ± standard deviation and median (IQR (Inter Quartile Ranges)) or count (percentile). ‡Abbreviations: AST: aspartate transaminase, NLR: neutrophil-to-lymphocyte ratio(NLR), dNLR: derived neutrophil-to-lymphocyte ratio, SII: systemic inflammation index, SIR-I: systemic inflammation response index, APRI: aspartate transaminase-to-platelet ratio, NICU: neonatal intensive care unit

ficity) was calculated to predict low birth weight in Table 5 and Figure 4.

Discussion

This is the first study to investigate the role of blood count indices in pregnancies with IBD. This study showed that first-trimester inflammatory indices such as SII and SIRI, especially NLR, dNLR, and APRI, can predict attacks in pregnant women with inflammatory bowel disease. Also, in the first trimester, APRI can predict low birth weight in IBD pregnancies. We believe these inflammatory indices may be practical and valuable in combination with other risk factors and parameters in pregnant women with IBD. This suggests that these indices may serve as markers of disease activity and may help in the management and monitoring of IBD during pregnancy.

Complete blood count parameters and indices are widely used for diagnosing and predicting adverse conditions due to their cost-effectiveness and rapidity [15, 16]. Thus, the utility of these parameters in predicting outcomes in a characteristic condition such as pregnancy has become a leading topic in obstetrics. Complications related to inflammation, such as placental invasion abnormalities, preeclampsia, and intrahepatic cholestasis of pregnancy, are the main topics of this obstetric research [17-19]. Neutrophils, lymphocytes, monocytes, and platelets, components of blood parameter indices, play an essential role in immune response processes in inflammatory diseases. Neutrophils, representing the first line of immunity, play a protective role in the immune system as they are the most abundant white blood cells in circulation. In addition to acute conditions, neutrophils play an essential role in chronic inflammatory and adaptive processes. The influence of neutrophils also affects the number of lymphocytes, which undergo increased apoptosis as a result of the inflammatory response [20]. Monocytes also participate in the pathogenesis of inflammatory and degenerative diseases, causing proinflammatory cytokine production by migrating to associated tissues during homeostasis and inflammation [21]. In addition, platelets that regulate inflammatory cytokine production are involved in processes such as coagulation and angiogenesis. It is widely accepted that these particular blood count parameters and indices are reliable indicators of alterations in maternal-fetal blood vessels due to inflammation during pregnancy. Studies showing that NLR is associated with gestational diabetes and cholestasis have suggested that it might be a helpful marker in the first trimester [22,23]. Significant values of both NLR and dNLR in severe COVID-19 disease underlined that these parameters could be used in increased inflammatory processes [12]. Research into the ordinary course of pregnancy and its effect on outcomes is limited. Few studies have evaluated biomarkers of birth outcomes with promising results. SII, which includes neutrophil platelets and lymphocytes, has been used as a prognostic index in obstetrics and other medical fields [24,25]. Tanacan et al. presented a study about the prediction of obstetric outcomes in pregnant women with preterm premature rupture of the membranes. They pointed to the fetal effects of maternal inflammation [26].

A previous study showed that SII and SIR-I could be used with other clinical parameters in predicting adverse outcomes in pregnant groups with risk factors [13]. Another study demonstrated that SII and SIR-I levels could be valuable biomarkers for predicting cervical cerclage's prognosis [27]. These parameters also help assess the immune-inflammatory status in various autoimmune diseases. A previous study showed significantly higher values of SII and SIR-I for predicting adverse pregnancy outcomes in systemic lupus erythematosus [28]. In another study, pregnant women with familial Mediterranean fever had higher SII and SIR-I values, which could predict adverse pregnancy outcomes [29]. Thus, it is imperative to identify high-risk patients by utilizing these markers and devising appropriate treatment plans, as these studies have determined their prognostic significance. Therefore, we aimed to identify patients with an attack during pregnancy by evaluating blood parameters in the first trimester in the IBD group, a vulnerable population.

During pregnancy, the maternal immune system undergoes adaptive changes to ensure a favorable interaction with the fetus, which is the basis for favorable obstetric outcomes. The destruction of the arrangement in the maternal-fetal interface formed by the cellular components causes an in-

Table 2. Comparison of laboratory parameters between patients with UC and CD, with and without attack.

Parameters	UC	CD	p-value	Attack +	Attack -	p-value
	(n=26)	(n=22)		(n=15)	(n=33)	
White blood cell (x10^9/L)	8.1 (6.6-9.2)	7.9 (6.8-8.9)	.468†	8.9 (7.3-9.9)	7.8 (6.9-8.8)	.057†
Neutrophils (x10^9/L)	5.8 (4.4-6.1)	5.5 (5-6.1)	.081†	5.9 (5.1-6.7)	5.3 (5.1-6.3)	.104†
Lymphocytes (x10^9/L)	1.8 (1.6-2.1)	1.9 (1-5-2.2)	.567†	1.7 (1.5-2.0)	1.9 (1.7-2.1)	.227†
Platelets (x10^9/L)	278 (261-307)	269 (244-312)	.439†	297 (288-313)	272 (266-308)	.301†
Monocytes (x10^9/L)	0.34 (0.29-0.51)	0.37 (0.31-0.48)	.637†	0.39 (0.33-0.44)	0.36 (0.32-0.41)	.694†
AST (IU/L)	16 (14-29)	19 (11-25)	.842†	20 (15-28)	21 (13-26)	.925†
NLR	3.24 (2.87-3.67)	3.09 (2.71-3.41)	.078†	3.38 (3.07-3.76)	3.12 (2.91-3.52)	.091†
dNLR	2.47 (2.16-2.61)	2.33 (2.09-2.66)	.103†	2.63 (2.06-2.79)	2.46 (1.97-2.71)	.139†
SII (x10^9/L)	991 (873-1024)	969 (931-1001)	.063†	999 (894-1037)	978 (942-1011)	.207†
SIRI (x10^9/L)	1.33 (1.20-1.51)	1.29 (1.21-1.60)	.589†	1.37 (1.21-1.46)	1.27 (1.20-1.51)	.089†
APRI	0.06 (0.05-0.08)	0.07 (0.05-0.08)	.621†	0.08 (0.07-0.08)	0.07 (0.06-0.08)	.071†

Values are presented as median (interquartile ranges).†Mann Whitney U test. Abbreviations: UC: Ulcerative colitis, CD: Crohn's disease, AST: aspartate transaminase, NLR: neutrophil-to-lymphocyte ratio (NLR), dNLR: derived neutrophil-to-lymphocyte ratio, SII: systemic inflammation index, SIR-I: systemic inflammation response index, APRI: aspartate transaminase-to-platelet ratio.

Table 3. Receiver operating characteristic (ROC) analysis for blood count indices in predicting attack during pregnancy.

	p-value	AUC (95% CI)	Cut-off	Sensitivity	Specificity
dNLR	**<.001**	.911 (.832-991)	2.12	86.7%	82.8%
NLR	**<.001**	.905 (.824-986)	2.89	86.7%	81.8%
SIRI (10^9/L)	**<.001**	.869 (.770-.968)	1.06	66.7%	72.7%
APRI	**.001**	.802 (.669-.935)	0.051	80%	75.8%
SII (10^9/L)	**.004**	.764 (.596-.932)	850.7	66.7%	63.6%

†Abbreviations: NLR: neutrophil-to-lymphocyte ratio(NLR), dNLR: derived neutrophil-to-lymphocyte ratio, SII: systemic inflammation index, SIR-I: systemic inflammation response index, APRI: aspartate transaminase-to-platelet ratio, AUC: area under the curve. The bold characters indicated the significant "p" values $p < 0.05$.

Table 4. Comparison of aspartate transaminase-to-platelet ratio (APRI) in low birth weight and average birth weight groups.

	APRI	p-value
LBW	.07 (.07-.08)	**.034***
ABW	.05 (.05-.07)	

†Mann Whitney U test ‡Abbreviations: APRI: aspartate transaminase-to-platelet ratio, LBW: low birth weight, ABW: average birth weight The bold characters indicated the significant "p" values $p < 0.05$.

Table 5. Receiver operating characteristic (ROC) curve analysis for the performance of aspartate transaminase-to-platelet ratio (APRI) in predicting low birth weight.

	p-value	AUC (95% CI)	Cut-off	Sensitivity	Specificity
APRI	**.034**	.753 (.574-931)	.0709	71.4%	73.2%

†Abbreviations: APRI: aspartate transaminase-to-platelet ratio, AUC: area under the curve. The bold characters indicated the significant "p" values $p < 0.05$.

flammatory response in the fetal/placental areas [30]. This inflammatory response, which increases levels of cytokines and chemokines, can cause damage to fetal tissues and lead to adverse pregnancy outcomes [31]. Diseases associated with inflammatory responses, such as IBD, have often been studied about pregnancy outcomes. A systematic meta-analysis showed that women with IBD have an increased risk for adverse pregnancy outcomes such as preeclampsia, preterm premature rupture of membranes, and preterm delivery [32]. Women with active disease are usually at greater risk of these adverse outcomes. Even so, it has been suggested that exacerbations during pregnancy may cause more harm to the fetus and mother than medications used to treat IBD. Overall, 30-40% of pregnant women with IBD experience an attack during pregnancy [33]. Our study found a 31.3% attack rate during pregnancy, consistent with the literature. When we investigated the predictive values of NLR, dNLR, APRI, SII, SIR-I, and SIR-I in the first trimester, we found that they might have prognostic values to predict an attack during pregnancy. We thought that predicting an attack as early as the first trimester might be beneficial for developing appropriate follow-up and treatment modalities for these patients.

A previous large cohort study showed an increased risk for low birth weight in pregnant women with IBD who had flares during pregnancy [34]. Similarly, the risk of low birth weight increases two-fold in UC exacerbation and three-fold in CD exacerbation [6]. Although adverse pregnancy outcomes are expected in pregnant women with IBD, sur-

prisingly, the only adverse outcome in our study was LBW. Considering that the mean gestational age at birth was 37 weeks, we concluded that LBW was not due to preterm birth. Therefore, we investigated the role of inflammatory indices in predicting LBW. Surprisingly, APRI was the only index to predict LBW compared to other inflammatory indices. The value of APRI in the LBW group was significantly higher than the average birth weight group. Although APRI was previously used to assess the prognosis of liver disease, it has not been used in IBD. Some studies have investigated the association between APRI and obstetric conditions. A previous study showed that APRI could be altered in cases of severe preeclampsia [35]. In another study, APRI was a valuable tool in predicting intrahepatic cholestasis of pregnancy and its adverse effects on pregnancy [36]. Elevated APRI levels may reflect the extent of liver involvement and could be used to monitor disease progression. Interestingly, the mean AST values of the patients in our study were within normal ranges. The absence of known liver disease at the gestational week in which the indices were obtained suggested that we could use the predictive value of APRI in LBW. LBW is associated with poorer cognitive, behavioral, and social outcomes and an increased risk of cardiovascular disease later in life. Considering these results of IBD, these patients should be followed closely. The study's outcomes have significant clinical implications, offering healthcare providers a practical toolset for early risk identification and personalized care strategies for pregnant women with IBD. Detecting disease exacerbations and predicting complications during the first trimester can facilitate convenient interventions, optimizing maternal and fetal well-being. This research also emphasizes the importance of collaboration between obstetrics, immunology, and gastroenterology to improve our understanding and management of high-risk pregnancies in the context of chronic inflammatory diseases.

The study's results have implications for the management of pregnant women with IBD. Predicting disease flares and complications early in pregnancy can guide treatment decisions and help improve pregnancy outcomes. The present study suggests that APRI when measured during the first trimester, can predict the possibility of low birth weight in pregnancies with IBD. This study also highlights the value of APRI as a potential predictor, even though it has traditionally been used to assess liver disease. Its association with LBW in the study indicates that it could offer insights into pregnancy outcomes beyond its typical use. This could provide valuable information for healthcare providers to take preventive measures and suggest appropriate care to ensure optimal fetal outcomes. As it is difficult to determine a validated blood parameter due to physiological adaptation in pregnancy, we believe these blood indices, which are a simple and inexpensive method, may have prognostic values. The study's limitations are the small number of the study group, the lack of laboratory parameters during the attack, and the low rates of adverse obstetric outcomes.

IBD is a chronic disorder that can progress with attacks and remissions during pregnancy. An attack during pregnancy plays a significant role in predicting adverse pregnancy outcomes. The findings suggest that specific blood count indices, including SII, SIRI, NLR, dNLR, and particularly APRI, hold promise in predicting disease attacks and complications and the risk of low birth weight in IBD pregnancies. So, our study provides valuable insights into the potential mechanisms underlying these connections by examining the complex relationship between the maternal immune response, inflammation, and adverse pregnancy outcomes. While acknowledging the study's limitations, including small sample size and limited occurrence of adverse outcomes, the research opens the door for further investigations into larger cohorts to validate and clarify these predictive markers.

Conclusion

In conclusion, the present study has investigated the potential of blood count indices as predictive markers for outcomes in pregnant women with IBD. Because of the accessibility and cost-effectiveness of these indices, our study sheds light on their application in early risk assessment and proactive management strategies during pregnancy.

Acknowledgments

I would like to express my special thanks to all the healthcare staff who have worked with devotion.

Disclosure statement

The authors report that there are no competing interests to declare.

Ethical approval

The Ministry of Health of the Republic of Turkey Ankara City Hospital Clinical Research Ethics Committee approved the study protocol (E2-22-2588).

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