

Could the Ratios of: Platelet to Lymphocyte, Monocyte to Lymphocyte and Neutrophil to Lymphocyte be Markers for Missed Abortion?

Noha Aziz Alrefaey Drag*, Mohamad Ahmad El sayed Mohamad Emam,
MohamadIbrahem Mohamad Eid, Khaled Samir Esmail Othman

Department of Obstetrics and Gynecology, Faculty of Medicine – Mansoura University, Egypt

*Corresponding author: Noha Aziz Alrefaey Drag, Mobile: (+20) 01092324848, Email: doctoranono15@gmail.com

ABSTRACT

Background: Abortion is defined as the termination of pregnancy (TOP) before the viability of the foetus.

Objective: This study aimed to evaluate the association of combination of platelet (PLT) to lymphocyte ratio (PLR), monocyte to lymphocyte ratio (MLR) and neutrophil to lymphocyte ratio (NLR) as markers for predicting missed abortion in 1st trimester.

Patients and methods: This cross-sectional study was conducted on 92 women who were divided into two groups: group (A) included 46 women diagnosed with missed abortion in the first trimester and group (B) included 46 women with normal pregnancies in the first trimester as the control group. This study was conducted in Department of Gynecology and Obstetrics, Mansoura University Hospitals, Mansoura University, Egypt, from July 2021 to December 2023.

Results: Combination of PLR, MLR and NLR had sensitivity (Sn) and specificity (Sp) of 78.3% and 73.9% respectively to diagnose missed abortion (Area under curve (AUC) = 0.820). A significant difference was recorded between both groups concerning lymphocytes, monocytes, PLR, MLR and NLR.

Conclusion: The dependence of PLR, MLR, and NLR on the prediction of missed abortion isn't certain because of moderate sensitivity and specificity of these ratios. However, combination of two ratios led to higher increase in sensitivity, specificity and accuracy in predicting missed abortion than using one ratio. Combination of the three ratios had higher sensitivity and specificity in predicting missed abortion than using two ratios.

Keywords: Missed abortion, PLR, MLR, NLR.

INTRODUCTION

Abortion is the termination of pregnancy (TOP) before the viability of the foetus. It has been demonstrated that viability occurs between 23 and 24 weeks of pregnancy when the foetus weighs slightly more than 600 grams⁽¹⁾. Missed miscarriage refers to a foetus that has died but is retained in the uterus⁽²⁾. The diagnosis of missed miscarriage in its initial stages is a challenging process as it has no distinctive manifestations and the role of ultrasound is limited. Unfortunately, any delay in diagnosis is associated with negative maternal consequences, which include extensive blood loss, infections, and blood coagulation disorders⁽³⁾.

Much research has recorded that complete blood count (CBC) parameters, PLR, NLR, and MLR may be considered as new predictors of systemic inflammation in different pathological conditions, including pregnancy adverse events such as preeclampsia (PE), gestational diabetes, and hyperemesis gravidarum⁽⁴⁾. A lot of studies have reported that PE and missed abortion are comparable placental disorders ending in placental dysfunction, as the two disorders have the same inflammatory component⁽⁵⁾.

There is much research on the correlation between these CBC indices and abortion. On the other hand, the roles of PLR, MLR, and NLR in missed abortion remain unclear, as these studies report some conflicting results^(5, 6, 7).

Biyik et al.⁽⁵⁾ recorded that there were significant increases in both NLR and PLR levels among cases with missed abortion. Such outcomes could indicate

abnormal placental function as regards missed abortion pathogenesis. On the other hand, **Wang et al.**⁽⁷⁾ recorded that MLR mightn't often be significantly different among females with missed abortion and healthy controls at certain gestation stages. They suggested that MLR could not be used as an appropriate indicator in the context of missed miscarriage. So, we aimed to assess the association of combination of PLR, MLR and NLR as markers for predicting missed abortion in the 1st trimester.

PATIENTS AND METHODS

This cross-sectional observational study was conducted on 92 women who were divided into two groups: group (A) included 46 women diagnosed with missed abortion in the first trimester and group (B) that included 46 women with normal pregnancies in the first trimester as the control group. The study was conducted in Department of Gynecology and Obstetrics, Mansoura University Hospitals, Mansoura University through the period from July 2021 to December 2023.

Sample size calculation: It was measured by using the IBM^a SPSS^a Sample Power^a version 3.0.1. According to previous literature, the mean NLR in the normal pregnancy group was 3.09 (SD 0.9) in **Wang et al.**⁽⁷⁾ study versus 2.36 (SD 0.93) in the missed abortion group. At fifty five percent level of significance and power of eighty percent, the minimal needed sample size calculated was 46 in each group.

Inclusion criteria: Missed abortion (Women were diagnosed in The Obstetrics and Gynecology Department). 1st trimester pregnant women with vaginal bleeding every now and then, retained intrauterine conception, closed cervical os and size of uterus less than gestational ages that were confirmed by ultrasonography.

Exclusion criteria: Impaired thyroid functions, diabetes, haematologic diseases, previous history of thrombosis, twins, infections, malignant disorders, chronic inflammatory diseases and those on anti-inflammatory agents or steroid therapy.

Methods: Evaluation of the participants (including both groups) by history taking, clinical examination and laboratory investigations.

Complete blood count (CBC) including hemoglobin, total leukocytic count, and platelet count. The differential leukocytic count was calculated including lymphocytes, monocytes, and neutrophils. Blood samples were withdrawn from the vein and put in tubes comprising K3EDTA. The CBC was analysed using an automatic CBC machine. PLR was calculated by dividing PLT count by lymphocyte count. By dividing the number of monocytes by the number of lymphocytes, MLR was measured. NLR was measured by dividing neutrophil count by lymphocyte count. Measuring PLT count was done by automated laboratory technology. Some automated cases needed to be established by utilizing a blood smear, an approach of manually measuring the number of PLT in a blood specimen. In this study the CBC of Mansoura university hospital was used as a reference for our results.

Intervention for the cases: Cases diagnosed with missed abortion were managed by staff members.

Outcomes: The predictive value of PLR, NLR, and MLR were used as a complementary tool to ultrasonography in the prediction of missed abortion.

Ethical consideration: The study gained approval from The Institutional Review Board of Faculty of Medicine, Mansoura University (IRB code: MS.21.06.1548). After obtaining all of the information, all participants gave their signed consents. All patients had the right to leave the study at any time. Patient confidentiality was preserved. The Helsinki Declaration was observed throughout the study's conduction.

Statistical analysis

The data were processed and analysed using SPSS version 22.0. Normal distribution was assessed utilizing the Shapiro Walk test. Qualitative data were expressed as frequencies. X²-test and Fisher exact test were used to calculate difference between qualitative variables. Quantitative data were expressed as mean ± SD. In addition, t-test and Mann Whitney U test were used to compare between two independent groups of normally distributed variables and non-normally distributed data respectively. ROC curve was utilized to measure the diagnostic ability of quantitative variable to predict the categorical outcomes. The level of significance was set at P ≤ 0.05.

RESULTS

The mean age of group A was 28.93 years compared to 26.72 years in group B. Regarding their occupation, most women were house wife as they formed 76.1% and 71.7% of participants in the missed abortion and healthy pregnant women respectively. The remaining participants were employees. Most participants were from rural areas (73.9% and 60.86% of cases and controls respectively). All of the previous parameters didn't show statistical differences between the two study groups (p > 0.05) (Table 1).

Table (1): Demographic data in group A and group B

Variables	Group A (N=46)		Group B (N=46)		Test of significance	P value
Age (years)	28.93 ± 6.79		26.72 ± 6.53		t= 1.59	0.115
Occupation	House wife		Employee		MC= 5.111	0.164
	35	76.1 %	33	71.7 %		
Residence	Rural		Urban		X ² = 0.239	0.624
	34	73.9 %	36	60.86 %		
	12	26.1 %	10	21.7%		

t= independent samples t-test, MC= Monte-Carlo test, X²: Chi square test

A significant difference was recorded between both groups regarding gravidity and number of previous missed abortions, while there was no statistically significant difference regarding parity and gestational age (Table 2).

Table (2): Obstetric history in group A and group B

Variables	Group A (N=46)	Group B (N=46)	Test of significance	P value
Gravidity	3 (1 – 7)	2 (1 – 7)	$z = 3.19$	0.0014*
Parity	2 (0 – 4)	1 (0 – 6)	$z = 1.366$	0.171
Gestational age (Weeks)	9.5 (6-13)	11 (6- 13)	$z = - 1.4$	0.161
Number of previous missed abortions	2 (0 – 4)	0	$z = 3.588$	<0.001*

z = Mann-Whitney U-test

There was a statistically significant difference between the two groups regarding lymphocytes, monocytes, PLR, MLR and NLR, while there was no statistically significant difference regarding WBCs, neutrophil and PLTs (Table 3).

Table (3): Complete blood count analysis in both groups

Variables	Group A (N=46)	Group B (N=46)	Test of Significance	P value
WBCs ($10^3/ml$)	9.25 (3.1 – 20.10)	8.8 (4.5 –14.5)	$z = - 0.551$	0.582
Lymphocytes ($10^3/ml$)	2.9 (0.9 –4.9)	2.3 (1 – 4.9)	$z = - 4.404$	<0.001*
Monocytes ($10^3/ml$)	1.25 (0.30 – 4.10)	0.6 (2 – 1.3)	$z = - 5.521$	<0.001*
Neutrophil ($10^3/ml$)	6.41 (1.80 – 10.20)	5.6 (2.12 –10.30)	$z = - 1.239$	0.196
PLTs ($10^3/ml/\mu l$)	262.24 ± 54.49	250.87 ± 63.08	$t = 0.925$	0.357
Platelet lymphocyte ratio	92.25 (41.86 – 277.80)	119.88 (51.40 – 196.50)	$z = - 2.928$	0.003*
Monocyte lymphocyte ratio	0.355 (0.14 – 2.33)	0.245 (0.11 – 0.90)	$z = - 3.277$	0.001*
Neutrophil lymphocyte ratio	2.11 (0.56 – 4.87)	2.535 (0.59 –8)	$z = - 2.300$	0.021*

Median and range: non-parametric test. t = independent samples t-test, Z = Mann-Whitney test, *: statistically significant ($P < 0.05$).

Combination of PLR, MLR and NLR had Sn and Sp were 78.3% and 73.9% respectively to diagnose missed abortion (AUC = 0.820) (Table 4).

Table (4): The diagnostic indices and predictive values of PLR, MLR, NLR and their combinations in differentiating group A from group B

Variables	AUC	P value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Cut off value	Accuracy
PLR	0.677	0.003*	73.9%	60.9%	72.4%	62.5%	<109.71	65.2%
MLR	0.698	0.001*	69.6%	63%	60.8%	64.5%	>0.301	75.3%
NLR	0.639	0.021*	69.6%	54.3%	50.4%	62.3%	<2.49	64.7%
PLR & NLR	0.692	0.002*	71.7 %	60.9%	68.2%	62.4 %		66.7%
PLR & MLR	0.788	< 0.001*	87%	65.2%	69.4 %	77.2 %		75.3%
NLR & MLR	0.668	0.005*	67.4%	60.9%	65.2 %	58.2 %		64.4%
PLR & NLR & MLR	0.820	< 0.001*	78.3%	73.9%	80.4 %	76.2 %		78.1%

PPV: Positive predictive value, NPV: negative predictive value, *: Statistically significant ($p \leq 0.05$).

DISCUSSION

The mean ages of group A and group B were 28.93 and 26.72 years respectively with no significant difference ($p = 0.115$). In agreement with our finding, **Biyiket et al.**⁽⁵⁾ found that the mean age was 29.27 years in missed abortion cases and 28.37 years in the controls, with no significant difference ($p=0.508$). In contrast, **Jiang et al.**⁽⁸⁾ do not agree with us as they reported that missed abortion was associated significantly with older maternal age.

No significant difference was noted in our study between both groups concerning the occupation state of the included women ($p = 0.164$). This is in agreement with **Gorkemet et al.**⁽⁹⁾ who found that the employment status did not differ between abortion cases compared to controls ($p = 0.507$).

There was a significant increase in gravidity in group A compared to group B (3 vs. 2, respectively – $p = 0.0014$). This may be clarified by the increase in the number of previous missed abortions in group A. This is not in agreement with study of **Eroglu et al.**⁽¹⁰⁾ as they reported that gravidity had mean values of 1.76 and 1.58 in the missed abortion cases and control groups respectively with no significant difference ($p=0.57$).

In our study, the parity of the included women had median values of 2 and 1, in group A and group B respectively with no significant difference in the statistical analysis ($p = 0.171$). Also, **Liu et al.**⁽¹¹⁾ are in agreement with the current study as they recorded that the same parameter had a median value of 1 in both abortion cases and controls ($p = 0.425$).

In our study, gestational ages ranged between 6 and 13 weeks in both groups, with no significant difference ($p = 0.161$). In agreement with our study, **Yakışturan et al.**⁽¹²⁾ showed no significance ($p=0.745$).

Our results demonstrated a significant rise in the numbers of previous missed abortions in group A, as it reached up to four attacks in some cases, while no women in group B reported even one attack ($p < 0.001$). In hand with hand with our study, **Biyik et al.**⁽⁵⁾ showed that the median numbers of previous abortions were one in the missed abortion group (range, 1 – 4) compared to 0 in the controls (range, 0 – 5), with a significant difference ($p < 0.0001$).

There was a significant difference between both groups with regard to lymphocytes, monocytes, PLR, MLR and NLR, while no significant difference was recorded concerning WBCs, neutrophils and PLTs. **Oğlak and Aydın**⁽¹³⁾ reported no significance regarding WBCs count ($p > 0.05$). Also, **Gorkem et al.**⁽⁹⁾ recorded no significant difference in platelet count between abortion cases and controls ($p = 0.521$) and statistically comparable neutrophil count between abortion cases and controls ($p = 0.527$). In contrast, **Biyik et al.**⁽⁵⁾ recorded a significant rise of lymphocyte count in health controls compared to the missed abortion group ($p = 0.025$). Also, **Wang et al.**⁽⁷⁾ reported that monocyte count had a median value of 0.35 in the cases group compared to 0.46 in healthy pregnant controls, with a significant decline in the former ($p = 0.001$) and MLR had a significant decline in association with missed abortion compared to controls ($p = 0.003$).

Our study revealed that there was a significant decline in NLR and PLR in group A compared to group B as NLR had median values of 2.11 and 2.535 in the two groups respectively, with a significant decline in the group A ($p = 0.021$). A cut-off value of 2.49 had Sn and Sp of 69.6% and 54.3%, respectively, to differentiate group A from group B ($AUC = 0.639 - p = 0.021$) and PLR had mean values of 92.25 vs. 119.88, in the two groups respectively ($p = 0.003$). Additionally, that ratio had a Sn of 73.9% and a Sp of 60.9% to diagnose missed abortion, using a cut-off value of < 109.71 . In the same line, **Bas et al.**⁽¹⁴⁾ recorded that included cases with spontaneous abortion had a significant decline of the PLR in abortion cases compared to controls ($p = 0.03$).

Combination of PLR, MLR and NLR had Sn and Sp of 78.3% and 73.9% respectively to diagnose missed abortion ($AUC = 0.820$). Combination of the three ratios had higher sensitivity and specificity in predicting missed abortion than using two ratios. To our knowledge till now, no previous studies had combined the three parameters together that constituted advantageous point in favor of our study.

CONCLUSION

Both PLR and NLR were decreased significantly in cases with missed abortion while MLR was increased compared to the control group. However, the dependence of PLR, MLR, and NLR on the prediction of missed abortion is not certain because of moderate sensitivity and specificity of these ratios. While, combination of two ratios led to a higher increase in sensitivity, specificity and accuracy in predicting missed abortion than using one ratio. Combination of the three ratios had higher sensitivity and specificity in predicting missed abortion than using two ratios.

Funding: None.

Conflict of interest: None.

REFERENCES

1. **Shakhatreh H, Salih A, Aldrou K et al. (2022):** Medico-Legal Aspects of Abortion: Updates of the Literature. *Medical Archives*, 76 (5): 373-78.
2. **Wu H, Marwah S, Wang P et al. (2017):** Misoprostol for medical treatment of missed abortion: a systematic review and network meta-analysis. *Scientific Reports*, 7 (1): 1664-69.

3. **Bottomley C, Van Belle V, Mukri F et al. (2009):** The optimal timing of an ultrasound scan to assess the location and viability of an early pregnancy. *Human Reproduction*, 24 (8): 1811-7.
4. **Sisti G, Faraci A, Silva J et al. (2019):** Neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and routine complete blood count components in HELLP syndrome: a matched case control study. *Medicina*, 55 (5): 123-28.
5. **Biyik I, Albayrak M, Keskin F (2020):** Platelet to lymphocyte ratio and neutrophil to lymphocyte ratio in missed abortion. *RBGO Gynecology and Obstetrics*, 42 (05): 235-9.
6. **Kim Y (2020):** Retrospective analysis of prognostic value of the neutrophil-to-lymphocyte ratio in early miscarriages: A 8-year survey. *Medicine*, 99 (27): e20888. doi: 10.1097/MD.00000000000020888.
7. **Wang Q, Liu F, Zhao Y et al. (2020):** Can neutrophil-to-lymphocyte and monocyte-to-lymphocyte ratios be useful markers for predicting missed abortion in the first trimester of pregnancy? *Journal of Obstetrics and Gynaecology Research*, 46 (9): 1702-10.
8. **Jiang W, Yang X, Luo J (2022):** Risk factors for missed abortion: retrospective analysis of a single institution's experience. *Reproductive Biology and Endocrinology*, 20 (1): 115-19.
9. **Gorkem U, Kan O, Bostanci M et al. (2021):** Kisspeptin and hematologic parameters as predictive biomarkers for first-trimester abortions. *Medeniyet Medical Journal*, 36 (2): 98-103.
10. **Eroglu M, Keskin U, Yildirim A et al. (2013):** Can mean platelet volume predict abortion? *Medicinski Glasnik*, 10 (2): 235-39.
11. **Liu D, Huang X, Xu Z et al. (2022):** Predictive value of NLR and PLR in missed miscarriage. *Journal of Clinical Laboratory Analysis*, 36 (3): e24250. doi: 10.1002/jcla.24250.
12. **Yakıştıran B, Tanacan A, Altınboğa O et al. (2021):** Can derived neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and delta neutrophil index predict spontaneous abortion? *Z Geburtshilfe Neonatol.*, 225 (05): 418-22.
13. **Oğlak S, Aydın M (2020):** Are neutrophil to lymphocyte ratio and platelet to lymphocyte ratio clinically useful for the prediction of early pregnancy loss?. *Ginekologia Polska*, 91 (9): 524-7.
14. **Bas F, Tola E, Sak S et al. (2018):** The role of complete blood inflammation markers in the prediction of spontaneous abortion. *Pakistan Journal of Medical Sciences*, 34 (6): 1381-85.