

Diagnostic and Prognostic Value of Platelet-Derived Hemostatic Indices in Threatened Miscarriage: A Retrospective Cohort Study

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ABSTRACT

Threatened miscarriage is a common complication of early pregnancy and is associated with an increased risk of subsequent pregnancy loss and adverse perinatal outcomes. Alterations in maternal platelet activation and hemostatic balance may contribute to impaired placentation; however, the clinical relevance of platelet-derived hemostatic indices in threatened miscarriage remains incompletely defined. This study aimed to evaluate the association between platelet-derived hemostatic indices and threatened miscarriage, as well as their ability to predict progression to pregnancy loss.

This retrospective study included 240 pregnant women: 160 with first-trimester threatened miscarriage and 80 healthy controls. Among the threatened miscarriage cases, 80 resulted in miscarriage and 80 progressed to childbirth. Platelet-derived hemostatic indices – mean platelet volume (MPV), platelet distribution width (PDW), platelet-large cell ratio (P-LCR), platelet mass index (PMI), plateletcrit (PCT), and platelet-to-albumin ratio (PAR) – were evaluated. Receiver operating characteristic (ROC) analysis was used to assess discriminative performance.

MPV, PDW, P-LCR, and PMI were significantly higher in patients with threatened miscarriage compared with controls (all $p < 0.05$). ROC analysis demonstrated modest but significant discrimination for threatened miscarriage for MPV (AUC=0.601), PDW (AUC=0.585), P-LCR (AUC=0.586), and PMI (AUC=0.586). Within the threatened miscarriage cohort, PAR (AUC=0.641, $p=0.002$) and MPV (AUC=0.596, $p=0.035$) showed significant ability predicting progression to miscarriage.

Platelet-derived hemostatic indices are associated with threatened miscarriage and may provide prognostic information regarding subsequent pregnancy loss. Given their low cost and routine availability, these indices may serve as adjunctive tools for early risk stratification, although prospective studies are needed to confirm their clinical utility.

Keywords: Platelet-derived hemostatic indices, Threatened miscarriage, Mean platelet volume, Platelet distribution width, Platelet mass index, Platelet-large cell ratio, Platelet albumin ratio

Introduction

Threatened miscarriage (TM), defined as vaginal bleeding with or without abdominal pain before 20 weeks of gestation in the presence of a closed cervix and confirmed fetal cardiac activity, is one of the most frequent and clinically significant complications of early pregnancy (1). It presents a substantial challenge for obstetric care by creating significant uncertainty in both clinical management and prognostic counseling. Affecting approximately 20–25% of all pregnancies, TM is

associated with a markedly increased risk of pregnancy loss, with affected women exhibiting a 2.6-fold higher likelihood of miscarriage and up to half of these pregnancies ending in loss (2,3).

Normal placental implantation requires a balanced interaction between trophoblast invasion and maternal hemostatic regulation at the maternal-fetal interface. During early gestation, remodeling of the spiral arteries depends on controlled platelet activation to maintain adequate placental perfusion. Excessive platelet activation and microthrombus formation can disrupt this

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Received: 16.02.2026, Accepted: 25.09.2026

process, leading to microvascular obstruction, impaired trophoblastic invasion, and local decidual bleeding (4,5). Platelet-derived hemostatic indices, including mean platelet volume, platelet distribution width, platelet mass index, and platelet-large cell ratio, reflect platelet activation and thrombotic potential, providing a biological link between altered hemostasis and defective implantation in TM (6).

In this context, the present study aimed to evaluate whether platelet-derived hemostatic indices, reflecting maternal hemostatic and thrombotic activity, are altered in pregnancies complicated by TM. We also sought to determine the ability of these indices to distinguish TM from uncomplicated pregnancies and to predict progression to pregnancy loss. By focusing on routinely available platelet-derived hemostatic indices, this study explores a practical approach to improving early risk stratification in women presenting with TM.

Materials and Methods

This retrospective study was conducted between December 1, 2023 and December 1, 2024. Ethics approval was obtained from the ethics committee of the institution (Approval number: AESH-BADEK-2025-129). The study was conducted in accordance with the Declaration of Helsinki. Informed consent was waived due to the retrospective design of the study, in accordance with institutional policy.

Based on the effect size (0.67) reported by Akin et al., an a priori power analysis was performed using G*Power software (version 3.1.9.7; Heinrich Heine University Düsseldorf, Düsseldorf, Germany), which indicated that a minimum of 59 patients per group would be required to achieve adequate statistical power (6). To enhance the robustness of the analyses, the study was intentionally designed with an expanded sample size. Accordingly, a total of 240 pregnant women who met the inclusion criteria were consecutively enrolled starting December 1, 2023, comprising the first 80 patients diagnosed with TM in the first trimester who subsequently experienced pregnancy loss, the first 80 patients with TM whose pregnancies progressed to childbirth, and 80 healthy pregnant women who served as the control group. Women aged between 18 and 45 years with a singleton pregnancy who were diagnosed with TM in the first trimester with confirmed fetal cardiac activity were eligible for inclusion in the study. Patients with maternal age

below 18 years or above 45 years, multiple gestation, a diagnosed fetal genetic anomaly, or incomplete laboratory or demographic data were excluded from the study.

Demographic characteristics, including maternal age, gravidity, parity, body mass index, smoking status, and obstetric history, as well as laboratory parameters and pregnancy outcomes, were obtained retrospectively from the hospital's electronic medical record system and recorded for all participants. Laboratory data included complete blood count parameters and biochemical measurements, with particular emphasis on platelet-derived hemostatic indices: mean platelet volume (MPV), platelet distribution width (PDW), platelet-large cell ratio (P-LCR), platelet mass index (PMI), plateletcrit (PCT), and platelet-albumin ratio (PAR). Pregnancy and neonatal outcome data included mode of delivery, gestational age at delivery, birth weight, Apgar scores at 1 and 5 minutes, admission to the neonatal intensive care unit, preterm birth, respiratory outcomes, and composite adverse perinatal outcomes.

PMI and PAR were calculated using the following formulas: Platelet Mass Index (PMI) = Platelet count (PLT) x Mean platelet volume (MPV)(fl/nl) / 10³, Platelet to Albumin ratio (PAR) = Platelet count / Albumin (g/dl).

Neonatal outcomes were compared between patients with TM who subsequently delivered and the control group using a composite adverse perinatal outcome (CAPO) measure. CAPO was defined as the occurrence of at least one of the following adverse neonatal events: admission to the neonatal intensive care unit, a 5-minute Apgar score below 7, respiratory distress syndrome, transient tachypnea of the newborn, requirement for continuous positive airway pressure, requirement for mechanical ventilation, need for phototherapy, intraventricular hemorrhage, neonatal hypoglycemia, neonatal sepsis, or low birth weight, defined as a birth weight below 2500 g.

All statistical analyses were carried out using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). The distribution of continuous variables was evaluated with the Kolmogorov-Smirnov test. Data showing a normal distribution were summarized as mean $\pm$ standard deviation, whereas non-normally distributed variables were reported as median with interquartile range (Q1-Q3). Comparisons of categorical variables were performed using the Pearson chi-square test or Fisher's exact test,

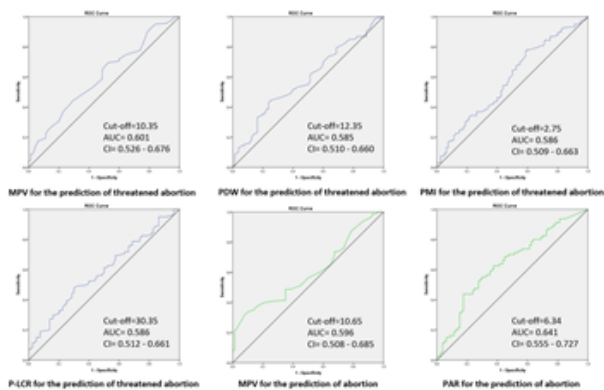


Fig. 1. ROC curves for the prediction of threatened miscarriage in the study group and for the prediction of miscarriage in threatened miscarriage groups

when appropriate. For continuous variables, between-group comparisons were conducted using the Student's *t* test for normally distributed data and the Mann–Whitney *U* test for non-normally distributed data. Receiver operating characteristic (ROC) curve analysis was applied to determine the discriminative performance of relevant parameters, with optimal cut-off values defined according to the Youden index. Statistical significance was set at a two-sided *p* value of <0.05 for all analyses.

Results

A total of 240 patients were studied, including 160 with TM and 80 control patients. Eighty of the 160 patients with TM progressed to pregnancy loss. The demographic characteristics of the cohort are shown in Table 1. There is no statistically significant difference between the groups in terms of age, body mass index, gravidity, parity, history of miscarriage, or smoking status.

Birth characteristics and neonatal outcomes are presented in Table 2. Patients who experienced TM but resulted in childbirth delivered at a significantly earlier gestational age than controls ($p<0.001$). The rate of cesarean delivery was higher in the TM group (72.5% vs. 56.3%, $p=0.032$). Neonates of patients who experienced TM during pregnancy had lower birth weights than controls ($p=0.007$) and were more frequently admitted to the NICU (20% vs. 7.5%, $p=0.022$). Additionally, the rate of composite adverse perinatal outcomes was higher in this group (22.5% vs. 10%, $p=0.032$), as were rates of preterm birth (25% vs. 11.3%, $p=0.024$) and respiratory distress syndrome (8.8% vs. 0%, $p=0.007$). No statistically significant difference

was found between the Apgar scores of the newborns.

Compared with controls, patients with TM had significantly higher median values of MPV (10.6 vs. 10.3 fL, $p=0.011$), PDW (12.4 vs. 12.05, $p=0.032$), P-LCR (30.55 vs. 27.95, $p=0.029$), and PMI (2.80 vs. 2.67, $p=0.030$). No significant differences were found for PCT, MPV/PLT ratio, PDW/PLT ratio or PAR (Table 3).

ROC analysis was performed to identify TM and showed that MPV (AUC=0.601, $p=0.011$), PDW (AUC=0.585, $p=0.032$), P-LCR (AUC=0.586, $p=0.029$), and PMI (AUC=0.586, $p=0.030$) had modest but statistically significant discriminative ability. An MPV cut-off of ≥ 10.35 fL yielded a sensitivity of 65% and a specificity of 51.3%, while PDW ≥ 12.35 , P-LCR ≥ 30.35 , and PMI ≥ 2.75 showed sensitivities of 51.9%, 52.5%, and 54.4%, and specificities of 60%, 60%, and 56.3%, respectively. Other platelet indices did not demonstrate significant predictive performance (Table 4).

Within the TM cohort, both PAR and MPV showed statistically significant, albeit modest, discrimination for predicting progression to miscarriage (AUC = 0.641, $p=0.002$ for PAR; and AUC=0.596, $p=0.035$ for MPV). A PAR cut-off of ≥ 6.34 provided a sensitivity of 56.3% and specificity of 67.5%, while an MPV cut-off of ≥ 10.65 fL provided a sensitivity of 51.3% and specificity of 55%. The remaining platelet-associated indices did not show significant predictive performance (Table 5).

Discussion

In this study, platelet-derived hemostatic indices were systematically evaluated to differentiate TM from uncomplicated pregnancy and to assess the risk of progression to pregnancy loss among the TM cohort, providing a comprehensive perspective on their clinical relevance in early pregnancy. We found that PDW, MPV, P-LCR and PMI were significantly associated with the presence of TM compared with healthy controls, whereas PAR and MPV demonstrated discriminatory ability for predicting pregnancy loss among patients who experienced TM. While previous studies have predominantly investigated platelet-related indices as surrogate markers of systemic inflammation, our study evaluated platelet-derived hemostatic indices with a specific focus on platelet function and hemostatic balance within early pregnancy.

Table 1: Comparison of Maternal Characteristics Among The Threatened Miscarriage and Control Groups

	Threatened miscarriage n= 160 (66.7%)	Control n= 80 (33.3%)	p value
Maternal age (year)	28.9 ± 5.1	27.8 ± 5.2	0.128a
Gravidity	2 (1-3)	2 (1-3)	0.736b
Parity	1 (0-2)	1 (0-2)	0.305b
Nulliparous	85 (53.1%)	44 (55.5%)	0.784c
Abortion history	46 (28.7%)	16 (20%)	0.144c
Smoking	3 (1.9%)	3 (3.8%)	0.380c
Height (cm)	161.9 ± 5.7	160.9 ± 6.9	0.244a
Weight (kg)	73.5 ± 14.2	75.8 ± 13.5	0.247a
BMI (kg/m2)	28.1 ± 5.1	29.3 ± 4.9	0.084a

Data are expressed as n (%), mean ± SD or median (Q1-Q3) where appropriate. A p value of <0.05 indicates a significant difference and statistically significant p-values are in bold. BMI: Body mass index, ^a: Student t-test, ^b: Mann Whitney-U test, ^c: Pearson chi-square test, ^d: Fisher's exact test.

Table 2: Birth Characteristics and Neonatal Outcomes of Newborns Threatened Miscarriage and Control Group

	Threatened miscarriage without miscarriage n= 80 (50%)	Control n= 80 (50%)	p value
Gestational age at delivery (week)	38 (37-39)	39 (38-40)	<0.001a
Cesarean section	58 (72.5%)	45 (56.3%)	0.032b
Gender			0.874b
Female	39 (48.8%)	38 (47.5%)	
Male	41 (51.2%)	42 (52.5%)	
Birth weight (gram)	2941 ± 548	3162 ± 466	0.007c
Apgar score at 1st minute	9 (9-9)	9 (9-9)	0.385a
Apgar score at 5th minute	10 (10-10)	10 (10-10)	0.390a
NICU admission	16 (20%)	6 (7.5%)	0.022b
CAPO	18 (22.5%)	8 (10%)	0.032b
Transient tachypnea of the newborn	4 (5%)	4 (5%)	1d
Neonatal sepsis	0 (0%)	0 (0%)	NA
Fetal distress	7 (8.8%)	7 (8.8%)	1b
Preterm birth	20 (25%)	9 (11.3%)	0.024b
Respiratory distress syndrome	7 (8.8%)	0 (0%)	0.007d
Continues positive airway pressure	10 (12.5%)	4 (5%)	0.160d
Mechanical ventilation	3 (3.8%)	0 (0%)	0.245d
Phototherapy for neonates	5 (6.3%)	3 (3.8%)	0.719d
Neonatal hypoglycemia	1 (1.3%)	0 (0%)	1d
Intraventricular hemorrhage	0 (0%)	0 (0%)	NA

Data are expressed as n (%), mean ± SD or median (Q1-Q3) where appropriate. A p value of <0.05 indicates a significant difference and statistically significant p-values are in bold. NICU: Neonatal intensive care unit, CAPO: Composite adverse perinatal outcome, ^a: Mann Whitney-U test, ^b: Pearson chi-square, ^c: Student t-test, ^d: Fisher's exact test.

Table 3: Comparison of The Platelet Associated Indices In Threatened Miscarriage and Control Groups

	Threatened miscarriage n= 160 (66.7%)	Control n= 80 (33.3%)	p value
MPV	10.6 (9.9 - 11.3)	10.3 (9.8 - 10.9)	0.011a
PCT	0.28 (0.25 - 0.33)	0.27 (0.24 - 0.31)	0.063a
PDW	12.4 (10.9 - 13.8)	12.05 (10.6 - 12.75)	0.032a
P-LCR	30.55 (24.6 - 36.1)	27.95 (23.1 - 32.9)	0.029a
MPV/PLT ratio	0.040 (0.034 - 0.047)	0.041 (0.034 - 0.047)	0.728a
PDW/PLT ratio	0.046 (0.038 - 0.056)	0.046 (0.039 - 0.055)	0.980a
PMI	2.80 (2.50 - 3.29)	2.67 (2.32 - 3.09)	0.030a
PAR	6.12 (5.20 - 7.32)	6.57 (5.56 - 7.79)	0.098a

Data are expressed as median (Q1-Q3). A p value of <0.05 indicates a significant difference and statistically significant p-values are in bold. MPV: Mean platelet volume, PCT: Plateletcrit, PDW: Platelet distribution width, P-LCR: Platelet-larger cell ratio, PLT: Platelet, PMI: Platelet mass index, PAR: Platelet albumin ratio, *: Mann whitney-U test.

Table 4: Evaluation of Platelet Associated Indices In Threatened Miscarriage and Control Groups For Prediction of Threatened Abortion by Using ROC Analysis

	LR+	LR-	Cut-off*	Sensitivity	Specificity	AUC	%95 CI	P-value
MPV	1.34	0.68	≥10.35	65%	51.3%	0.601	0.526 - 0.676	0.011
PCT	-	-	-	-	-	0.574	0.497 - 0.650	0.063
PDW	1.30	0.80	≥12.35	51.9%	60%	0.585	0.510 - 0.660	0.032
P-LCR	1.31	0.79	≥30.35	52.5%	60%	0.586	0.512 - 0.661	0.029
MPV/PLT ratio	-	-	-	-	-	0.514	0.436 - 0.592	0.728
PDW/PLT ratio	-	-	-	-	-	0.501	0.424 - 0.578	0.980
PMI	1.24	0.81	≥2.75	54.4%	56.3%	0.586	0.509 - 0.663	0.030
PAR	-	-	-	-	-	0.565	0.488 - 0.643	0.098

*Cut-off values were found according to Youden index, LR+: Positive likelihood ratio, LR-: Negative likelihood ratio, AUC: Area under the curve, CI: Confidence Interval, MPV: Mean platelet volume, PCT: Plateletcrit, PDW: Platelet distribution width, P-LCR: Platelet-larger cell ratio, PLT: Platelet, PMI: Platelet mass index, PAR: Platelet albumin ratio

The findings of this study are particularly noteworthy when considered alongside a recent meta-analysis evaluating platelet indices in early pregnancy loss. That meta-analysis consistently identified PDW as significantly elevated in spontaneous miscarriage, whereas MPV showed substantial heterogeneity and did not demonstrate a consistent association across studies (7). Our results align with these observations by confirming that PDW as a marker associated with TM (AUC=0.585, p=0.032), while MPV showed significant, albeit modest, ability to distinguish TM from uncomplicated pregnancy (AUC=0.601, p=0.011) and to predict progression to pregnancy loss (AUC=0.596, p=0.035). This pattern suggests that platelet size heterogeneity, reflected by PDW, may be a more stable indicator of platelet

activation and hemostatic disturbance at the maternal-fetal interface, whereas MPV appears to be influenced by dynamic platelet turnover and compensatory hematopoietic responses, which may explain its inconsistent performance across studies. Importantly, by extending the analysis beyond isolated platelet indices, our study adds nuance to the meta-analytic findings and supports the hypothesis that platelet-derived hemostatic indices should be interpreted within a functional and mechanistic framework rather than as standalone inflammatory markers.

Mean platelet volume (MPV) has been extensively studied in early pregnancy complications; however, its clinical relevance in TM remains controversial. Several studies have reported elevated MPV values in cases of early pregnancy

Table 5: Evaluation of platelet associated indices in threatened miscarriage groups for prediction of miscarriage by using ROC analysis

	LR+	LR-	Cut-off*	Sensitivity	Specificity	AUC	%95 CI	P-value
MPV	1.14	0.88	≥10.65	51.3%	55%	0.596	0.508 - 0.685	0.035
PCT	-	-	-	-	-	0.501	0.411 - 0.591	0.978
PDW	-	-	-	-	-	0.548	0.457 - 0.639	0.295
P-LCR	-	-	-	-	-	0.549	0.457 - 0.640	0.286
MPV/PLT ratio	-	-	-	-	-	0.522	0.432 - 0.612	0.635
PDW/PLT ratio	-	-	-	-	-	0.540	0.449 - 0.631	0.383
PMI	-	-	-	-	-	0.566	0.477 - 0.655	0.151
PAR	1.73	0.65	≥6.34	56.3%	67.5%	0.641	0.555 - 0.727	0.002

*Cut-off values were found according to Youden index, LR+: Positive likelihood ratio, LR-: Negative likelihood ratio, AUC: Area under the curve, CI: Confidence Interval, MPV: Mean platelet volume, PCT: Plateletcrit, PDW: Platelet distribution width, P-LCR: Platelet-larger cell ratio, PLT: Platelet, PMI: Platelet mass index, PAR: Platelet albumin ratio

loss, suggesting increased platelet reactivity and thrombotic tendency, whereas others have not demonstrated a significant association (7–10). In the present study, MPV was significantly higher in patients with threatened miscarriage than in healthy controls; however, its standalone discriminative performance was limited. This finding suggests that MPV may not be a reliable marker for the initial presence of TM, but may become clinically relevant as pathological placentation processes advance toward irreversible pregnancy failure. Given that MPV reflects platelet size and turnover rather than platelet heterogeneity or total hemostatic burden, its performance may be influenced by compensatory thrombopoiesis and temporal fluctuations, which could explain the inconsistent results reported in the literature. From this perspective, although MPV is susceptible to short-term physiological fluctuations, the relatively chronic and progressive nature of the processes leading to pregnancy loss may make MPV more suitable for predicting progression to miscarriage rather than for identifying TM at initial.

Platelet mass index (PMI), calculated by integrating platelet count and mean platelet volume, has been proposed as a surrogate marker of overall platelet mass and thrombotic burden rather than isolated platelet activation. Previous studies have suggested an association between elevated PMI and placentation-related disorders, such as preeclampsia, supporting its potential role in reflecting sustained hemostatic stress during pregnancy (11). In the context of TM, however, data remain limited. A study by Uckan et al. showed that patients who experienced missed abortions had higher PMI values compared to the control group (12). In the study, PMI demonstrated a significant association with the presence of TM (AUC=0.586, $p=0.030$) but not

progression to pregnancy loss ($p=0.151$). Taken together, these findings suggest that PMI may reflect the hemostatic alterations accompanying the clinical presentation of TM, but lacks sufficient discriminatory capacity to predict which pregnancies will subsequently progress to loss.

PAR is a composite marker that integrates platelet burden with serum albumin levels, thereby reflecting both hemostatic activity and microvascular homeostasis (13). In a study by Okutucu et al., PAR was higher in the group that experienced TM compared to the control group (2). In this study, PAR was not significantly associated with the presence of TM compared to healthy controls ($p=0.098$) but importantly, emerged as a predictor of progression to pregnancy loss among patients with TM (AUC=0.641, $p=0.002$). These findings are consistent with the literature and suggest that impaired intravascular oncotic balance and platelet-mediated microcirculatory dysfunction may contribute to defective implantation.

P-LCR reflects the proportion of large, metabolically and functionally active platelets in circulation and is considered an indicator of increased platelet reactivity and thrombotic potential (14). P-LCR has been associated with obstetric pathologies such as preeclampsia. Studies by Li et al. and Umezulike et al. found that P-LCR values were higher in preeclampsia patients than in the control group (for both $p<0.001$) (15,16). However, no studies directly investigating P-LCR in TM have been identified in the literature. In our study, P-LCR was significantly associated with the presence of TM (AUC=0.586, $p=0.029$) but did not predict progression to pregnancy loss among affected patients ($p=0.286$). Several limitations should be acknowledged. The single-center design may limit generalizability. Additionally, platelet indices were measured at a

single time point, which precludes assessment of dynamic changes during pregnancy. Future prospective, multicenter studies with longitudinal measurements are warranted to validate these findings and to explore whether combining platelet-derived hemostatic indices with clinical or biochemical markers can further enhance predictive performance.

In conclusion, this study demonstrates that platelet-derived hemostatic indices are differentially associated with both the presence of TM and the risk of subsequent pregnancy loss. While MPV, PDW, P-LCR, and PMI reflecting platelet heterogeneity and reactivity were associated with the clinical presentation of TM, PAR and MPV showed prognostic value in predicting progression to pregnancy loss among patients with TM. These findings support the concept that alterations in maternal hemostasis and platelet-related microvascular regulation play a relevant role in early pregnancy complications, possibly via implantation. Given their low cost and routine availability, platelet-derived hemostatic indices may serve as useful adjunctive tools for early risk stratification in TM; however, prospective studies are needed to confirm their clinical utility and to define their role within comprehensive predictive models.

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