

## Could Red Cell Distribution Width and Mean Platelet Volume to Lymphocyte Ratio Predict Missed Abortion?

### Eritrosit Dağılım Genişliği ve Ortalama Trombosit Volümünün Lenfosit Sayısına Oranı Missed Abortusu Öngörebilir Mi?

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#### Abstract

Missed abortion (MA) is a common pregnancy complication; however, the pathophysiology of MA is still not entirely clear. Mean platelet volume (MPV), and red cell distribution width (RDW) have been found to be associated with obstetrics disorders such as first trimester miscarriage and recurrent miscarriage. We evaluated the association between RDW, MPV to lymphocyte (MPV/L) ratio and MA. A total of 230 cases were included in the present study. Patients were selected from women who had missed abortion (n=125) and controls were selected from the women who had given birth at term (> 37 weeks of gestation) to healthy infants (n=105). In all cases, blood samples were drawn at admission before starting any medication. The MPV, RDW, WBC, L/M ratio and MPV/L ratio levels were significantly higher in the MA group than in the control group. Using multivariate logistic regression analysis, we found that RDW [odds ratio (OR)=1.737, 95% confidence interval (CI)=1.346-2.242, p<0.001] and MPV/L ratio [odds ratio (OR)=1.518, 95% confidence interval (CI) =1.047-2.199, p=0.028] were independent predictors of MA. RDW may be a strong independent predictor of MA. MPV/L ratio was also an independent predictor of MA and it showed superior predictive value than MPV.

**Keywords:** Lymphocyte, Mean Platelet Volume, Missed Abortion, Red Cell Distribution Width

#### Öz

Missed abortus (MA) yaygın görülen bir gebelik komplikasyonu olmasına karşın patofizyolojisi tam aydınlatılmamıştır. Ortalama trombosit volümü (MPV) ve eritrosit dağılım genişliği (RDW) ilk trimester düşüklüğü ve tekrarlayan gebelik kayıpları gibi obstetrik patolojilerle ilişkili bulunmuştur. Biz de RDW ile MPV'nin lenfosit (MPV/L) oranı ve MA arasındaki ilişkiyi araştırdık. Toplamda 230 hasta çalışmaya alındı. Hastalar çalışma grubu olarak missed abortus olan gebeler (n=125) ve kontrol grubu olarak miadında (> 37 gebelik haftası üzeri) sağlıklı doğum yapmış gebeler (n=105) olmak üzere ikiye ayrıldı. MA'lı gebelerin başvuru esnasındaki hemogram parametreleri ve kontrol grubunda olan gebelerin de ilk trimesterde vermiş oldukları hemogram parametreleri çıktı. MPV, RDW, WBC, L/M oranı ve MPV/L oranı seviyeleri MA grubunda kontrol grubuna göre anlamlı derecede yüksekti. Multivaryat lojistik regresyon analizi kullanarak RDW [Olasılık oranı (OR)=1.737, %95 güven aralığı CI=1.3462.242, p <0.001] ve MPV/L oranının [OR=1.518, %95 güven aralığı CI=1.047-2.199, p=0.028] MA'nın bağımsız prediktörleri olduğu saptandı. Çalışmamızda RDW'nin, MA'nın güçlü bir bağımsız belirleyicisi olabileceği görülmüştür. MPV/L oranı da aynı zamanda MA'nın bağımsız bir öngörücüsüdür ve MPV'den daha üstün prediktif değer göstermiştir.

**Anahtar Kelimeler:** Eritrosit Dağılım Genişliği, Lenfosit, Missed Abortus, Ortalama Trombosit Volümü

#### Introduction

Missed abortion, a common and unpredictable complication of early pregnancy, is defined as intrauterine fetal death before twenty weeks' gestation in which the cervical os remains closed and no bleeding (1). MA is very common pregnancy complication, which occurs approximately 15 % of all pregnancies (2). The underlying pathophysiological mechanisms of MA are not clearly explained yet. Most common cause of MA is chromosomal abnormalities, especially trisomies which account for approximately 50% of all miscarriages (3). Some other possible pathophysiological mechanisms that are involved in the MA include acquired thrombophilia, immune disorders, diabetes and radiation exposure (4).

RDW reflects variation in the size of circulating red blood cells (coefficient of variability of red blood cell volume) (5). Serum RDW level increases over time during the last 4–6 weeks leading up to the onset of labor but not between 16 and 34 weeks' gestation (6). This unexpected increase in serum RDW level suggests that RDW could predict impending parturition. Recent clinical studies suggest a possible association of red cell distribution width (RDW) with preeclampsia and recurrent pregnancy loss (7,8). Mean platelet volume (MPV), which is a simple marker of platelet function and systemic inflammation, has been found to be associated with obstetrics disorders such as first trimester miscarriage and recurrent miscarriage (9,10). However, MPV to lymphocyte (MPV/L) ratio has been emerged as a new simple marker of platelet function. Only a few recent studies have evaluated the association between MPV/L ratio and coronary artery disease (11,12). To our best of knowledge, there are no published data on the association of RDW and MPV/L ratio with MA. Early and simple prediction of MA is important if we want to improve the management and prognostic of this complication. Therefore, in this study, we aimed

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to determine the association between hematological markers such as RDW and MPV/L ratio, and MA.

## Material and Method

The present case-control study has been conducted in accordance with the principles of the Helsinki Declaration and approved by the Muğla Sıtkı Koçman University Clinical Research Ethics Committee (26/10/2017-18/I). Medical records of 230 patients admitted to the Department of Obstetrics and Gynecology of our tertiary center, November 2015 between and November 2017, were retrospectively reviewed. Patients were selected from women who had a missed abortus (MA group) and controls were selected from the women who had given birth at term (>37 weeks of gestation) to healthy infants (control group). Women with multiple pregnancies (as per ultrasonography), bleeding subsequent to a local pathology (e.g. a tear or a polyp), or an ectopic pregnancy were excluded. We also excluded patients with chronic inflammatory diseases and coronary artery disease.

In all cases, blood samples were drawn at admission before starting any medication. All laboratory tests were performed immediately after sampling. Blood samples were collected in EDTA tubes. Hemoglobin, monocyte, and white blood cell (WBC) count were measured on Cell-Dyne counter of Abbott Laboratories (Cell-dyne 3700 Abbott Laboratories, IL, USA). The N/L ratio was obtained by dividing total count of neutrophils by lymphocytes count. The MPV/L ratio was obtained by dividing total count of MPV by lymphocytes count. The L/M ratio was obtained by dividing total count of lymphocytes by monocyte count. All measurements were performed at the hospital's central laboratory.

All analyses were performed using SPSS 20.0 (released 2011, IBM statistics for Windows version 20, IBM Corp., Armonk, NY). All data are presented as mean±standard deviation unless otherwise stated. Comparison of parametric values between the 2 groups was performed by means of independent samples t test. Comparisons of non-parametric values between the 2 groups were performed by the Mann-Whitney U test. Categorical variables were compared by the Chi-square test. Logistic regression analysis was used to assess the predictors of MA. Those variables with p<0.1 by univariate analysis were included in the multivariate logistic regression analysis model and the respective odds ratios (OR) with 95% confidence intervals (CI) were calculated. The capacity of the RDW and MPV/L ratio values in predicting MA were analysed using ROC (Receiver Operating Characteristics) curve analyses. When a significant cut-off value was observed, the sensitivity and specificity values were presented. All statistical tests were two-sided and statistical significance was determined at a p-value <0.05.

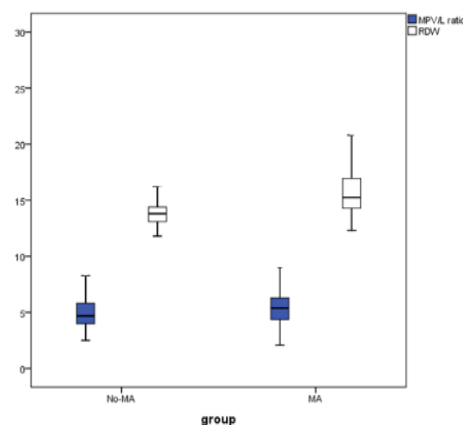
## Results

Demographic and clinical properties of patients in groups are shown in Table 1. Among the 230 participants, 125 patients had MA with a mean age of 30.4±6, and 105 had almost normal pregnancy with a mean age of 27.9±5. Both groups did not differ from each other by means of number of pregnancy, number of parity, history of miscarriage, hemoglobin, N/L ratio and PDW. Mean gestational week (8.9±2.8 vs. 8.2 ±1.8, p=0.033) and the number of gravidity (2.4±1.2 vs. 2±1, p=0.012) were higher in the MA group than in the control group. The RDW and MPV/L ratio were significantly higher in the MA group than in the control group. (15.8 ±2.4 vs 13.9±1.1, p<0.001 and 5.5±1.8 vs 4.9±1.4, p=0.004, respectively) (Figure 1). The MPV, Platelet count and L/M ratio were also significantly higher in the MA group than in the control group. The monocyte count was significantly lower in the MA group than in the control group (0.48 ±0.1 vs 0.55±0.1, p=0.002).

**Table 1.** Baseline clinical and laboratory characteristics of control and MA groups

	Control (n=105)	MA (n=125)	P value
Age, years	27.9±5	30.4±6	0.001
Gravidity	2±1	2.4±1.2	0.012
Parity	0.8 ±0.7	1 ±0.9	0.101
Gestational week	8.9 ±2.8	8.2 ±1.8	0.033
Abort	0.25±0.3	0.45±0.4	0.066
Hemoglobin (g/dl)	12.7±0.9	12.5±1.1	0.232
WBC, x 10 <sup>3</sup> /mm <sup>3</sup>	8.9±2	8.1±2	0.006
Platelet count, x 10 <sup>3</sup> /mm <sup>3</sup>	241±51	258±64	0.035
Mean platelet volume (fl)	8.9±1	9.3±1	<0.001
PDW, %	16.5±2.3	16.5±1.8	0.878
RDW, %	13.9±1.1	15.8 ±2.4	<0.001
N/L ratio	3.4±1.9	3.4±1.4	0.963
Monocyte count	0.55±0.1	0.48 ±0.1	0.002
L/M ratio	3.7±1.3	4.1±1.4	0.032
Mpv/r	4.9 ±1.4	5.5 ±1.8	0.004

Abbreviations: L/M ratio; lymphocyte/monocyte ratio; MPV, mean platelet volume; MPV/L ratio, mean platelet volume /lymphocyte ratio; N/L ratio, neutrophil/lymphocyte ratio; RDW, red cell distribution width; WBC, white blood cell.



**Figure 1.** RDW and MPV/L ratio of patients with MA and control group

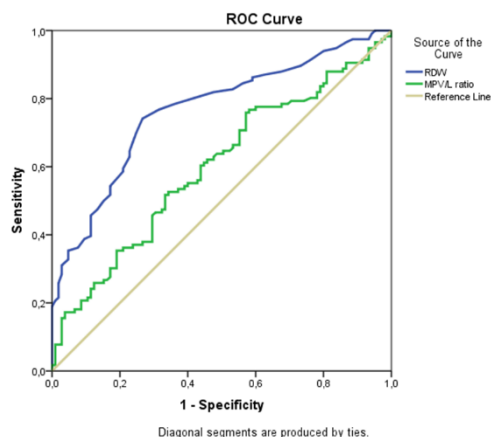
To further explore the independent predictor(s) of MA, various regression models were analyzed based on risk factors affecting MA. By univariate logistic regression analyses, risk factors associated with the MA at the  $p < 0.05$  level included age, gravidity, gestational week, MPV, RDW, WBC, monocyte count, L/M ratio and MPV/L ratio (Table 2). After adjusting for all covariates, MA was independently associated with RDW [odds ratio (OR)=1.737, 95% confidence interval (CI)=1.346-2.242,  $p < 0.001$ ] and MPV/L ratio [odds ratio (OR)=1.518, 95% confidence interval (CI)=1.047-2.199,  $p = 0.028$ ].

**Table 2.** Independent predictors of MA in multivariate logistic regression analysis.

Variables	Odds Ratio	95% Confidence Interval	P
Age	1.077	1.017-1.149	0.027
Gravidity	0.964	0.591-1.592	0.877
Gestational week	0.873	0.730-1.030	0.094
WBC, $\times 10^3/\text{mm}^3$	30.902	0.751-1.080	0.258
Platelet count, $\times 10^3/\text{mm}^3$	1.008	1.000-1.015	0.051
Mean platelet volume (fl)	1.145	0.693-1.882	0.581
RDW, %	1.737	1.346-2.242	<0.001
Monocyte count	1.113	0.019-66.43	0.960
L/M ratio	1.256	0.744-2.123	0.393
MPV/L ratio	1.5	1.047-2.199	0.028

Abbreviations: L/M ratio; lymphocyte/monocyte ratio, MPV/L ratio; mean platelet volume /lymphocyte ratio; RDW, red cell distribution width; WBC, white blood cell

The ROC analysis yielded a cut-off value of 14.1, for RDW to predict MA with 78% sensitivity and 74% specificity (ROC area under curve: 0.766, 95% CI=0.703-0.828,  $p < 0.001$ ). The area under the ROC curve of the MPV/L ratio was 0.600 (0.520-0.676,  $p = 0.010$ ) to predict MA. The best cutoff value of the MPV/L ratio to predict MA was 48, (61% sensitivity and of 57% specificity) (Figure 2).



**Figure 2.** Receiver operating characteristic (ROC) curve for RDW and MPV/L ratio as a predictors of MA.

## Discussion

In our study, we found a significant association between RDW and MA. We also found that serum MPV and MPV/L ratio levels were significantly higher in the MA group but only MPV/L ratio was independent predictor of MA in the regression analysis.

It was reported that RDW increases over time during pregnancy. Shehata et al. (6) investigated the RDW changes in pregnancy. In their study serum RDW level was significantly increased during the last 4-6 weeks leading up to the onset of labor although the mechanism remains unclear. Their study suggests that RDW may be a simple important marker of impending parturition.

Although the exact precise mechanism of MA remains unclear, inflammation may play an important role in the pathophysiology of MA. It was reported that, there is an increased inflammatory state in normal pregnancy compared with the non-pregnant state, but this inflammatory reaction was excessive in women presenting with miscarriage (13). Mollamahmutoglu et al. (14) reported that, maternal serum CRP levels were significantly higher in the missed abortion patients when compared with normal pregnancy. A previous study investigating the role of Th1 type immune response in the pathophysiology of MA, found an increased Th1 type of immune response in patients with MA and threatened miscarriage (15). Paradisi et al. (16) reported that maternal serum levels of pro-inflammatory cytokines particularly interleukin (IL)-12 were increased in patients with missed and threatened abortion. Previous studies suggest that RDW may be a simple marker of inflammation. Inflammation may inhibit erythropoietin-induced erythrocyte maturation and impair iron metabolism. (17,18) As a result inflammation may contribute to increased serum RDW levels. In a recent study, RDW has been linked with recurrent pregnancy loss (8). Consistently, in our study RDW was found to be an independent predictor of MA.

Pregnancy itself is a prothrombotic state as natural prothrombotic events are physiological variations observed during pregnancy. Exaggerated prothrombotic state which may change the hemostatic balance in placental vessels has been proposed as one of the main causes of MA. It was reported that, women with a history of unexplained recurrent miscarriage who subsequently miscarry again have reduced platelet function (19). Recently Flood et al. (20) showed that, patients with unexplained RM have significantly increased platelet aggregation in response to arachidonic acid. Mean platelet volume (MPV), an accurate measure of platelet size, represents platelet function. Larger platelets with higher MPV values are more reactive, have more granules, aggregate more rapidly with collagen, and produce higher amounts of the

prothrombotic factor thromboxane A 2. In contrast, relatively low lymphocyte counts have been found to be associated with inflammation and thrombosis (12). Mean platelet volume-to-lymphocyte ratio has been found to be associated with thrombus burden and poor short- and long-term prognosis in patients with acute myocardial infarction (12,21). In the present study, MPV/L ratio but not MPV was found to be significantly associated with MA.

In conclusion, RDW and MPV/L ratio are independent predictors of MA. MPV was significantly higher in patients with MA, but it was not found as an independent predictor of MA. RDW and MPV/L ratio, which are inexpensive and easily measurable laboratory variables, could be used as novel risk markers of MA. With frequent follow-up we can prevent unregarded cases and with early diagnosis improve the quality of life and prognosis of high risk patients.

**Ethics Committee Approval:** Muğla Sıtkı Koçman University Clinical Research Ethics Committee Permission was obtained with the letter dated 26/10/2017 and numbered 18/I.

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