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The Utility of Complete Blood Count Inflammatory Markers in First-Trimester Missed Miscarriage

Mohammed Fatih Haseeb ^{1,*}, Aseel Ghazi Rifat ², Shlair Ibrahim Mohammed ³

¹Department of Pathology, College of Medicine, University of Kirkuk, Kirkuk, Iraq

²Department of Obstetrics and Gynecology, College of Medicine, University of Kirkuk, Kirkuk, Iraq

³Department of Physiology, College of Medicine, University of Kirkuk, Kirkuk, Iraq

*Corresponding author email: mohammedhaseeb@uokirkuk.edu.iq

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ABSTRACT

Background: Missed miscarriage is defined by retention of a non-viable intrauterine pregnancy and may be associated with altered maternal inflammatory responses. Complete blood count (CBC)-derived inflammatory markers may serve as simple indicators of adverse early pregnancy outcomes. This study evaluated the utility of CBC-derived inflammatory markers in first-trimester missed miscarriage.

Methods: This retrospective case-control study included 150 pregnant women: 50 with missed miscarriage and 100 with viable pregnancies. In both groups, the CBC used for analysis was obtained from medical records at 5-7 weeks of gestation. In the case group, missed miscarriage was diagnosed by ultrasound 2-5 weeks after CBC sampling. In the control group, women were recruited at the 13-week follow-up visit, where fetal viability was confirmed by ultrasound, and the earlier CBC obtained at 5-7 weeks was used for comparison. Women with major medical comorbidities or other conditions affecting inflammatory markers were excluded. Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) were calculated from CBC data.

Results: Mean NLR was significantly higher in the missed miscarriage group than in controls (3.45 vs. 2.80, $P = 0.01$). Mean PLR was also higher in the missed miscarriage group (161.2 vs. 125.0), with borderline statistical significance ($P = 0.05$), whereas LMR did not differ significantly between the two groups. In logistic regression analysis, only NLR was significantly associated with missed miscarriage (OR = 3.65, 95% CI 1.86–7.60). NLR showed the best discriminatory performance; at a cutoff value of > 4.6 , it yielded 91% sensitivity and 82% specificity.

Conclusion: Elevated NLR was significantly associated with first-trimester missed miscarriage and showed the best discriminatory performance among the studied CBC-derived inflammatory markers. Larger prospective multicenter studies are needed before clinical application can be recommended.

Key words: Missed miscarriage; Complete blood count; Inflammatory markers; Neutrophil-to-lymphocyte ratio; Platelet-to-lymphocyte ratio.



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INTRODUCTION

Missed miscarriage is a form of pregnancy loss characterized by intrauterine retention of a non-viable pregnancy [1]. It is a common yet relatively understudied type of miscarriage, accounting for approximately 15% of clinically recognized pregnancy losses [2, 3]. In addition to the risks of bleeding and infection, missed miscarriage is associated with considerable emotional distress for affected women and their partners [4].

Although several etiological factors have been implicated, including genetic abnormalities, infections, and endocrine disorders, the underlying cause remains unidentified in 40%–50% of affected pregnancies [5].

A regulated maternal inflammatory response is essential for successful implantation and placentation [6]. Abnormal maternal inflammatory activity may contribute to defective placentation, trophoblastic ischemia, endothelial damage, and subsequent pregnancy complications, including missed miscarriage [7]. Increasing evidence supports the role of inflammatory and immunological factors in the pathogenesis of missed miscarriage [8]. Serum levels of several inflammatory markers, such as tumor necrosis factor- α (TNF- α) and interleukins (IL-6, IL-10, and IL-1 β), have been reported to correlate with miscarriage risk [1, 5]. However, assessment of these markers is costly, technically demanding, and not routinely performed in clinical practice [9].

In contrast, the complete blood count (CBC) is inexpensive, simple, and widely used as a routine test during pregnancy [10]. Neutrophils, monocytes, lymphocytes, and platelets play important roles in systemic inflammation, and CBC-derived inflammatory markers may reflect the balance between inflammatory and regulatory immune responses [11]. Accordingly, the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) have been investigated as inflammatory markers in various pathological conditions, including preeclampsia and early pregnancy loss [12–14]. The potential association between CBC-derived inflammatory markers and missed miscarriage may be explained by interconnected pathways involving inflammation, immune dysregulation, and thrombosis, all of which may impair placental function and trophoblastic invasion [15].

Although several studies have examined these inflammatory markers [16, 17], data regarding their utility in missed miscarriage, particularly among asymptomatic women in early pregnancy, remain limited. In addition, there is a paucity of research evaluating these markers in Iraqi women. Therefore, this study aimed to investigate the utility of CBC-derived inflammatory markers, specifically NLR, PLR, and LMR, in first-trimester missed miscarriage.

PATIENTS AND METHODS

Study design, setting, and ethical approval

This retrospective case–control study was conducted at Azadi Teaching Hospital, a referral hospital in Kirkuk Province, Iraq, between June 2024 and June 2025. The study was performed in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Ethical Committee of the University of Kirkuk, College of Medicine (document No. 55). Verbal informed consent was obtained from all participants before inclusion in the study.

Study sample

A total of 150 pregnant women aged 18–40 years with singleton pregnancies were included in the study. The participants were divided into two groups: a missed miscarriage group comprising 50 women and a control group comprising 100 women with viable intrauterine pregnancies.

Sample size calculation was performed using OpenEpi based on the reported mean neutrophil-to-lymphocyte ratio (NLR) in women with miscarriage (3.51) compared with women with normal pregnancies (2.62), with a pooled standard deviation of 1.51 [18]. Assuming a control-to-case ratio of 2:1, a minimum of 46 cases and 92 controls was required to achieve 80% power at a significance level of 5%. For convenience, the sample size was increased to 50 cases and 100 controls.

Women in the case group were enrolled when the ultrasound diagnosis of missed miscarriage was established and before any medical or surgical intervention. In this group, the complete blood count (CBC) used for analysis had been obtained earlier from medical records at 5–7 weeks of gestation, and the diagnosis of missed miscarriage was subsequently established by ultrasound 2–5 weeks after CBC sampling. Women in the control group were recruited during a routine 13-week antenatal follow-up visit, at which an ongoing viable intrauterine pregnancy with fetal cardiac activity was confirmed by ultrasound. For these women, the earlier CBC obtained at 5–7 weeks of gestation was retrieved from the medical records and used for comparison.

Participants were excluded if they had multiple pregnancy, conception by in vitro fertilization, cervical insufficiency, uterine anomalies, anemia (hemoglobin level < 110 g/L in the first trimester) [19], thyroid disease, diabetes mellitus, hypertension, renal or hepatic disease, thrombophilia, autoimmune disease, hematologic disorders, chronic inflammatory disease, active infection, a history of smoking, or the use of medications that could affect inflammatory markers, including progesterone, corticosteroids, and anti-inflammatory agents.

Data collection

Demographic and obstetrical data were obtained from the medical records, including maternal age, last menstrual period (LMP), gestational age, gravidity, parity, number of previous miscarriages, weight, and height. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Gestational age was calculated from the LMP and verified by ultrasound dating.

Missed miscarriage was diagnosed on ultrasound according to the following criteria: (1) crown–rump length (CRL) ≥ 7 mm with absent fetal cardiac activity, or (2) mean gestational sac diameter ≥ 25 mm with no visible fetal pole. To confirm the diagnosis, two ultrasound examinations at least 24 hours apart were performed by two experienced sonographers with concordant findings. Ultrasound examinations were performed using a Hitachi Aloka Prosound F37 ultrasound machine.

CBC parameters for both groups were collected retrospectively from medical records. In both groups, the analyzed CBC samples had been obtained at the first-trimester antenatal visit between 5 and 7 weeks of gestation, while the women were still asymptomatic. CBC analysis had been performed using the Mindray BC-6800 automated five-part differential hematology analyzer with routine internal and external quality-control procedures. The following CBC-derived inflammatory markers were calculated:

- Neutrophil-to-lymphocyte ratio (NLR): neutrophil count divided by lymphocyte count.
- Platelet-to-lymphocyte ratio (PLR): platelet count divided by lymphocyte count.
- Lymphocyte-to-monocyte ratio (LMR): lymphocyte count divided by monocyte count.

Statistical analysis

Statistical analysis was performed using SPSS version 25.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA). Continuous variables were tested for normality using the Shapiro–Wilk test. A P value ≥ 0.05 was considered indicative of an approximately normal distribution, whereas a P value < 0.05 indicated non-normal distribution. In the present dataset, the Shapiro–Wilk test showed no significant deviation from normality for the analyzed continuous variables. Therefore, continuous variables were summarized as mean \pm standard deviation and compared between the two groups using the independent-samples t -test. Categorical variables, where applicable, were expressed as number (%) and compared using the chi-square test or Fisher's exact test. Binary logistic regression analysis was performed to evaluate the association between CBC-derived inflammatory markers and missed miscarriage. Receiver operating characteristic

(ROC) curve analysis was used to assess the discriminatory performance of NLR, PLR, and LMR and to determine their optimal cutoff values. A two-tailed P value of < 0.05 was considered statistically significant.

RESULTS

Demographic and obstetrical characteristics

A total of 150 pregnant women were included in the study, comprising 50 women with missed miscarriage and 100 women with viable intrauterine pregnancies. In both groups, the CBC used for analysis had been obtained at 5–7 weeks of gestation. In the control group, pregnancy viability was subsequently confirmed at the routine 13-week follow-up visit.

As shown in Table 1, the mean maternal age and body mass index (BMI) did not differ significantly between the missed miscarriage and control groups. Likewise, no significant between-group differences were observed in gestational age at the time of CBC sampling, gravidity, or parity. However, women in the missed miscarriage group had a significantly higher mean number of previous miscarriages than controls ($P < 0.001$).

Hematologic parameters and CBC-derived inflammatory markers

As shown in Table 2, neutrophil and platelet counts were comparable between women with missed miscarriage and controls. In contrast, lymphocyte and monocyte counts were significantly lower in the missed miscarriage group than in the control group (1.66 ± 0.56 vs. $2.24 \pm 0.82 \times 10^3/\mu\text{L}$, $P = 0.003$; and 0.40 ± 0.12 vs. $0.56 \pm 0.16 \times 10^3/\mu\text{L}$, $P < 0.001$, respectively). Among the CBC-derived inflammatory markers in Table 2, the mean NLR was significantly higher in the missed miscarriage group than in controls (3.45 ± 1.19 vs. 2.80 ± 1.53 , $P = 0.01$). The mean PLR was also higher in the missed miscarriage group (161.2 ± 60.84 vs. 125.01 ± 63.14), with borderline statistical significance ($P = 0.05$). No significant difference was observed in LMR between the two groups ($P = 0.10$).

Receiver operating characteristic (ROC) curve analysis

The ROC curve analysis of NLR, PLR, and LMR is presented in Table 3 and Figure 1. Among the studied markers, NLR demonstrated the best discriminatory performance, with an area under the curve (AUC) of 0.83 (95% CI: 0.68–0.96, $P < 0.001$). The optimal cutoff value for NLR was > 4.6 , which yielded a sensitivity of 91% and a specificity of 82%. In contrast, PLR and LMR showed poor discriminatory performance and were not statistically significant, with AUC values of 0.52 (95% CI: 0.30–0.73, $P = 0.82$) and 0.51 (95% CI: 0.31–0.72, $P = 0.84$), respectively.

Table 1. Demographic and obstetrical characteristics of women with missed miscarriage and controls at the time of CBC sampling.

Characteristic	Missed miscarriage (n = 50)	Control (n = 100)	P-value
Age (years)	27.78 ± 6.31	27.47 ± 6.31	0.86
Body mass index (kg/m ²)	23.52 ± 4.74	22.77 ± 4.90	0.84
Gestational age at CBC sampling (weeks)	6.245 ± 0.637	6.14 ± 0.654	0.34
Gravidity	3.28 ± 1.41	3.23 ± 1.90	0.84
Parity	1.0 ± 0.85	1.48 ± 1.10	0.48
Previous miscarriage	1.28 ± 0.99	0.74 ± 0.66	< 0.001

Data are presented as mean ± standard deviation.
Comparisons were performed using the independent-samples *t*-test.
CBC, complete blood count.

Table 2. Hematologic parameters and CBC-derived inflammatory markers in women with missed miscarriage and controls.

Characteristic	Missed miscarriage (n = 50)	Control (n = 100)	P-value
Neutrophils (10 ³ /μL)	5.61 ± 2.96	5.30 ± 1.39	0.49
Lymphocytes (10 ³ /μL)	1.66 ± 0.56	2.24 ± 0.82	0.003
Monocytes (10 ³ /μL)	0.40 ± 0.12	0.56 ± 0.16	< 0.001
Platelets (10 ³ /μL)	236.8 ± 44.30	237.63 ± 45.15	0.87
Neutrophil-to-lymphocyte ratio (NLR)	3.45 ± 1.19	2.80 ± 1.53	0.01
Platelet-to-lymphocyte ratio (PLR)	161.2 ± 60.84	125.01 ± 63.14	0.05
Lymphocyte-to-monocyte ratio (LMR)	4.57 ± 2.30	4.44 ± 2.46	0.10

Data are presented as mean ± standard deviation.
Comparisons were performed using the independent-samples *t*-test.
CBC, complete blood count; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio.

Table 3. Receiver operating characteristic (ROC) curve analysis of CBC-derived inflammatory markers for discriminating missed miscarriage.

Marker	AUC (95% CI)	Cutoff value	Sensitivity	Specificity	P-value
Neutrophil-to-lymphocyte ratio (NLR)	0.83 (0.68–0.96)	4.6	91%	82%	< 0.001
Platelet-to-lymphocyte ratio (PLR)	0.52 (0.30–0.73)	220	55.5%	43%	0.82
Lymphocyte-to-monocyte ratio (LMR)	0.51 (0.31–0.72)	73	52%	50%	0.84

AUC, area under the curve; CI, confidence interval; CBC, complete blood count.

Logistic regression analysis

Multivariable binary logistic regression analysis was performed to evaluate the association between demographic, obstetrical, hematologic, and inflammatory variables and missed miscarriage, as shown in Table 4. Maternal age (OR 1.15, 95% CI 1.02–1.30, *P* = 0.027) and gravidity (OR 6.7, 95% CI 2.6–27.3, *P* = 0.001) were independently associated with missed miscarriage. BMI, parity, and previous miscarriage were not significantly associated with missed miscarriage

(*P* > 0.05).

With regard to hematologic and inflammatory variables, neutrophil count, lymphocyte count, monocyte count, platelet count, PLR, and LMR were not significantly associated with missed miscarriage in the multivariable model (*P* > 0.05). NLR was the only CBC-derived inflammatory marker that remained significantly associated with missed miscarriage (OR 3.65, 95% CI 1.86–7.60, *P* < 0.001). This indicates that each unit increase in NLR was associated with higher odds of missed miscarriage.

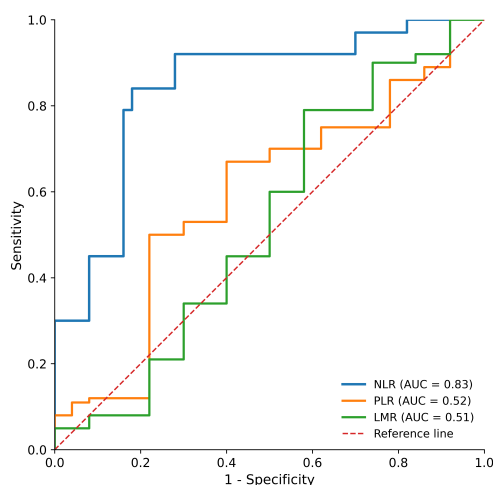


Figure 1. Receiver operating characteristic (ROC) curves of neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) for discriminating missed miscarriage.

Table 4. Multivariable binary logistic regression analysis of factors associated with missed miscarriage.

Parameter	Coefficient estimate	Standard error	Odds ratio (95% CI)	P-value
Age (years)	0.139	0.063	1.15 (1.02–1.30)	0.027
Body mass index (kg/m ²)	0.113	0.07	1.12 (0.99–1.34)	0.06
Gravidity	1.9	0.6	6.7 (2.6–27.30)	0.001
Parity	0.42	0.4	1.5 (0.7–3.6)	0.28
Previous miscarriage	0.31	0.34	1.4 (0.72–2.7)	0.35
Neutrophils (10 ³ /μL)	0.29	0.2	1.33 (0.88–2.13)	0.19
Lymphocytes (10 ³ /μL)	−0.265	0.5	0.77 (0.28–2.03)	0.06
Monocytes (10 ³ /μL)	−0.2	2.85	0.82 (0.003–2.985)	0.94
Platelets (10 ³ /μL)	−0.003	0.007	0.99 (0.98–1.01)	0.35
Neutrophil-to-lymphocyte ratio (NLR)	1.3	0.38	3.65 (1.86–7.60)	<0.001
Platelet-to-lymphocyte ratio (PLR)	−0.002	0.09	0.99 (0.97–1.01)	0.72
Lymphocyte-to-monocyte ratio (LMR)	−0.07	0.13	0.92 (0.70–1.2)	0.55

CI, confidence interval.

DISCUSSION

Missed miscarriage is an important and distressing complication of early pregnancy [16, 20]. Although several biomarkers have been investigated, no standardized laboratory marker has yet been established for routine clinical discrimination of missed miscarriage [17, 20]. In the present study, CBC samples obtained at 5–7 weeks of gestation were evaluated in women who were later diagnosed with first-trimester missed miscarriage and in women whose pregnancies remained viable at the 13-week follow-up visit. The main findings were that lymphocyte and monocyte counts were lower in the missed miscarriage group, NLR was higher and remained independently associated with missed miscarriage, and NLR showed the best discriminatory performance among the studied CBC-derived inflammatory markers. In contrast, PLR showed only borderline elevation and LMR was not associated

with missed miscarriage.

Maternal age and body mass index did not differ significantly between the missed miscarriage and control groups in the descriptive analysis. Likewise, no significant between-group differences were observed in gestational age at CBC sampling, gravidity, or parity, whereas the number of previous miscarriages was higher in the missed miscarriage group. However, in the multivariable logistic regression model, maternal age and gravidity were independently associated with missed miscarriage, while body mass index, parity, and previous miscarriage were not. These findings indicate that the effects of baseline demographic and obstetrical variables may differ between unadjusted group comparisons and multivariable analysis. Previous studies have shown that the risk of miscarriage may increase with maternal age and reproductive history [21, 22], whereas other case-control studies have not

demonstrated a consistent association with parity [23]. The relatively young age of our participants and the exclusion of several comorbid and high-risk conditions may partly explain these findings.

With regard to hematologic parameters, neutrophil and platelet counts did not differ significantly between the two groups, whereas lymphocyte and monocyte counts were significantly lower in women with missed miscarriage. These findings are partly consistent with the study by Yazdizadeh et al., who reported no significant difference in neutrophil count but lower lymphocyte counts in women with pregnancy loss [18]. Pregnancy is accompanied by dynamic immunologic adaptation, and alterations in circulating immune-cell populations may reflect disruption of maternal immune tolerance and abnormal placentation [24, 25]. The lower lymphocyte count observed in the missed miscarriage group in the present study may therefore reflect an altered maternal inflammatory or immune response in pregnancies that subsequently failed. In addition, the absence of a significant difference in platelet count may be related to the exclusion of women with thrombophilia and other conditions associated with abnormal coagulation [9].

Among the CBC-derived inflammatory markers, NLR was the most informative marker in the present study. Women with missed miscarriage had higher NLR values than controls, and NLR was the only marker that remained independently associated with missed miscarriage in the multivariable model. Moreover, NLR showed the highest AUC on ROC analysis, and a cutoff value of > 4.6 yielded 91% sensitivity and 82% specificity. These findings support the view that NLR may reflect the maternal systemic inflammatory response associated with defective implantation, placental dysfunction, or trophoblastic injury in early pregnancy [11, 16, 26]. Our findings are in line with those of Oğlak et al. [2] and Yazdizadeh et al. [18], who reported significantly higher NLR values in women with early pregnancy failure. However, other studies found no significant difference in NLR between miscarriage and control groups [1, 9]. Such discrepancies may be explained by differences in study design, inclusion criteria, timing of blood sampling, and the specific type of pregnancy loss evaluated.

PLR was higher in the missed miscarriage group, but this difference showed only borderline statistical significance, and PLR was not independently associated with missed miscarriage in logistic regression analysis. This suggests that, in our cohort, PLR had limited discriminatory value compared with NLR. Previous studies have reported conflicting findings regarding PLR in early pregnancy loss. Ata et al. [27] and Bas et al. [28] found higher PLR values in women with early pregnancy loss, whereas Liu et al. [1] found no association between PLR and missed miscarriage. In addition, Wang et al. [17] concluded in a recent meta-analysis that PLR has

limited predictive significance for miscarriage. The lack of a clear association in our study may be related to the absence of a significant difference in platelet count between groups and to the exclusion of women with thrombophilia and other inflammatory or hematologic disorders.

LMR did not differ significantly between the study groups and was not associated with missed miscarriage in the present analysis. This finding contrasts with reports by Wang et al. [29] and Feng et al. [5], who suggested that lower LMR values may be associated with early pregnancy loss. However, our findings agree with other studies that did not demonstrate a significant difference in LMR between women with missed miscarriage and controls [12, 19]. One possible explanation is that both lymphocyte and monocyte counts were reduced in the missed miscarriage group, resulting in little net change in their ratio.

The present study has some strengths. It evaluated CBC-derived inflammatory markers in Iraqi women, a population for which published data remain limited, and focused on asymptomatic women whose CBC had been obtained early in the first trimester before the diagnosis of missed miscarriage. Nevertheless, several limitations should be acknowledged. The study was retrospective and conducted at a single center with a relatively modest sample size. In addition, residual confounding cannot be excluded, and genetic causes of pregnancy loss were not systematically assessed. These limitations should be considered when interpreting the findings.

CONCLUSION

Elevated NLR was significantly associated with first-trimester missed miscarriage and showed the best discriminatory performance among the studied CBC-derived inflammatory markers. In contrast, PLR showed only borderline elevation without an independent association, and LMR was not significantly associated with missed miscarriage. Because NLR is inexpensive and routinely available as part of the complete blood count, it may merit further evaluation as an adjunctive marker in early pregnancy. However, larger prospective multicenter studies are required before clinical application can be recommended.

ETHICAL DECLARATIONS

• Ethics Approval and Consent to Participate

The study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Ethical Committee of the College of Medicine, University of Kirkuk, Iraq (Document No. 55). Verbal informed consent was obtained from all participants prior to their inclusion in the study.

• Consent for Publication

Not applicable.

• Availability of Data and Material

The datasets are available from the corresponding author upon reasonable request.

• Competing Interests

The authors declare that there is no conflict of interest.

• Funding

Self-funded.

• Use of Generative Artificial Intelligence

The authors declare that ChatGPT, a generative AI tool developed by OpenAI, was used solely to enhance clarity and grammatical accuracy during the final editing phase. It was not used for content generation, data analysis, or interpretation.

• Authors' Contributions

All authors contributed equally to the design and conception of the study. All authors reviewed the manuscript and approved the final manuscript.

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