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Could fibrinogen to albumin ratio be a predictive marker for recurrent pregnancy loss

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Abstract

Aims: Recurrent pregnancy loss (RPL) is usually defined by two or more consecutive clinical miscarriages, which causes psychological trauma for couples. In this study, we aimed to investigate the predictive role of fibrinogen to albumin ratio (FAR) in patients with RPL.

Methods: Pregnant women in their first trimester of pregnancy were included in the study and divided into two groups as RPL patients (n: 44) and patients with no previous recurrent miscarriage (n: 60) as control group. Demographical parameters and routine blood parameters (fibrinogen, D-dimer, FAR, neutrophil to lymphocyte ratio [NLR], platelet count, main platelet volume [MPV], and red cell distribution width [RDW] values) were compared between the RPL group and the control group.

Results: The groups were determined to be statistically different in regard to gravidity and parity ($P < .001$). The difference between the groups was statistically different in regard to fibrinogen (mg/dL), albumin (g/dL), FAR (%), NLR (%), RDW-coefficient of variation (%), RDW-standard deviation (fl), and platelet counts (10^{-3}/μL). However, MPV (fl) and D-dimer (μg/L) levels were similar in both groups. The receiver operating characteristic curve analysis revealed that the NLR levels were 84.1% sensitive and 75% specific with a cut-off value of 4.27 and the FAR levels were 79.5% sensitive and 88.3% specific with a cut-off value of 105.69 for predicting RPL.

Conclusion: Our results indicate that the FAR and NLR levels seem to be effective parameters for predicting RPL with high sensitivity and specificity.

1 | INTRODUCTION

Early pregnancy loss is a frequently occurring disorder during the reproductive period, which causes many psychological, social, and economic problems. Recurrent abortions worsen these problems. Recurrent pregnancy loss (RPL) is defined as two or more consecutive abortions that occur before the 20th gestational week in the absence of a previous delivery.[1-3] The incidence of spontaneous pregnancy loss was reported in almost 1 in 300 pregnancies.[1] According to epidemiological studies, recurrent abortion was seen in 1%-2% of all women in a lifetime. Many factors have a role in RPL, such as aging, bad obstetric history, and genetic and thrombotic problems.[4]

The prothrombotic conditions affect maternal-fetal circulation and can impair placental development. These thrombotic processes lead to venous and/or arterial thrombosis, which can be responsible for or contribute to RPL. Therefore, antithrombotic strategies and/or prophylaxis regimens are already being employed for medical management of recurrent abortions. Thrombophilia panels were investigated to determine risky populations.[1,5] However, these panels are expensive and their use is limited in the follow-up of treatment efficacy. Recently, investigators focused on developing new and effective biomarkers for monitoring prothrombotic populations. Especially, routine blood parameters were investigated for vascular thrombotic processes.[6,7] The immunopathological theory of RPL depends on decidual inflammation, perivillous and decidual fibrin deposition, and micro-thrombosis in

decidual vessels that can result in placental implantation abnormalities. Moreover, many reports were focused on the direct roles of the thrombotic and inflammatory processes in miscarriage[7]. However, the changes of standard laboratory markers that are investigated in other thrombotic and/or inflammatory disorders were not comprehensively studied in RPL patients in previous studies.

The objective of this study was to reveal the differences in routine blood parameter tests as fibrinogen, D-dimer, fibrinogen to albumin ratio (FAR), neutrophil to lymphocyte ratio (NLR), platelet count, main platelet volume (MPV), and red cell distribution width (RDW) values between pregnant women with RPL and had no previous recurrent miscarriage.

What's known

- Recurrent pregnancy loss (RPL) is usually defined by two or more consecutive clinical miscarriages, which causes psychological trauma for couples.
- The prothrombotic conditions affect maternal-fetal circulation and can impair placental development. These thrombotic processes lead to venous and/or arterial thrombosis, which can be responsible or contribute to RPL. Thrombophilia panels including genetic analysis were investigated to determine risky populations.

What's new

- Fibrinogen to albumin ratio and neutrophil to lymphocyte ratio levels seem to be possible predictors for RPL risk with high sensitivity and specificity.
- Especially, higher fibrinogen to albumin ratio levels may be related to an increase in thrombotic processes in recurrent miscarriage.
- Routine simple blood test parameters in the first trimester of pregnancy may be useful in predicting RPL rather than expensive genetic analysis.

2 | METHODS

Ethical approval was obtained from Alaaddin Keykubat University Local Ethical Committee (Ethical approval No. 23-10, 18/09/20). Signed informed consent was obtained from all participants. The study protocols were designed in accordance with the principles of the Helsinki Declaration and in adherence to the local guidelines for good clinical practice. This single-center prospective study was conducted between September 2020 and December 2020.

The subjects taken were all in the first trimester of their pregnancy. Signed informed consent was obtained from all participants. The patients were divided into two groups as RPL group or those who had at least two abortions in the first trimester (n: 44) and control group or those who continued their pregnancy in a healthy way (n: 60). Blood sample was taken from the RPL group immediately after their third abortion. The patients in the RPL group were followed routine clinical controls (1 week later after abortion) and the uterine cavity was evaluated with transvaginal ultrasound. Healthy pregnant women were followed up monthly until labour. RPL was defined as two or more consecutive abortions that occur before the 20th gestational week in the absence of a previous delivery. All participants were non-smokers, non-obese (<30 kg/m^2) and did not use vitamin supplementation other than folic acid.

The exclusion criteria were determined as diabetes, hypertension, obesity, malignancy, chronic disease, chronic venous insufficiency, and assisted conception treatments (such as intrauterine insemination, and in vitro fertilization). Additionally, patients with abortion who did not meet RPL criteria and patients who were undergoing anticoagulant and hormone therapy were excluded from the study.

The demographical findings (age, parity, and gravidity) and routine blood counting parameters {neutrophil [%] and lymphocyte [%] for obtaining the NLR [%], albumin [g/dL] and fibrinogen [μg/mL] for obtaining FAR [%], D-dimer [μg/L], MPV [fl], platelet count [10^{-3}/μL], and RDW [standard deviation (SD): fl and coefficient of variation (CV): %]} were recorded.

Two groups were compared in regard to the recorded parameters. Thereafter, the RPL patients were divided into two subgroups—one subgroup of patients who have had two abortions (n: 23) and one subgroup of patients who have had three or more abortions (n: 21)—and the biochemical parameters were analysed between the subgroups.

2.1 | Statistical analysis

Data analysis was performed using the Statistical Product and Service Solutions (SPSS) software program (ver. 22.0). The Kolmogorov-Smirnov test was used to obtain the normality distribution of variances. The categorical variables were expressed as percentages (%) and counts (n). The continuous values were given as mean ± SD. The continuous variables were analysed using an independent *t* test, and the categorical variables were compared using the chi-square test. The Kendall tau-b correlation coefficient was employed for the evaluation of correlation. An optimal cut-off value of the significant parameters was detected using receiver operator characteristic (ROC) curve analysis. The sensitivity and specificity, which were evaluated by the area under the curve (AUC), were applied to determine the accuracy of the test. A *P* value less than .05 was considered significant.

3 | RESULTS

The ages of patients were similar between the groups (*P*: .503). However, the groups were determined to be statistically different in

regard to gravidity and parity ($P < .001$). The comparison of the blood parameters between the groups revealed that the fibrinogen (mg/dL), albumin (g/dL), FAR (%), NLR (%), RDW CV (%), RDW SD (fl), and platelet counts (10^{-3}/μL) were statistically different between the groups ($P < .001$). The MPV (fl) and D-dimer (μg/L) were measured in similar ranges between the groups ($P > .05$). Especially, higher fibrinogen, FAR, NLR, and platelet count values were obtained for the RPL group. Unlikely, higher albumin, RDW CV, and RDW SD values were obtained for the control group. A comparison between the demographical samples and the blood sample variables is summarised in Table 1.

The gravidity was significantly different when the RPL subgroups were compared (P: .731). Other parameters were determined to be statistically similar when the variables were compared with respect to abortion in the RPL group ($P > .05$). A moderate positive correlation was observed between gravidity count and abortion count when evaluated with the Kendall tau-b correlation coefficient ($P < .01$; $b = 0.544$). A comparison of variables according to abortion in the RPL group is presented in Table 2.

Higher FAR levels above the reference lines were observed in the ROC curve analysis (Figure 1). A cut-off point of 105.69% was selected to predict abortion risk with 79.5% sensitivity and 88.3% specificity (AUC: 0.877, 95% CI: 0.806-0.949). Additionally, the NLR levels were 84.1% sensitive and 75% specific for predicting RPL with a cut-off value of 4.27%. The ROC curve analysis of the NLR and FAR values is presented in Figure 1.

TABLE 1 Descriptive statistics and analysis results of variables in patient groups

Variables	RPL (n: 44)	Normal delivery (n: 60)	P
Age (y)	30.5 ± 5.6	29.7 ± 6.0	.503[a]
Gravidity			
1	0 (0%)	5 (8.3%)	*.002*[b,*]
2	3 (6.8%)	19 (31.7%)	
3	18 (40.9%)	20 (33.3%)	
4	14 (31.8%)	7 (11.7%)	
≥5	9 (20.5%)	9 (15%)	
Parity			
0	9 (20.5%)	0 (0%)	*<.001*[b,*]
1	20 (45.5%)	6 (10%)	
2	13 (29.5%)	18 (30%)	
3	1 (2.3%)	20 (33.3%)	
≥4	1 (2.3%)	16 (26.7%)	
Fibrinogen, mg/dL	460.0 ± 87.1	363.1 ± 70.9	*<.001*[a,*]
Albumin, g/dL	3.54 ± 0.39	4.12 ± 0.36	*<.001*[a,*]
FAR: fibrinogen to albumin ratio, %	130.7 ± 28.3	88.6 ± 17.9	*<.001*[a,*]
NLR: neutrophil to lymphocyte ratio, %	4.83 ± 0.71	3.71 ± 0.88	*<.001*[a,*]
MPV: mean platelet volume, fl	10.6 ± 1.7	10.8 ± 1.1	.454[a]
RDW: red cell distribution width, CV %	12.5 ± 1.1	13.1 ± 1.0	*.005*[a,*]
RDW: red cell distribution width, SD fl	37.9 ± 3.0	39.5 ± 2.7	*.005*[a,*]
Platelet count, 10^{-3}/μL	299.3 ± 95.6	250.5 ± 62.6	*.004*[a,*]
D-dimer, μg/L	293.4 ± 116.0	242.0 ± 101.2	.071[a]

Abbreviation: RPL, recurrent pregnancy loss.

[a] Independent *t* test.

[b] Chi-square test.

* P value less than 0.05 was considered significant.

4 | DISCUSSION

Although the prothrombotic gene panel or some inflammatory markers were investigated in previous studies of patients with RPL, the routine blood parameters were not compared comprehensively. Our results indicated that the serum fibrinogen, albumin, RDW, NLR, and FAR values can be related to RPL. According to our knowledge, this analysis is the first study that determines a cut-off FAR value for specifying RPL. Moreover, the serum NLR and FAR levels were determined to be quite sensitive for identifying RPL risk.

RPL is an important female reproductive disorder that is related with multifactorial etiology. The anatomic, endocrine, infection, immune, and thrombophilic factors are the main reported etiologies for this disorder.[1,8] Although RPL is a challenging disease, note that a successful pregnancy may be achieved by comprehensive management for etiological factors.[1] Especially, the inflammation and coagulation disorders that cause RPL can be more easily explained and managed by clinicians.[8] Previous studies described decidual inflammation, perivillous and decidual fibrin deposition, and thromboembolic changes in decidual vascular structures after an immunopathological examination of gestational structures following a spontaneous recurrent abortion in RPL patients.[8] Higher cytokine levels, such as mononuclear cells secreted from TNF-a, IFN-g, TNF-b, and IL-2, and increased inflammatory response were detected in RPL patients when compared with normal pregnancy.[8,9] Incremental neutrophil and leukocyte counts were reported from the first trimester to the third trimester in non-complicated pregnancy cases, and conversely, decremental lymphocyte counts were identified from the first trimester to the second trimester.[10] Therefore, the NLR was investigated as a predictive marker for pathologic gestational events.[11-15] The NLR is the current concerted version as a predictor for inflammatory disorders, is especially investigated in atherosclerotic, thrombotic, and/or immune vascular events, and is suggested as a potentially useful biomarker for prediction and follow-up for inflammatory processes.[7,16] Gezer et al[11] investigated NLR values in determining the predictive value of subsequent preeclampsia.

TABLE 2 Descriptive statistics and analysis findings for the comparison of variables according to abortion in the RPL group

	2 abortions (n: 23)	≥3 abortions (n: 21)	*P*
Age (y)	30.8 ± 5.5	30.1 ± 5.7	.731[a]
Gravidity			
2	3 (13%)	0 (0%)	*.001*[b,*]
3	14 (60.9%)	4 (19%)	
≥4	6 (26.1%)	17 (81%)	
Parity			
0	3 (13%)	6 (28.6%)	.094[b]
1	14 (60.9%)	6 (28.6%)	
≥2	6 (26.1%)	9 (42.9%)	
Fibrinogen, mg/dL	449.0 ± 80.9	472.0 ± 93.8	.386[a]
Albumin, g/dL	3.61 ± 0.45	3.46 ± 0.32	.201[a]
FAR: fibrinogen to albumin ratio, %	126.0 ± 27.5	135.9 ± 29.0	.251[a]
NLR: neutrophil to lymphocyte ratio, %	4.86 ± 0.72	4.79 ± 0.71	.728[a]
MPV: mean platelet volume, fl	10.7 ± 2.2	10.5 ± 1.1	.755[a]
RDW: red cell distribution width, CV %	12.5 ± 1.2	12.6 ± 1.0	.753[a]
RDW: red cell distribution width, SD fl	37.5 ± 3.3	38.3 ± 2.7	.398[a]
Platelet count, 10^{-3}/μL	292.7 ± 89.9	306.6 ± 103.1	.634[a]
D-dimer, μg/L	316.4 ± 143.8	270.4 ± 82.0	.417[a]

[a] Independent *t* test.

[b] Chi-square test.

* P value less than 0.05 was considered significant.

According to their report, a higher value of NLR (with a cut-off value of NLR ≥ 3.08) can be associated with an increase in subsequent preeclampsia risk. Similarly, Serin et al[12] reported higher NLR values in patients with preeclampsia compared with normal controls. In another clinical study, Ilhan et al[13] evaluated the diagnostic accuracy of NLR in premature ovarian insufficiency. They reported similarities between serum NLR levels and ovarian reserve markers, such as follicle stimulating hormone and anti-müllerian hormone levels. According to the findings, these researchers claimed that the NLR can be a potential diagnostic marker for ovarian insufficiency. There are limited data about NLR levels and the relation with miscarriage. Karakus et al[14] investigated NLR values in vaginal bleeding related to ectopic pregnancy or miscarriage cases. They obtained higher NLR values in miscarriage patients and suggested that the NLR can be employed as an early diagnostic marker for miscarriage in the absence of infection. A conflict report was presented by Christoforaki et al[15] with a retrospective analysis that revealed similarly distributed NLR values in failed or successful pregnancies. They suggested that "it is not possible to select a single NLR value that will split failed and successful pregnancies with reasonable sensitivity and specificity." We obtained markedly higher NLR levels in patients with RPL.

The RDW is a numerical indicator of the variation in the size of circulating erythrocytes and is routinely applied in the differential diagnosis of anaemia. The RDW was suggested as a significant and independent predictor of pathological conditions in community scanning.[17] Although the RDW is a conventionally accepted routine marker in the group of complete blood counting parameters, the reference ranges for pregnancy were not well established. In a systematic review, RDW values were suggested as possible markers for diagnostic and prognostic use in clinical practice for pregnancy complications, including anaemia, preeclampsia, diabetes, and recurrent miscarriage.[18] We found relatively higher RDW levels in RPL patients when compared with the control group. However, this difference is not statistically strong for the NLR and FAR values. In gene polymorphism studies, prothrombotic gene mutations were determined to be the etiological reason for RPL. Jeddi-Tehrani beta fibrinogen and methylenetetrahydrofolate reductase gene polymorphisms were positively associated with RPL.[19] Factor V Leiden, plasminogen activated inhibitor gene mutations, and elevated fibrinolytic activity and platelet levels are described in recurrent miscarriage and related disorders.[20] Additionally, gene groups that regulate platelet functions were examined in RPL patients.[21] Karami et al[21] suggested that the polymorphism of these gene groups can trigger platelet activation and thrombosis and disrupt placental blood diffusion. They added that the enhanced platelet activation and triggered thrombosis formation can also be attributed to RPL. The routine blood parameters that indicate platelet functions were also investigated and compared in RPL and normal gestation cases. Aynıoglu et al[22] reported higher platelet counts and MPV levels in the RPL population. They claimed that these values have a predictive role for RPL risk. We obtained higher platelet counts in RPL patients but did not observe a difference between RPL and normal patients in regard to MPV levels. Because of previously reported decidual fibrin deposition on the histopathologic examination of the placenta in miscarriage cases and increased fibrinolytic activity, we investigated

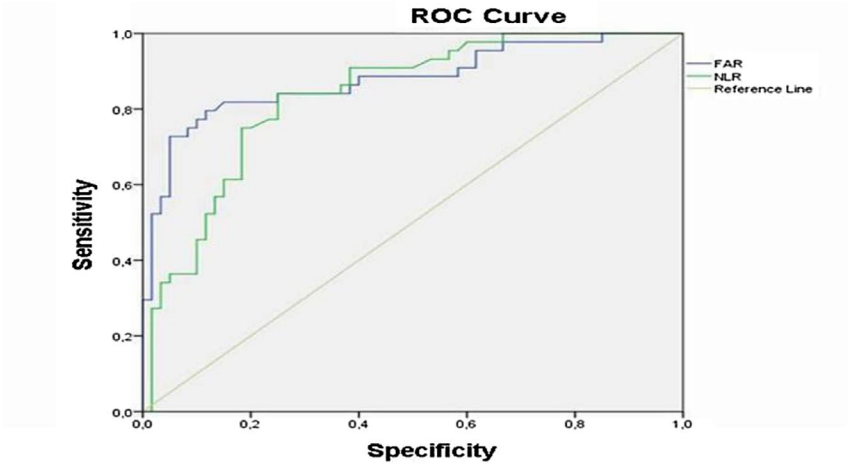

FIGURE 1 Sensitivity and specificity for the FAR and NLR; $P < .001$ is significant

Variables	Area	Standard Error	p value	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
FAR	0.877	0.037	0.000	0.806	0.949
NLR	0.836	0.039	0.000	0.760	0.913

fibrinogen and D-dimer levels in RPL. We observed markedly higher fibrinogen levels in RPL patients. However, D-dimer levels were found as similar with the normal gestation group. In recent cardiovascular studies, the FAR was utilised as a predictive marker for venous and arterial disorders.[23,24] These previous studies claimed that blood viscosity and oncotic pressure can be affected by fibrinogen and albumin and contribute to the development of vascular thrombosis and insufficient perfusion.[23,24] Similarly, we obtained higher FAR levels in RPL patients compared with the normal gestation group.

In addition, Covid-19 pandemic is a current and serious health problem.[25] Several studies conducted over the past 1 year have revealed that Covid-19 cases showed significantly higher plasma levels of fibrinogen and D-dimer than healthy controls, and significant hypercoagulation was observed in Covid-19 patients.[25] Since we reached a conclusion that RPL is associated with hypercoagulability in our work, further studies are needed to determine whether Covid-19 is related to pregnancy loss or not.

5 | CONCLUSION

Our findings indicate that NLR and FAR levels seem to be possible predictors for RPL risk with high sensitivity and specificity. Especially, higher FAR levels may be related to an increase in thrombotic processes in recurrent miscarriage. These relationships should be investigated in larger cohorts, and mechanisms of the action of serum fibrinogen, albumin values, and elevated FAR levels should be clarified with comprehensive studies.

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DISCLOSURES

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

MTC designed the research study. MSY and MSY performed the research. MSY analysed the data. MTC wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

STATEMENTS OF ETHICS

This case control study complied with the ethics of the World Medical Association Declaration of Helsinki and was approved by Alaaddin Keykubat University Local Ethics Committee (Ethical Approval No. 23-10, 18/09/20). Signed informed consent was obtained from all participants.

DATA AVAILABILITY STATEMENT

The data used to support the findings of this study are included within the article.

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