ORIGINAL RESEARCH ARTICLE

Predictive value of platelet distribution width, neutrophil-to-lymphocyte ratio, and alanine aminotransferase for recurrence of pregnancy loss in early gestation

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Abstract

This study aimed to evaluate the value of combined platelet distribution width, neutrophil-to-lymphocyte ratio, and alanine aminotransferase detection in predicting recurrence risk among patients with recurrent pregnancy loss in early pregnancy. A retrospective case-control study was conducted among 305 patients with early pregnancy RPL from January 2024 to May 2025. Patients were divided into a pregnancy loss group (n=116) and a live birth group (n=189). Peripheral blood platelet distribution width, neutrophil-to-lymphocyte ratio, alanine aminotransferase, and related laboratory parameters were compared between the groups. Platelet distribution width, neutrophil-to-lymphocyte ratio, and alanine aminotransferase levels were significantly higher in the pregnancy loss group than in the live birth group. Multivariate logistic regression identified platelet distribution width, neutrophil-to-lymphocyte ratio, and alanine aminotransferase as independent risk factors for recurrent pregnancy loss. Receiver operating characteristic analysis showed that the combined platelet distribution width+neutrophil-to-lymphocyte ratio+alanine aminotransferase model had an area under the curve of 0.706, outperforming any single marker. These findings suggest that combined detection of platelet distribution width, neutrophil-to-lymphocyte ratio, and alanine aminotransferase may provide a simple and effective tool for early risk stratification in patients with recurrent pregnancy loss, reflecting potential platelet activation, inflammatory immune imbalance, and hepatic metabolic stress. *(Afr J Reprod Health 2026; 30 [16]:81-92).*

Keywords: Recurrent pregnancy loss; early pregnancy; platelet distribution width; neutrophil-lymphocyte ratio; alanine aminotransferase; recurrence risk; predictive value

Résumé

Cette étude visait à évaluer la valeur de la détection combinée de la largeur de distribution plaquettaire (Platelet Distribution Width, PDW), du rapport neutrophiles/lymphocytes (Neutrophil-to-Lymphocyte Ratio, NLR) et de l'alanine aminotransférase (ALT) pour prédire le risque de récidive chez les patientes présentant des pertes de grossesse récurrentes (Recurrent Pregnancy Loss, RPL) en début de grossesse.Une étude rétrospective cas-témoins a été menée auprès de 305 patientes atteintes de RPL en début de grossesse entre janvier 2024 et mai 2025. Selon l'issue de la grossesse, les patientes ont été réparties en un groupe perte de grossesse (n = 116) et un groupe naissance vivante (n = 189). Les paramètres biologiques, notamment la largeur de distribution plaquettaire, le rapport neutrophiles/lymphocytes, l'alanine aminotransférase et d'autres indicateurs de laboratoire associés, ont été comparés entre les deux groupes.Les taux de PDW, de NLR et d'ALT étaient significativement plus élevés dans le groupe perte de grossesse que dans le groupe naissance vivante. L'analyse de régression logistique multivariée a identifié la PDW, le NLR et l'ALT comme des facteurs de risque indépendants de perte de grossesse récurrente. L'analyse de la courbe ROC a montré que le modèle combinant PDW + NLR + ALT présentait une aire sous la courbe (AUC) de 0,706, supérieure à celle obtenue avec chacun des marqueurs pris isolément.Ces résultats suggèrent que la détection combinée de la PDW, du NLR et de l'ALT pourrait constituer un outil auxiliaire simple, efficace et économique pour la stratification précoce du risque chez les patientes présentant des pertes de grossesse récurrentes, en reflétant une éventuelle activation plaquettaire, un déséquilibre immuno-inflammatoire et un stress métabolique hépatique.*(Afr J Reprod Health 2026; 30 [16]: 81-92).*

Mots-clés : Pertes de grossesse récurrentes ; début de grossesse ; largeur de distribution plaquettaire ; rapport neutrophiles/lymphocytes ; alanine aminotransférase ; risque de récidive ; valeur prédictive

Introduction

Recurrent Pregnancy Loss (RPL) generally refers to the occurrence of two or more consecutive pregnancy losses with the same partner[1]. It is a common clinical complication, affecting about 1% to 5% of pregnancies[2]. The etiology is complex and multifactorial, involving genetic, anatomical, immunological, hormonal, and environmental factors.[3] However, the cause is unidentified in approximately 50% of cases, which are classified as "idiopathic".[4] This poses significant challenges for early prediction, precise intervention, and prognosis assessment in clinical practice.[5] The first trimester represents a critical window for embryo implantation, development, and placentation. The successful maintenance of pregnancy during this stage is vital for the final outcome. Therefore, exploring biomarkers that can non-invasively, and conveniently assess the risk of pregnancy loss in RPL patients holds significant clinical value for achieving early risk stratification and personalized management.

In recent years, the roles of systemic inflammatory response, prothrombotic state, and metabolic abnormalities in the pathogenesis of RPL have garnered increasing attention. The neutrophil-to-lymphocyte ratio (NLR), serving as a composite indicator that comprehensively reflects neutrophil-dominated systemic inflammation and lymphocyte-mediated immune regulation, has been found to be abnormally elevated in miscarriage and associated with an increased risk of its occurrence[6]. Platelet distribution width (PDW) is a parameter reflecting the heterogeneity of platelet volume in peripheral blood[7]. Elevated PDW often indicates increased platelet activation, and higher PDW has been shown to predict the risk of RPL.[8] Alanine aminotransferase (ALT) is a classic indicator of liver cell damage. It may have physiological changes during normal pregnancy, but abnormal elevation may also indicate potential metabolic liver disease or systemic stress, which may indirectly affect the stability of the internal environment of pregnancy.[9] At present, although some studies have explored the correlation between inflammatory markers, coagulation-related parameters or liver function and RPL, there are few studies on the combination of PDW, NLR and ALT to systematically evaluate their predictive value for the risk of pregnancy recurrence in the early pregnancy of RPL patients. Based on this, the purpose of this study was to investigate the changes of PDW, NLR and ALT levels in peripheral blood of patients with RPL in early pregnancy by retrospective analysis, and to further evaluate the efficacy of single and combined detection of the above indicators in evaluating the risk of pregnancy loss in patients with RPL in early pregnancy by multivariate regression analysis and receiver operating characteristic curve (ROC).

Methods

Study subjects

A total of 305 patients with RPL in their first trimester, who attended the Gynecology Outpatient Department of Chuzhou Integrated Traditional Chinese and Western Medicine Hospital between January 2024 and May 2025, were enrolled in this study. Based on pregnancy outcomes, eligible subjects were divided into the following two groups. The pregnancy loss group included patients with a history of RPL who experienced a recurrent embryo or fetal loss before 28 weeks of gestation in the current pregnancy, confirmed clinically (including missed abortion confirmed by ultrasound, inevitable abortion, or incomplete abortion).

The live birth group included patients with a history of RPL whose current pregnancy resulted in a live birth, confirmed by follow-up through delivery. RPL refers to the occurrence of two or more consecutive pregnancy losses with the same partner. In this study, patients have experienced at least two consecutive pregnancy losses (including biochemical pregnancies) prior to the current pregnancy with the same partner would be considered as RPL. Pregnancy loss was confirmed by ultrasound (absence of fetal heartbeat, empty gestational sac, or missed miscarriage), histopathological examination of products of conception, or clinical assessment (inevitable or incomplete abortion). All patients completed standardized RPL etiology screening before enrollment: (1)Anatomical factors: transvaginal ultrasound, if necessary, hysteroscopy, excluding uterine malformations, intrauterine adhesions; (2)Genetic factors: chromosome karyotype analysis

of both husband and wife, excluding chromosomal abnormalities; (3) Endocrine factors: TSH, FT4, TPOAb, fasting blood glucose, insulin and sex hormones were detected to evaluate thyroid function, glucose metabolism and luteal function; (4)Immune thrombosis factors: detection of antiphospholipid antibody spectrum (aCL, β2-GPI, LA), coagulation function, exclusion of antiphospholipid syndrome; (5)Infection factors: TORCH, vaginal secretion detection, excluding acute infection.

Inclusion criteria: (1) Age between 20 and 40 years; (2) History of RPL meeting the diagnostic criteria for RPL[10]; (3) Singleton pregnancy in the current pregnancy; (4) Peripheral blood samples collected and complete blood count as well as liver function tests performed at our hospital during the first trimester (4–12 weeks of gestation); (5) Complete clinical data with definitive follow-up records of pregnancy outcomes.

Exclusion criteria: (1) RPL clearly explained by a single etiology (e.g., confirmed parental chromosomal structural abnormalities, definite uterine anatomical malformations requiring surgical correction, confirmed antiphospholipid syndrome, etc.); (2) Pregnancy conceived via assisted reproductive technology (ART); (3) Complicated with acute or chronic infectious diseases (e.g., active phase of viral hepatitis, active TORCH infection, etc.); (4) Severe hepatic, renal, cardiac, or pulmonary dysfunction, or hematological disorders; (5) Use of medications during the first trimester that may affect CBC or LFT results (e.g., anticoagulants, glucocorticoids, immunosuppressants, etc.); (6) Presence of severe hyperemesis gravidarum or other pregnancy complications during the first trimester that could interfere with liver function test results; (7) Incomplete clinical data or loss to follow-up.

Collection of clinical data

The clinical data of the subjects were collected through the hospital's electronic medical record system and structured follow-up records: (1) General demographic data: age, gravidity and parity, body mass index (BMI), smoking history, alcohol consumption history, gestational age at enrollment, etc.; (2) History of RPL: number of previous miscarriages; (3) Pregnancy outcomes: recording whether pregnancy loss occurred and the gestational age at loss; (4) Biochemical indicators: complete blood count, liver and kidney function parameters.

Sample collection and testing

For all subjects, 5 mL of cubital venous blood was collected in the morning under fasting conditions during their visit in the first trimester (4-12 weeks of gestation). The blood samples were aliquoted into EDTA anticoagulant tubes (for complete blood count) and plain biochemical tubes (for liver function tests) and were sent for analysis within 2 hours.

A Mindray BC-7500 automated hematology analyzer was used to detect white blood cell count (WBC), platelet count (PLT), platelet distribution width (PDW), hematocrit (HCT), hemoglobin (Hb), neutrophil count, lymphocyte count, and red blood cell count (RBC). The neutrophil-to-lymphocyte ratio (NLR) was calculated as neutrophil count / lymphocyte count. A Hitachi 7600 automatic biochemistry analyzer was used to detect alanine aminotransferase (ALT) and aspartate aminotransferase (AST). All tests were performed strictly in accordance with the instrument operating procedures and reagent instructions.

Quality control

To ensure the accuracy and reliability of the research data, the following quality control measures were implemented: (1) Standardization of sample collection and processing: All blood samples were collected in the morning under fasting conditions. Unified protocols for collection, transportation, processing, and testing were strictly followed, and all detection instruments were regularly calibrated. (2) Double-entry verification of data: Clinical and laboratory data were independently entered by two researchers and cross-checked for consistency. (3) Standardization of outcome determination: Pregnancy outcomes were independently determined by two senior obstetricians. Any discrepancies were resolved through discussion or consultation with a third expert to reach a consensus.

(4) Blinded assessment: Laboratory personnel were blinded to the clinical data and group allocation of the subjects.

Statistical analysis

Statistical analyses were performed using SPSS 27.0 software (IBM Corp., Armonk, NY, USA) and R software (version 4.2.2). The Shapiro-Wilk test was used to assess the normality of continuous variables ($P > 0.05$ indicated a normal distribution). Normally distributed data were expressed as mean ± standard deviation, and comparisons between groups were made using the independent samples t-test. Non-normally distributed data were expressed as median and interquartile range [M (P25, P75)], and comparisons were performed using the Mann-Whitney U test. Categorical variables were presented as frequencies and percentages, and group comparisons were conducted using the Chi-square test or Fisher's exact test. Pearson or Spearman correlation analysis was used to evaluate the correlations among PDW, NLR, and ALT levels. Univariate logistic regression analysis was performed with pregnancy loss as the dependent variable and various clinical indicators as independent variables to screen for potential predictors. Variables with $P < 0.10$ in the univariate analysis were included in the multivariate logistic regression model to identify independent risk factors for RPL in RPL patients, and odds ratios (OR) with 95% confidence intervals (CI) were calculated.

ROC curves were plotted to calculate the area under the curve (AUC), sensitivity, and specificity for each indicator alone and in combination. The DeLong test was used to compare the differences in AUC among the ROC curves. The optimal cut-off values for each indicator were determined using the Youden index (Youden index = Sensitivity + Specificity-1). All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant.

Ethical approval

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Medical Ethics Committee of Chuzhou Integrated Traditional Chinese and Western Medicine Hospital (Approval No. CZZXYLLSC-2026-10, approved on November 9, 2023). As this was a retrospective analysis of existing clinical data and specimens, and all procedures were part of standard care, the requirement for informed consent was waived by the ethics committee.

Results

Comparison of baseline characteristics between the two groups

A total of 305 eligible patients with a history of RPL were enrolled in this study. Of these, 116 were assigned to the pregnancy loss group (pregnancy loss) and 189 to the live birth group (continued pregnancy to live birth). There were no statistically significant differences in baseline characteristics between the two groups, indicating that they were comparable ($P > 0.05$) (Table 1).

Comparison of laboratory indicators between the two groups

The levels of PDW, NLR, and ALT in the live birth group were significantly lower than those in the pregnancy loss group ($P<0.05$). There were no statistically significant differences in PLT and WBC between the two groups ($P>0.05$). Similarly, coagulation parameters (INR, APTT, TT) showed no statistically significant differences ($P>0.05$), as shown in Table 2.

Correlation analysis among PDW, NLR, and ALT

Pearson correlation analysis was performed to evaluate the correlations among PDW, NLR, and ALT. PDW was moderately positively correlated with NLR (r=0.640, $P<0.001$) (Figure 1A). PDW showed a weak positive correlation with ALT (r=0.143, $P=0.012$) (Figure 1B), and NLR was weakly positively correlated with ALT (r=0.150, $P=0.009$) (Figure 1C).

Univariate analysis of RPL patients with pregnancy loss

Univariate logistic regression analysis was performed with pregnancy loss as the dependent

Table 1: Comparison of baseline characteristics between the two groups

Variables	Pregnancy loss group (n=116)	Live birth group (n=189)	t/χ^2	*P*-value
Age (years)	31.5±4.2	30.8±3.9	1.282	0.201
BMI (kg/m$^{2)}$	23.9±2.6	24.3±2.9	1.208	0.228
Parity (times)	0 (0,1)	0 (0,1)	0.442	0.506
Number of previous abortions (times)	2 (2,3)	2 (2,3)	1.505	0.220
Smoking history, n (%)	5 (4.3)	8 (4.2)	0.067	0.795
Drinking history, n (%)	23 (19.8)	25 (13.2)	2.361	0.124
Gestational weeks of enrollment	6.3±2.1	6.6±2.4	0.864	0.389

BMI: Body Mass Index

Table 2: Comparison of laboratory indicators between the two groups

Variables	Pregnancy loss group (n=116)	Live birth group (n=189)	t	*P*-value
WBC (10^9/L)	8.7 ± 3.7	8.5 ± 3.4	0.460	0.646
NLR	4.3 ± 1.9	3.7 ± 1.1	3.541	<0.001
RBC (10^{12}/L)	4.4 ± 0.3	4.4 ± 0.4	0.751	0.453
MCV (%)	87.2 ± 12.5	87.8 ± 8.5	0.466	0.642
PLT (10^9/L)	251.7 ± 54.3	259.6 ± 69.7	1.035	0.302
PDW (%)	16.6 ± 3.0	15.3 ± 1.6	4.74	<0.001
ALT (U/L)	21.3 ± 6.1	18.2 ± 5.2	4.776	<0.001
AST (U/L)	20.4 ± 4.6	19.8 ± 4.3	1.155	0.249
INR (%)	1.0 ± 0.1	1.0± 0.1	0.093	0.926
APTT (s)	32.7 ± 5.4	33.0 ± 4.7	0.504	0.614
TT (s)	15.0 ± 0.9	15.0 ± 0.9	0.219	0.826

WBC: White Blood Cell; NLR: Neutrophil-to-Lymphocyte Ratio; RBC: Red Blood Cell; MCV: Mean Corpuscular Volume; PLT: Platelet; PDW: Platelet Distribution Width; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; INR: International Normalized Ratio; APTT: Activated Partial Thromboplastin Time; TT: Thrombin Time

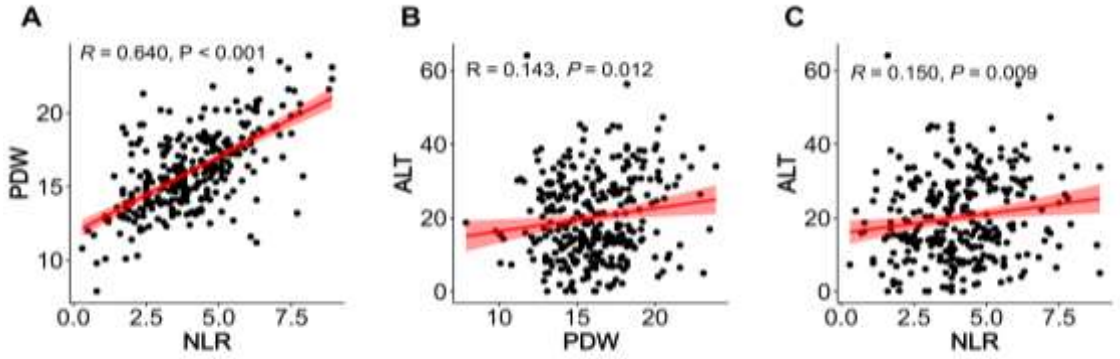

Figure 1: Correlation analysis among PDW, NLR, and ALT. A. The correlation scatter plot of PDW and NLR. B. The correlation scatter plot of PDW and ALT. C. The correlation scatter plot of ALT and NLR

variable and age, pre-pregnancy BMI, number of previous abortions, PDW, NLR, ALT and other variables as independent variables (Table 3). Univariate analysis showed that the number of previous abortions, PDW, NLR and ALT were significantly correlated with pregnancy loss (*P* <

Table 3: Univariate analysis of RPL patients with pregnancy loss

Variables	β	S.E	Z	*P*	OR (95% *CI*)	VIF
NLR	0.29	0.09	3.41	<.001	1.34 (1.13 ~ 1.58)	1.374
PDW	0.25	0.06	4.39	<.001	1.28 (1.15 ~ 1.43)	1.434
ALT	0.10	0.02	4.45	<.001	1.11 (1.06 ~ 1.16)	1.226
Parity	0.16	0.25	0.66	0.506	1.18 (0.73 ~ 1.91)	1.038
Number of previous abortions	0.41	0.23	1.83	0.067	1.51 (0.97 ~ 2.35)	1.062
Smoking history						1.039
No					1.00 (Reference)	
Yes	0.02	0.58	0.03	0.974	1.02 (0.33 ~ 3.19)	
Drinking history						1.030
No					1.00 (Reference)	
Yes	0.48	0.32	1.53	0.127	1.62 (0.87 ~ 3.02)	
Age	0.04	0.03	1.28	0.201	1.04 (0.98 ~ 1.10)	1.082
BMI	-0.05	0.04	-1.21	0.228	0.95 (0.87 ~ 1.03)	1.041
WBC	0.02	0.03	0.46	0.645	1.02 (0.95 ~ 1.09)	1.083
RBC	0.22	0.29	0.75	0.452	1.24 (0.71 ~ 2.19)	1.055
MCV	-0.01	0.01	-0.47	0.641	0.99 (0.97 ~ 1.02)	1.060
PLT	0	0	-1.03	0.301	1.00 (0.99 ~ 1.00)	1.051
AST	0.03	0.03	1.15	0.249	1.03 (0.98 ~ 1.09)	1.073
INR	-0.14	1.40	-0.10	0.922	0.87 (0.06 ~ 13.66)	1.063
APTT	-0.01	0.02	-0.51	0.613	0.99 (0.94 ~ 1.04)	1.033
TT	-0.03	0.14	-0.22	0.826	0.97 (0.74 ~ 1.27)	1.053

BMI: Body Mass Index; WBC: White Blood Cell; NLR: Neutrophil-to-Lymphocyte Ratio; RBC: Red Blood Cell; MCV: Mean Corpuscular Volume; PLT: Platelet; PDW: Platelet Distribution Width; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; INR: International Normalized Ratio; APTT: Activated Partial Thromboplastin Time; TT: Thrombin Tim

0.1). Other variables showed no significant association (Table 3).

Multivariate analysis of RPL patients with pregnancy loss

The variables with $P < 0.10$ in univariate analysis (previous abortion times, PDW, NLR, ALT) were included in the multivariate logistic regression model, and the independent risk factors were screened by forward stepwise regression method. The results are shown in Table 4. Multivariate analysis showed that PDW (OR = 1.19, 95 % *CI*: 1.05-1.34, $P = 0.006$), NLR (OR = 1.33, 95 % *CI*: 1.10-1.60, $P = 0.003$) and ALT (OR = 1.10, 95 % *CI*: 1.05-1.16, $P < 0.001$) were independent risk factors for early pregnancy loss in patients with RPL (Table 4). The number of previous abortions did not reach a statistically significant level in multivariate analysis ($P = 0.124$).

Predictive performance of PDW, NLR, and ALT alone

ROC curves were generated using PDW, NLR, and ALT as test variables and pregnancy loss as the state variable. The AUC and optimal cut-off values (based on the maximum Youden index) were calculated. For PDW, the AUC was 0.645 (95% *CI*: 0.576-0.715), with an optimal cut-off value of 17.65 fL (sensitivity 37.9%, specificity 92.6%).

For NLR, the AUC was 0.604 (95% *CI*: 0.533-0.675), with an optimal cut-off value of 4.75 (sensitivity 43.1%, specificity 79.9%). For ALT, the AUC was 0.647 (95% *CI*: 0.582-0.712), with an optimal cut-off value of 21.25 U/L (sensitivity 54.3%, specificity 60.8%). DeLong's test showed no statistically significant difference among the AUCs of PDW, NLR, and ALT ($P>0.05$) (Figure 2).

Predictive performance of the combined detection of PDW, NLR, and ALT

The combined predicted probability (P) derived from the multivariate logistic regression model was used as the test variable to plot ROC curves and evaluate the predictive efficacy of the combined detection. The results are shown in Figure 3. The AUC for the combination of all three markers was 0.706 (95% *CI*: 0.644-0.768). The AUCs for the combinations of NLR+PDW, NLR+ALT, and

Table 4: Multivariate analysis of RPL patients with pregnancy loss

Variables	β	S.E	Z	*P*	OR (95% *CI*)
NLR	0.28	0.10	2.96	0.003	1.33 (1.10 ~ 1.60)
PDW	0.17	0.06	2.75	0.006	1.19 (1.05 ~ 1.34)
ALT	0.10	0.03	3.81	<.001	1.10 (1.05 ~ 1.16)
Number of previous abortions	0.38	0.25	1.54	0.124	1.46 (0.90 ~ 2.38)

NLR: Neutrophil-to-Lymphocyte Ratio; PDW: Platelet Distribution Width; ALT: Alanine Aminotransferase

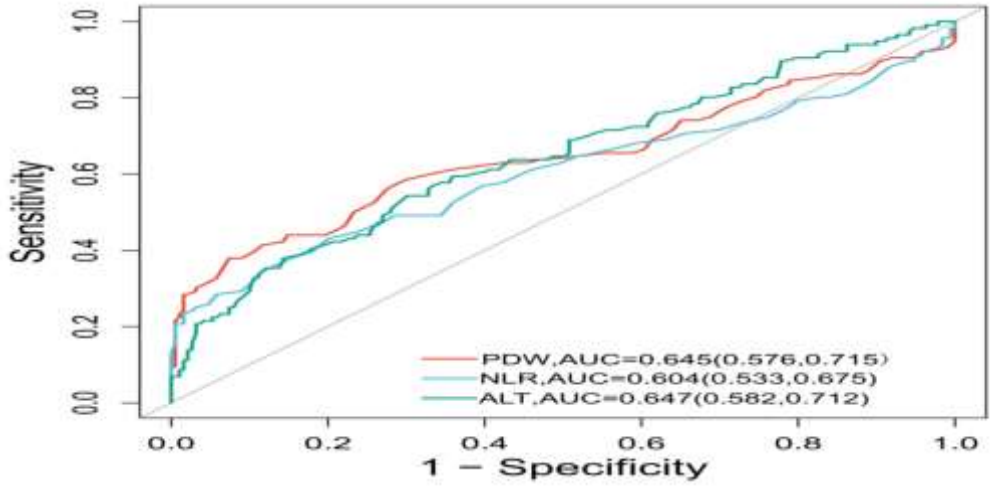

Figure 2: Predictive performance of PDW, NLR, and ALT alone. NLR: Neutrophil-to-Lymphocyte Ratio; PDW: Platelet Distribution Width; ALT: Alanine Aminotransferase; ROC: Receiver Operating Characteristic curve; AUC: Area Under the Curve

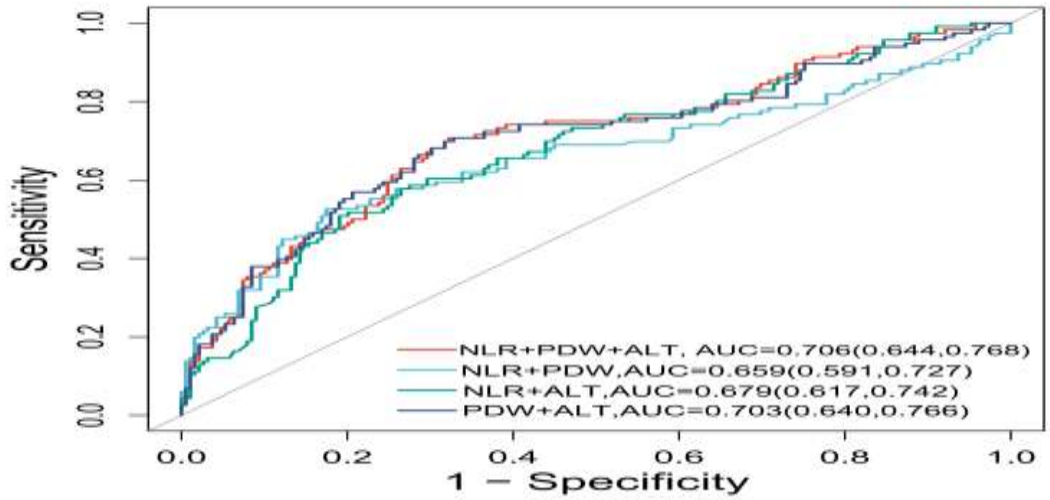

Figure 3: Predictive performance of the combined detection of PDW, NLR, and ALT. NLR: Neutrophil-to-Lymphocyte Ratio; PDW: Platelet Distribution Width; ALT: Alanine Aminotransferase; ROC: Receiver Operating Characteristic curve; AUC: Area Under the Curve

ALT+PDW were 0.659 (95% *CI*: 0.591-0.727), 0.679 (95% *CI*: 0.617-0.742), and 0.703 (95% *CI*: 0.640-0.766), respectively. No statistically significant difference was found among the AUCs of any pairwise combined detections (*P*>0.05).

However, the AUC of the NLR+ALT combination was significantly higher than that of NLR alone (Z=2.27, *P*=0.023). The AUC of the ALT+PDW combination was significantly higher than those of PDW alone (Z=2.31, *P*=0.021), NLR alone (Z=2.38, *P*=0.017), and ALT alone (Z=1.98, *P*=0.048). Furthermore, the AUC of the three-marker combination was significantly higher than those of PDW alone (Z=2.29, *P*=0.022), NLR alone (Z=2.89, *P*=0.004), and ALT alone (Z=2.09, *P*=0.037).

At the optimal cut-off values determined by the maximum Youden index, the sensitivity and specificity for the three-marker combination were 67.7% and 71.7%, respectively. For the NLR+PDW combination, sensitivity was 52.6% and specificity was 82.5%. For the NLR+ALT combination, sensitivity was 50.9% and specificity was 81.0%. For the ALT+PDW combination, sensitivity was 69.8% and specificity was 68.3%

Discussion

RPL represents one of the most challenging clinical issues in reproductive medicine, with a high incidence, complex etiology, and considerable psychological distress, which seriously affects the reproductive health and family well-being of couples of childbearing age.[11] In recent years, with the continuous progress of genetic testing technology, imaging examination methods and immunological diagnosis methods, the identifiable etiology of RPL has been expanded. However, there are still a large number of patients who cannot obtain a clear etiological diagnosis after detailed etiological screening. This high proportion of idiopathic state means that clinicians lack targeted therapeutic targets in the face of these patients and can only take empirical interventions. However, the existing evidence does not fully support that any empirical intervention program has a clear and effective effect.[5] In this context, it is particularly important to predict the risk of pregnancy loss in patients with RPL. This study found that the levels of PDW, NLR and ALT in early pregnancy were significantly higher in the pregnancy loss group than in the live birth group. Multivariate Logistic regression analysis showed that PDW, NLR and ALT were independent risk factors for RPL. More importantly, the combined predictive value of the three indicators was significantly better than that of any single marker alone. These findings suggest that a combined panel of PDW, NLR, and ALT can serve as a simple and practical tool for early risk stratification in RPL patients.

In this study, the PDW level in the pregnancy loss group was significantly higher than that in the live birth group, and multivariate logistic regression analysis showed that RPL was an independent risk factor for the recurrence of recurrent abortion, which was consistent with previous studies. A meta-analysis conducted by Shi et al.included 11 studies involving 1847 patients with unexplained recurrent pregnancy loss (URPL) and 2475 healthy women. The results showed that the PDW level in the URPL group was significantly higher than that in the control group[8]. The association mechanism between elevated PDW and the risk of RPL can be explained from the perspective of platelet activation and prethrombotic state. PDW is an index reflecting the heterogeneity of platelet size, and its increase is a characteristic manifestation of platelet activation[12]. Upon activation, platelets undergo an increase in volume and heterogeneity, while simultaneously releasing various procoagulant substances, such as platelet factors, the platelet glycoprotein IIb/IIIa (GPIIb/IIIa) receptor, and P-selectin.[13] During pregnancy, excessively activated platelets can promote the formation of microthrombi in the placental villi, thereby impairing placental perfusion and oxygen supply. This leads to embryonic ischemia and hypoxia, ultimately resulting in miscarriage.[14] Furthermore, activated platelets can activate immune cells by releasing inflammatory mediators, leading to endocrine dysfunction and exacerbating the inflammatory response at the maternal-fetal interface, which further impairs embryo implantation and development.[15,16] As RPL is a condition closely associated with both a prothrombotic state and chronic inflammation, elevated PDW effectively captures the intersection of these two pathological states.

The NLR level in the pregnancy loss group was also significantly higher than that in the live birth group, and NLR was confirmed as an independent risk factor for recurrent miscarriage, which is consistent with previous reports. A meta-analysis by Hantoushzadeh et al., incorporating 14 studies, clearly demonstrated that the standardized mean difference of NLR was significantly higher in the pregnancy loss group than in healthy controls, suggesting that NLR can serve as a simple and cost-effective auxiliary tool for the diagnosis of RPL.[17] The pathophysiological mechanism of RPL caused by elevated NLR can be explained from the perspective of inflammatory-immune imbalance. Neutrophils are the first line of defense of the body 's innate immune system.[18] Excessive activation of neutrophils can release a large amount of reactive oxygen species, proteases and pro-inflammatory cytokines (such as TNF-α, IL-6, IL-1β, etc.), causing damage to trophoblast cells and disrupting the homeostasis of the maternal-fetal interface microenvironment.[19] At the same time, lymphocytes (especially regulatory T cells) play a central role in maintaining maternal-fetal immune tolerance by inhibiting rejection of semi-allogeneic fetuses and protecting embryos from maternal immune system attacks.[20] The relative reduction of lymphocyte count can weaken this protective mechanism and break the state of immune tolerance. Therefore, the increase of NLR not only directly reflects the enhancement of pro-inflammatory state (increase of neutrophils), but also indirectly indicates the impairment of immune regulation function (relative decrease of lymphocytes). The superposition of the two can lead to the imbalance of inflammatory microenvironment at the maternal-fetal interface and increase the risk of embryo rejection or injury.

In the present study, ALT was significantly higher in the pregnancy loss group and was identified as an independent risk factor for RPL, providing new evidence for the metabolic etiology of RPL. Elevated ALT indicates potential liver cell damage or metabolic stress. In non-pregnant population, elevated ALT is most common in metabolic dysfunction-associated fatty liver disease (MASLD), which is a liver manifestation of metabolic syndrome and is closely related to insulin resistance, obesity, dyslipidemia and hypertension.[21] It is worth noting that the prevalence of MASLD in women of childbearing age worldwide has increased significantly in the past three decades.[22] Although large-scale prospective studies on the direct relationship between ALT and RPL are still limited, Zhu et al.'s research shows that there is a causal relationship between ALT and spontaneous abortion, and the increase of ALT level indicates that it plays a role in oxidative stress.[23] This inflammatory response may also affect placental blood perfusion and change the environment for fetal growth and development, thereby increasing the risk of miscarriage.[24]

The most important finding of this study was that the combined detection of PDW, NLR, and ALT achieves significantly better predictive performance than any single marker. The sensitivity and specificity of combined detection reached a high level under the optimal cutoff value. The theoretical advantages of joint detection can be understood from several aspects. The first is pathophysiological complementarity. RPL is a multifactorial disorder resulting from interactions among anatomical, endocrine, immune, and metabolic factors[25-27]. Even if the cases classified as ' unexplained ' after detailed etiological screening, there may be a variety of subclinical abnormalities behind them. PDW reflects platelet activation and prethrombotic state, NLR reflects inflammatory immune imbalance, and ALT reflects metabolic stress state. The combination of the three just covers the three core pathological pathways of RPL, so as to identify those high-risk patients who have not yet reached the abnormal threshold in a single dimension but have slight abnormalities in multiple dimensions. Secondly, synergistic amplification: insulin resistance activates platelets and the coagulation system[28]. Microthrombus formation can aggravate tissue ischemia and inflammation. Therefore, when the three indicators rise at the same time, the risk is not a simple accumulation, but there is a multiplier amplification effect. Finally, cost-effectiveness: PDW, NLR, and ALT are derived from routine complete blood count and liver function tests, requiring no specialized equipment or reagents. Compared with complex machine learning models[29], this panel is inexpensive, rapid, and highly suitable for clinical application in primary and resource-limited medical settings. This low-cost and high-efficiency feature makes the joint prediction model

of this study particularly suitable for promotion and application in primary medical institutions with limited resources, and has good health economics benefits.

The strengths of this study are primarily reflected in the following aspects. First, to our knowledge, this is the first study to jointly apply three routine and cost-effective blood indicators—PDW, NLR, and ALT—for early risk prediction of RPL. Second, the combined predictive model achieved an AUC of 0.706, which was significantly superior to any single indicator. This highlights the complementary advantages of using multiple markers across three pathological pathways: pre-thrombotic state, inflammatory-immune imbalance, and metabolic stress. Finally, by implementing rigorous quality control measures (including independent double-entry, blinded outcome assessment, and clear exclusion of known single-factor etiologies), we minimized bias as much as possible within a retrospective design. Ultimately, this provides primary healthcare institutions with a simple, economical, and effective tool for early risk stratification.

The study also has some limitations. This study is a retrospective design, and its inherent selection bias and information bias are difficult to completely avoid. There is a lack of independent external validation queues, and the generalization ability of the model needs to be further verified. The sample size of this study is limited, which may affect the stability of regression coefficients and the accuracy of cut-off values. Although the main confounding factors have been screened, subclinical indicators such as thyroid autoantibodies and insulin resistance index have not been included in multivariate analysis. In the future, it may be considered to integrate demographic characteristics with laboratory indicators to further optimize predictive performance.

The implications of our findings for policy and practice are as follows:In clinical practice, the combined detection of PDW, NLR, and ALT can be promoted as a simple and cost-effective risk stratification tool for recurrent pregnancy loss (RPL) during early pregnancy. This approach helps identify patients with "unexplained" RPL and guides individualized monitoring and empirical treatment. From a health policy perspective, these findings support the integration of such routine inflammatory-metabolic indicators into the basic evaluation pathway for RPL. This would facilitate early screening in primary healthcare institutions, alleviate the financial and logistical burdens on patients, and provide an evidence base for medical insurance reimbursement and health economic evaluations. Furthermore, we call for multi-center prospective studies and dynamic monitoring to generate higher-level evidence-based recommendations, ultimately optimizing the comprehensive management strategies for RPL.

Conclusion

PDW, NLR and ALT have a potential auxiliary screening value in predicting the risk of recurrence in RPL patients in early pregnancy. The combined prediction model based on the three is simple, economical and effective, which can be popularized and applied in clinical practice, and provide scientific basis for early risk stratification and individualized intervention decision-making in patients with RPL. It is suggested that the predictive efficacy of the model should be further confirmed and optimized through prospective multicenter studies and external validation in the future.

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Author contributions

Zhifang H designed and performed the research and wrote the paper; Haixia Z designed the research and supervised the report; Junwei Y designed the research and contributed to the analysis;Yun W and Qili Z provided clinical advice and supervised the report.

Confict of interests

The authors declare that they have no competing interests.

Data availability

Constrained by research ethics, personal privacy protection and related confidentiality agreements, the original data of this study does not support full public disclosure, so as to avoid compliance risks caused by data leakage. However, the effective data set processed by desensitization and deidentification can support all the conclusions of this study and can be used for compliance research. Relevant researchers can contact the correspondent to obtain the corresponding data after making a reasonable application, submitting a compliant use instruction and signing a data confidentiality agreement. All data use is limited to academic research, and commercial use, tampering and secondary dissemination are strictly prohibited.

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