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ORIGINAL RESEARCH

Association Between Red Cell Distribution Width-Coefficient of Variation (RDW-CV) and Bacterial Vaginosis: A Cross-Sectional Study and External Validation

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Purpose: Bacterial vaginosis (BV) is a common condition resulting from vaginal microbiota dysbiosis. The red cell distribution width-coefficient of variation (RDW-CV) is a hematological parameter derived from routine blood tests, indicating the variation in red blood cell size. This study aimed to investigate the correlation between RDW-CV and BV.

Patients and Methods: Data were derived from NHANES (2001–2004), a U.S. national survey. Propensity score matching balanced group differences. Associations were evaluated using conditional logistic regression and restricted cubic splines. XGBoost identified key predictors, and mediation analysis explored serum uric acid's role. For external validation, consistency analysis used MIMIC-IV, where the outcome was "vaginitis" per ICD codes due to data limitations.

Results: In the NHANES study, a positive correlation was found between elevated RDW-CV and BV. Individuals in the highest RDW-CV quartile had significantly higher odds of BV compared to those in the lowest quartile (OR=1.565, 95% CI: 1.128–2.173, P=0.007), after adjusting for confounders. Findings were consistent across subgroups and supported by RCS. Mediation analysis revealed that serum uric acid, a marker linked to inflammation and oxidative stress, mediated 5.81% of this relationship. In the MIMIC cohort, RDW-CV was positively associated with vaginitis (OR=4.265, 95% CI: 1.129–16.117, P=0.0325), but caution is advised due to the wide confidence interval resulting from the limited number of vaginitis cases (n=87).

Conclusion: This study revealed a significant positive association between elevated RDW-CV and BV, partially corroborated by external validation. The consistent directional trends observed across cohorts reinforce this association. However, the broader outcome definition in the MIMIC database presents an inherent limitation. Causality cannot be established due to the cross-sectional design, underscoring the need for prospective studies.

Keywords: bacterial vaginosis, RDW-CV, cross-sectional study, NHANES, mediation analysis

Introduction

Bacterial vaginosis (BV) ranks among the most prevalent vaginal conditions in women of childbearing age, with a global prevalence of approximately 25%.[1] This condition poses a significant challenge, especially in resource-limited regions. BV, characterized by an imbalance in vaginal microbiota, increases the risk of premature birth, spontaneous abortion, infertility, postoperative infections in obstetrics and gynecology, as well as HIV and other sexually transmitted infections.[2–4]These complications severely impact women's quality of life. Statistics indicate that the global annual cost of treating BV exceeds 4.8 billion US dollars.[1] Consequently, addressing BV-related issues has become a critical public health challenge.

Current understanding acknowledges BV as a complex disorder of the vaginal microbiome. It involves not only microbial shifts but also host immune-inflammatory responses, with host factors critically influencing clinical outcomes.[5] This emerging paradigm highlights the importance of examining systemic inflammatory markers in relation to BV risk.[6]

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Currently, clinical diagnosis primarily depends on the Nugent score and Amsel criteria. However, these methods are subjective and limited, lacking objective biological markers for early detection. These constraints hinder their utility for large-scale screening and early risk identification. Exploring the relationship between readily available biological indicators, such as blood routine parameters, and BV may help identify individuals at higher risk and guide future research on BV risk assessment.

Red cell distribution width (RDW) measures the variability in red blood cell size and is commonly expressed as the coefficient of variation (RDW-CV) or the standard deviation (RDW-SD).[7] RDW-CV, calculated as (standard deviation of red blood cell volume/mean corpuscular volume) × 100%, normalizes for MCV variations, offering a more standardized assessment of anisocytosis in the context of systemic inflammation compared to RDW-SD.[8] Recently, researchers have identified its close association with inflammation and oxidative stress, suggesting its potential as a prognostic marker for various chronic diseases.[9–11] BV is linked to vaginal inflammation and systemic oxidative stress.[12] Consequently, it is hypothesized that RDW-CV might be associated with the risk of BV. However, epidemiological evidence supporting this association remains insufficient.

Existing studies have linked systemic inflammatory markers[13] and hematological indicators[14,15] to the occurrence of BV. Nonetheless, the specific relationship between RDW-CV and BV has not been extensively studied. This study addresses this gap by investigating the association between RDW-CV and BV using large-sample NHANES data from 2001 to 2004. Additionally, we examine whether serum uric acid, an indicator of oxidative stress and inflammation, mediates this relationship. These findings may offer new insights for BV risk assessment and mechanistic research of BV.

Materials and Methods

Research Population and Data Sources

The National Health and Nutrition Examination Survey(NHANES) database is an ongoing cross-sectional survey in the United States, sanctioned by the Centers for Disease Control and Prevention (CDC), aimed at evaluating the health and nutritional status of non-institutionalized American civilians. Conducted biennially, this survey employs a multi-stage probability sampling method that involves home visits, physical examinations, and the collection of biological samples at the Mobile Examination Center (MEC). NHANES has secured ethical approval and informed consent from participants.[16]

This study analyzed data from two periods between 2001 and 2004. Initially, 3,323 participants were considered; however, we excluded 803 samples without BV data and 91 samples missing RDW-CV indicators. Ultimately, 2,429 participants were included: 888 were patients with BV, and 1,541 formed the control group (see Figure 1). The data for this study are accessible through the publicly available NHANES data files.

Definition of the Main Variables

Diagnosis of BV

The Nugent scoring method diagnoses BV by evaluating the quantities of Lactobacillus, Gardnerella, and anaerobic bacteria in vaginal secretions through Gram staining. This method assigns a score ranging from 0 to 10. Scores of 7 to 10 indicate a positive diagnosis for BV, while scores from 0 to 6 indicate a negative result.[5]

RDW-CV Index

RDW-CV is calculated as (standard deviation of red blood cell volume / mean corpuscular volume) × 100%.[7] Theoretically, RDW-CV and RDW share similar clinical significance. Participants were categorized into four groups based on RDW-CV quartiles: Q1 (<1.32%), Q2 (1.32–1.4%), Q3 (1.4–1.51%), and Q4 (≥1.51%), with Q1 serving as the reference group.

Covariates

Covariates were collected using structured questionnaires and laboratory tests. Sociodemographic variables included race and the poverty-to-income ratio (PIR). Health-related factors comprised body mass index (BMI), smoking history,

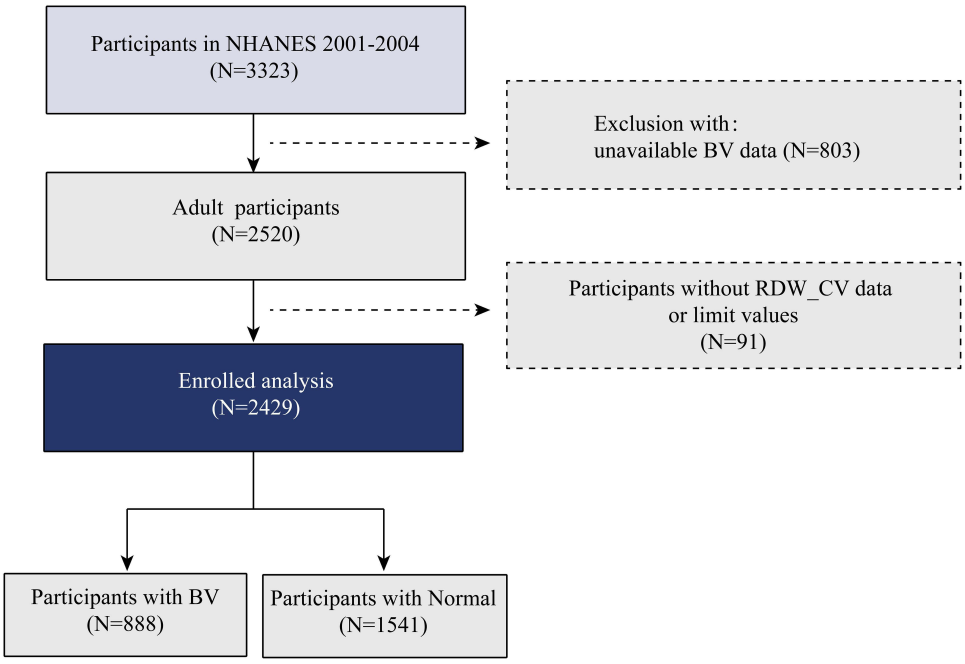

Figure 1 Flowchart of the participant selection process from the NHANES 2001–2004 database. A total of 3,323 participants were initially identified from the NHANES 2001–2004 cycles. After excluding 803 individuals with unavailable Bacterial Vaginosis (BV) data, 2,520 adult participants remained. Further exclusion of 91 participants due to missing or limit values for RDW-CV data resulted in a final study population of 2,429 participants, consisting of 888 individuals with BV and 1,541 individuals in the normal (control) group.

C-reactive protein (CRP), lymphocyte count, neutrophil percentage, globulin, red blood cell count, and uric acid.[14] These metabolic and inflammatory markers were selected because systemic physiological stress and glucose metabolism disturbances (eg., glycated hemoglobin) can alter the vaginal microenvironment, potentially predisposing individuals to dysbiosis. To ensure a rigorous selection process, we first screened candidate variables using univariate logistic regression (Table S13), including those with $P < 0.05$ in the final models. Furthermore, to ensure model stability and avoid over-fitting, a multicollinearity test was performed; all included covariates demonstrated a Variance Inflation Factor (VIF) <4 (Table S14), indicating no significant collinearity.

Data Processing and Statistical Analysis

Missing Data Interpolation

In this study, we employed the Classification and Regression Tree (CART) algorithm within the Chain Equation Multiple Imputation Method (MICE) to address missing data. We conducted five iterations of imputation using the mice package (version 3.15.0) in R software. Ensuring the original data's distribution characteristics were preserved, as verified by the K–S test ($P>0.05$), we filled missing values in variables with a missing rate of ≤20% using the terminal node observations of the decision tree. This algorithm effectively handles both categorical and continuous variables, maintaining the stability of the interpolation results.

Propensity Score Matching

Propensity Score Matching (PSM) is a statistical technique designed to address data bias and confounding variables in observational studies, facilitating a more reasonable comparison between experimental and control groups. PSM is widely applied in fields such as medicine, public health, and economics to align baseline characteristics. In this study, a 1:1 PSM ratio was utilized to ensure comparability of baseline data between the disease and control groups. This approach aimed to minimize the influence of baseline data on research outcomes, thereby enhancing the robustness and accuracy of the analytical results.

Statistical Analysis Methods

In this study, we utilized R software (version 4.5.0) for all data processing and analysis. Baseline characteristics were described by expressing continuous variables as mean ± standard deviation (SD) and categorical variables as frequency and percentage. To assess feature differences across various RDW-CV query arrays, we employed the Wilcoxon rank-sum test for continuous variables and either the chi-square test or Fisher's exact test for categorical variables. For datasets with missing data (less than 20% missing), we applied the multiple imputation method (m=5 iterations) for data processing. To identify key predictive factors for BV, we developed an extreme gradient boosting (XGBoost) machine learning model. This model enabled us to screen the most predictive features using variable importance scores and to stratify and interact subgroups. All statistical analyses were performed using two-sided tests, with a significance threshold set at $p<0.05$.

Correlation Analysis

Conditional logistic regression analyzed the association between RDW-CV and BV. Three models were constructed: the Crude Model was unadjusted; Model 1 adjusted for race, BMI, smoking history; and Model 2 adjusted for race,BMI, smoking history, C-reactive protein, globulin, lymphocyte count, percentage of neutrophils, red blood cell count, uric acid. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated, and trend tests were conducted.

Nonlinear verification involved constructing a conditional logistic regression model, utilizing restricted cubic splines (RCS) to examine the nonlinear relationship between RDW-CV and BV.

To assess prediction importance, we employed the XGBoost machine learning model with a learning rate of 0.08 and a maximum depth of 6. The model's tree number accounted for 80% of the total. We evaluated the significance of RDW-CV in predicting BV by analyzing the average SHAP value.

Robustness verification involved conducting subgroup analyses based on age, race, and BMI. Heterogeneity was assessed through interaction tests. Sensitivity analysis was performed by employing the "deleting missing values" method.

To analyze the mediating effect, we utilized the "mediation" package in R 4.5.0, considering serum uric acid as the mediating variable. We adjusted for age, race, and PIR to evaluate how relevant indicators mediate the relationship between RDW-CV and BV. For the mediating effect to be valid, it must demonstrate significant direct, indirect, and total effects, as well as a significant proportion of the effect being mediated.

Results

Overview of Research Analysis

The analytical workflow comprised two phases: primary analyses quantifying the RDW-CV and bacterial vaginosis association using NHANES data with conditional logistic regression, propensity score matching, and restricted cubic splines; followed by secondary exploratory analyses assessing feature importance with XGBoost, biological pathways via mediation analysis, and findings robustness through consistency analysis in the MIMIC-IV database.

Baseline Characteristics

To address missing values, multiple imputation was performed (Table S1). Prior to propensity score matching (PSM), significant baseline imbalances existed between the BV and control groups across most demographic and clinical parameters ($P < 0.05$; Table 1 and Table S2). After 1:1 PSM, a matched cohort of 1,776 participants (888 per group) was established. Covariate balance was assessed using standardized mean differences (SMD; Figure S4). Following matching, variables including age (P=0.14) and PIR (P=0.78) were well-balanced (SMD < 0.1). Specifically, 42.85% of matched participants (n=761) were from low-income households (PIR ≤ 1.3), with no intergroup difference (Table S3).

However, residual imbalances persisted for race and BMI ($P < 0.001$; Table 1; Figure S4), which were subsequently adjusted as covariates in multivariable regression models. After controlling for these and other metabolic factors, RDW-CV remained an independent risk factor for BV (Model 2, Q4: OR = 1.565, 95% CI: 1.128–2.173, P = 0.007; Table 2). This association was robust in sensitivity analyses (Table S5), confirming stability across adjustment strategies.

Table 1 Baseline Characteristics of the Participants Before and After Propensity Score Matching (PSM)

Variable	Before PSM				After PSM			
	Overall N = 2,429	BV N = 888	Normal N = 1,541	p-value	Overall N = 1,776	BV N = 888	Normal N = 888	p-value
Age	31.18 (9.81)	31.22 (10.14)	31.16 (9.62)	0.97	30.85 (9.94)	31.22 (10.14)	30.47 (9.73)	0.14
Race				<0.001				<0.001
Mexican American	589 (24.25%)	215 (24.21%)	374 (24.27%)		506 (28.49%)	215 (24.21%)	291 (32.77%)	
Non-Hispanic Black	546 (22.48%)	323 (36.37%)	223 (14.47%)		546 (30.74%)	323 (36.37%)	223 (25.11%)	
Non-Hispanic White	1,101 (45.33%)	277 (31.19%)	824 (53.47%)		554 (31.19%)	277 (31.19%)	277 (31.19%)	
Other Hispanic	103 (4.24%)	41 (4.62%)	62 (4.02%)		99 (5.57%)	41 (4.62%)	58 (6.53%)	
Other Race	90 (3.71%)	32 (3.60%)	58 (3.76%)		71 (4.00%)	32 (3.60%)	39 (4.39%)	
PIR				<0.001				0.78
≤ 1.3	873 (35.94%)	375 (42.23%)	498 (32.32%)		761 (42.85%)	375 (42.23%)	386 (43.47%)	
1.3–3.5	870 (35.82%)	325 (36.60%)	545 (35.37%)		636 (35.81%)	325 (36.60%)	311 (35.02%)	
> 3.5	686 (28.24%)	188 (21.17%)	498 (32.32%)		379 (21.34%)	188 (21.17%)	191 (21.51%)	
Height,cm	162.45 (6.78)	162.53 (6.74)	162.41 (6.80)	0.58	161.95 (6.78)	162.53 (6.74)	161.36 (6.77)	<0.001
Weight,kg	73.81 (19.94)	77.03 (21.54)	71.95 (18.71)	<0.001	74.75 (20.58)	77.03 (21.54)	72.47 (19.31)	<0.001
Waist circumstance,cm	92.21 (16.53)	94.41 (17.26)	90.93 (15.95)	<0.001	93.20 (16.91)	94.41 (17.26)	91.98 (16.48)	0.005
BMI	27.95 (7.24)	29.14 (7.82)	27.27 (6.80)	<0.001	28.46 (7.42)	29.14 (7.82)	27.79 (6.94)	<0.001
Smoking History				<0.001				<0.001
NonSmoked	1,442 (59.37%)	487 (54.84%)	955 (61.97%)		1,078 (60.70%)	487 (54.84%)	591 (66.55%)	
Smoked	987 (40.63%)	401 (45.16%)	586 (38.03%)		698 (39.30%)	401 (45.16%)	297 (33.45%)	
Alanine aminotransferase ALT,U/L	21.24 (41.95)	20.71 (13.51)	21.54 (51.66)	0.42	21.64 (48.55)	20.71 (13.51)	22.57 (67.32)	0.13
Albumin,g/L	41.03 (4.06)	40.91 (3.76)	41.11 (4.22)	0.005	40.97 (3.94)	40.91 (3.76)	41.03 (4.11)	0.040
Albumin urine,ug/mL	21.22 (94.05)	24.18 (85.55)	19.51 (98.60)	<0.001	23.57 (103.70)	24.18 (85.55)	22.97 (119.16)	<0.001
Aspartate aminotransferase AST,U/L	21.68 (12.09)	22.31 (13.14)	21.31 (11.43)	0.010	21.76 (13.07)	22.31 (13.14)	21.21 (12.98)	0.004
Blood Urea Nitrogen,mg/dL	9.95 (3.75)	9.91 (3.61)	9.98 (3.84)	0.86	9.81 (3.64)	9.91 (3.61)	9.72 (3.68)	0.23
C-reactive protein,mg/dL	0.49 (0.83)	0.56 (0.95)	0.45 (0.74)	<0.001	0.51 (0.89)	0.56 (0.95)	0.45 (0.82)	0.006
Chloride,mmol/L	103.78 (2.41)	103.88 (2.37)	103.72 (2.44)	0.093	103.82 (2.43)	103.88 (2.37)	103.76 (2.48)	0.34
Globulin,g/L	31.12 (4.02)	31.99 (4.31)	30.62 (3.76)	<0.001	31.65 (4.07)	31.99 (4.31)	31.30 (3.78)	0.002
Glycohemoglobin	5.25 (0.63)	5.30 (0.65)	5.22 (0.62)	<0.001	5.29 (0.70)	5.30 (0.65)	5.28 (0.74)	0.008
Hematocrit (%)	39.28 (3.46)	39.06 (3.69)	39.41 (3.31)	0.027	39.11 (3.54)	39.06 (3.69)	39.16 (3.39)	0.71
Hemoglobin,g/dL	13.34 (1.23)	13.20 (1.35)	13.42 (1.15)	<0.001	13.25 (1.28)	13.20 (1.35)	13.30 (1.20)	0.21
Lymphocyte count,1000 cells/uL	2.19 (0.66)	2.27 (0.69)	2.14 (0.64)	<0.001	2.22 (0.67)	2.27 (0.69)	2.17 (0.64)	0.003
Mean cell hemoglobin,pg	30.25 (2.34)	29.73 (2.66)	30.56 (2.07)	<0.001	29.99 (2.44)	29.73 (2.66)	30.26 (2.18)	<0.001
Mean Cell Hgb Conc,g/dL	33.95 (0.81)	33.77 (0.87)	34.05 (0.76)	<0.001	33.86 (0.83)	33.77 (0.87)	33.95 (0.77)	<0.001
Mean platelet volume,fL	8.25 (0.90)	8.30 (0.91)	8.22 (0.89)	0.087	8.29 (0.91)	8.30 (0.91)	8.28 (0.92)	0.72

(*Continued*)

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Table 1 (Continued).

Variable	Before PSM				After PSM			
	Overall N = 2,429	BV N = 888	Normal N = 1,541	p-value	Overall N = 1,776	BV N = 888	Normal N = 888	p-value
Mononuclear cell count	0.53 (0.17)	0.54 (0.18)	0.53 (0.17)	0.11	0.54 (0.17)	0.54 (0.18)	0.53 (0.17)	0.11
Neutrophil count	4.83 (2.01)	4.78 (1.99)	4.85 (2.03)	0.58	4.78 (1.99)	4.78 (1.99)	4.78 (1.99)	0.96
Percentage of neutrophils	60.50 (9.70)	59.50 (10.10)	61.07 (9.42)	<0.001	59.99 (9.85)	59.50 (10.10)	60.49 (9.59)	0.049
Platelet count	284.96 (68.99)	289.63 (70.92)	282.27 (67.73)	0.005	286.76 (68.17)	289.63 (70.92)	283.90 (65.22)	0.081
Potassium,mmol/L	3.91 (0.30)	3.93 (0.29)	3.91 (0.31)	0.010	3.92 (0.30)	3.93 (0.29)	3.91 (0.31)	0.039
Red blood cell count,million cells/uL	4.42 (0.39)	4.45 (0.40)	4.40 (0.39)	0.005	4.43 (0.40)	4.45 (0.40)	4.40 (0.39)	0.014
Sodium,mmol/L	138.20 (2.10)	138.27 (2.03)	138.16 (2.14)	0.26	138.21 (2.13)	138.27 (2.03)	138.15 (2.21)	0.37
Total Calcium,mg/dL	9.37 (0.37)	9.39 (0.38)	9.36 (0.37)	0.12	9.37 (0.38)	9.39 (0.38)	9.36 (0.37)	0.11
Total Cholesterol,mg/dL	192.54 (42.13)	190.15 (42.65)	193.92 (41.77)	0.028	191.44 (42.28)	190.15 (42.65)	192.74 (41.90)	0.19
Total Protein,g/dL	7.21 (0.52)	7.29 (0.53)	7.17 (0.52)	<0.001	7.26 (0.52)	7.29 (0.53)	7.23 (0.52)	0.073
Triglycerides refrig serum,mg/dL	116.46 (97.42)	117.79 (118.89)	115.69 (82.60)	0.52	116.23 (98.03)	117.79 (118.89)	114.67 (71.35)	0.35
Uric acid,mg/dL	4.35 (1.04)	4.49 (1.10)	4.27 (1.00)	<0.001	4.37 (1.05)	4.49 (1.10)	4.25 (0.97)	<0.001
White blood cell count,1000 cells/uL	7.77 (2.34)	7.82 (2.34)	7.75 (2.34)	0.38	7.76 (2.32)	7.82 (2.34)	7.70 (2.30)	0.31
Diabetes				0.24				0.51
No	2,344 (96.50%)	852 (95.95%)	1,492 (96.82%)		1,707 (96.11%)	852 (95.95%)	855 (96.28%)	
Borderline	14 (0.58%)	8(0.90%)	6(0.39%)		12 (0.68%)	8(0.90%)	4(0.45%)	
Yes	71 (2.92%)	28 (3.15%)	43 (2.79%)		57 (3.21%)	28 (3.15%)	29 (3.27%)	
Hypertension				0.056				0.38
No	2,102 (86.54%)	753 (84.80%)	1,349 (87.54%)		1,519 (85.53%)	753 (84.80%)	766 (86.26%)	
Yes	327 (13.46%)	135 (15.20%)	192 (12.46%)		257 (14.47%)	135 (15.20%)	122 (13.74%)	
RDW-CV	1.44 (0.23)	1.49 (0.27)	1.41 (0.21)	<0.001	1.46 (0.25)	1.49 (0.27)	1.43 (0.22)	<0.001

Notes: Data are presented as mean (standard deviation) for continuous variables and as frequency (percentage) for categorical variables.

Abbreviations: BV, Bacterial Vaginosis; PIR, poverty income ratio; BMI, body mass index; RDW-CV, red blood cell distribution width coefficient of variation; PSM, propensity score matching.

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Primary Analysis: Association Between RDW-CV and Bacterial Vaginosis

Conditional logistic regression demonstrated a significant positive association between RDW-CV and BV risk. In the unadjusted model, participants in the highest RDW-CV quartile (Q4: ≥1.51) had significantly higher BV odds versus the lowest quartile (OR=2.372, 95% CI: 1.791–3.143, P<0.001). This association persisted after adjusting for race, BMI, and smoking history (Model 1, Q4: OR=1.626, 95% CI: 1.189–2.225, P=0.002) and further adjusting for clinical and metabolic factors (Model 2, Q4: OR=1.565, 95% CI: 1.128–2.173, P=0.007). Trend tests using quartile medians as a continuous variable confirmed a dose-response relationship across all models (all P for trend ≤0.003; Table 2).

Restricted cubic spline (RCS) analysis with three knots confirmed a significant overall association in all models (all P for overall <0.001; Figure 2A–C). Non-linearity was not significant (P=0.291, 0.474, and 0.525 for crude, Model 1, and Model 2, respectively), indicating a positive linear relationship where BV prevalence increases with RDW-CV levels.

Exploratory Machine Learning Analysis and Feature Importance

In the XGBoost machine learning model, RDW-CV ranked first in importance with a mean SHAP value of 0.0297, substantially higher than uric acid (0.0136), percentage of neutrophils (0.0083), and total protein (0.0075) among the nine variables analyzed (eight covariates plus RDW-CV; Figure 3A). The SHAP dependence plot revealed a positive correlation: increasing RDW-CV was associated with higher SHAP values, indicating greater BV likelihood (Figure 3B).

Population Distribution and Subgroup Analyses

The research results indicated that the prevalence of BV increased progressively across the quartiles of RDW-CV (Figure 4A). Specifically, the fourth quartile group (Q4) exhibited the highest prevalence at 62.39%, while the first quartile group (Q1) had the lowest at 42.12%. Additionally, the prevalence rate was notably highest among the non-Hispanic black population (Figure 4B).

Subgroup analysis revealed that the predictive value of RDW-CV for BV risk was consistent across all subgroups. Furthermore, interaction analysis demonstrated that the association strength between RDW-CV and BV did not significantly vary among the subgroups, as indicated by an interaction P value greater than 0.05 (Figure 5).

Robustness Check: Sensitivity Analysis

To assess the reliability of our research findings, we conducted a sensitivity analysis by excluding missing values. The analysis demonstrated that our conclusions were highly robust. After matching age and PIR using PSM analysis, the total sample size consisted of 1,258 cases, with 629 in the BV group and 629 in the control group. Post-PSM matching, the correlation between RDW-CV and BV remained significant (P < 0.001) (Table S4). In the conditional logistic regression model, RDW-CV showed a significant positive correlation with the risk of BV. Quartile analysis of RDW-CV in the unadjusted Crude Model indicated that, compared to Q1, the OR value for Q4 was 2.228 (95% CI: 1.616–3.07, P < 0.001). In Model 1, the OR for Q4 was 2.169 (95% CI: 1.572–2.995, P < 0.001), and in Model 2, the OR was 1.95 (95% CI: 1.212–3.137, P = 0.0059). The P for trend test was significant across all models (Crude Model: P < 0.001; Model 1: P < 0.001; Model 2: P = 0.0191) (Table S5), confirming the stability of the dose-response relationship even after excluding missing values.

Exploratory Mediation Analysis of the Association Between RDW-CV and BV

This study performed a mediation analysis to investigate the link between serum uric acid and BV. The analysis revealed that serum uric acid mediated 5.81% of the relationship between RDW-CV and BV. The total effect was 0.2687 (P < 0.001), while the direct effect was 0.2532 (P < 0.001). The indirect effect was measured at 0.0155 (P < 0.001) (Table S6, Table S7 and Figure 6). This suggests that uric acid-related pathways may contribute to the association between RDW-CV and BV, warranting further investigation.

Table 2 Association Between RDW-CV and the Prevalence of Bacterial Vaginosis (BV) in Different Models

Characteristic			Crude Model			Model 1			Model 2		
	Exposure cutoff	Case (%)	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
RDW- CV											
RDW-CV continuous			3.39	(2.173,5.286)	P < 0.001	1.712	(1.076,2.724)	0.023	1.633	(1.003,2.659)	0.049
RDW-CV quantile											
Q1 (low)	< 1.32	444 (25%)	Ref	Ref		Ref	Ref		Ref	Ref	
Q2	1.32-< 1.4	444 (25%)	1.096	(0.84,1.43)	0.499	1.115	(0.845,1.473)	0.441	1.085	(0.817,1.44)	0.574
Q3	1.4-< 1.51	444 (25%)	1.485	(1.137,1.939)	0.004	1.447	(1.09,1.919)	0.011	1.375	(1.025,1.845)	0.034
Q4 (high)	≥ 1.51	444 (25%)	2.372	(1.791,3.143)	P < 0.001	1.626	(1.189,2.225)	0.002	1.565	(1.128,2.173)	0.007
p for trend					P < 0.001			P < 0.001			0.003

Notes: Data are presented as Odds Ratio (OR) and 95% Confidence Interval (CI). Crude Model: Unadjusted model. Model 1: Adjusted for Race, BMI, and Smoking History. Model 2: Adjusted for Race, BMI, Smoking History, C-reactive protein, Globulin, Lymphocyte count, Percentage of neutrophils, Red blood cell count, and Uric acid.

Abbreviations: BV, Bacterial Vaginosis; RDW-CV, Red blood cell distribution width coefficient of variation; OR, odds ratio; CI, confidence interval.

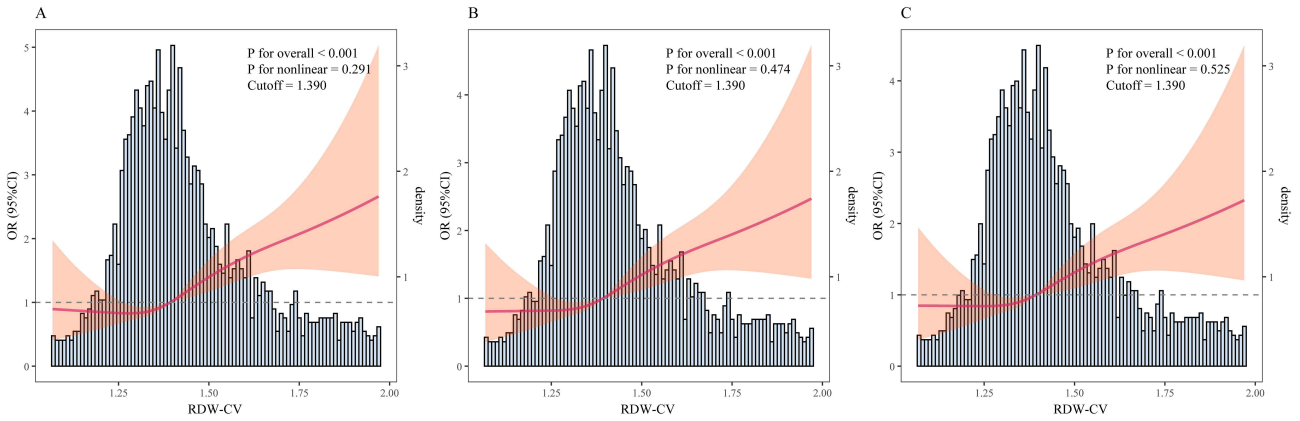

Figure 2 Restricted cubic spline (RCS) plots of the association between RDW-CV and Bacterial Vaginosis (BV). The solid lines represent the estimated odds ratios (ORs), and the shaded areas represent the 95% confidence intervals (CIs). The density plots at the bottom show the distribution of RDW-CV. (**A**) Crude Model (unadjusted); (**B**) Model 1, adjusted for race, BMI, and smoking history; (**C**) Model 2, adjusted for race, BMI, smoking history, C-reactive protein, globulin, lymphocyte count, percentage of neutrophils, red blood cell count, and uric acid. In all three models, the P for overall association was < 0.001, while the P for non-linearity was 0.291, 0.474, and 0.525, respectively, indicating a consistent linear dose-response relationship.

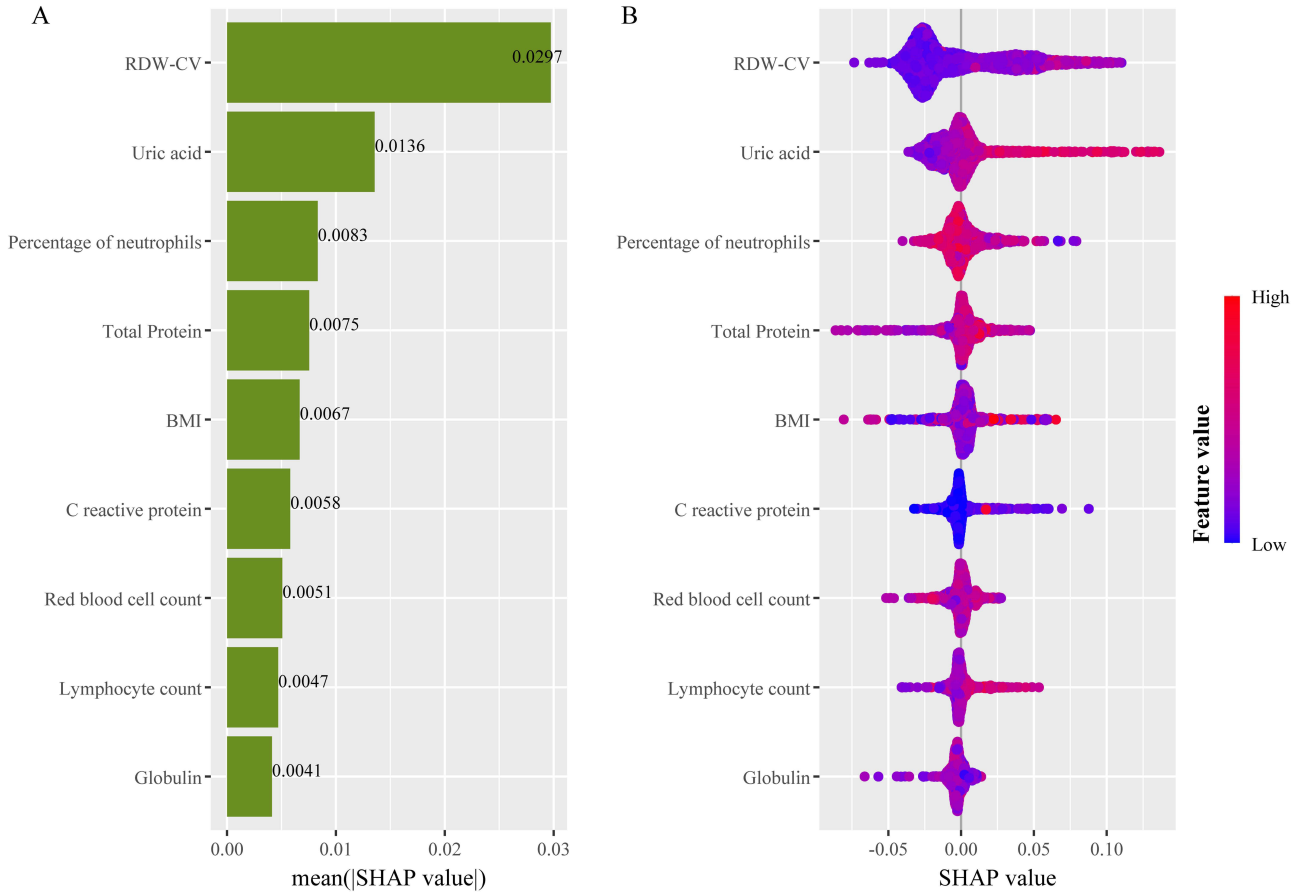

Figure 3 SHAP summary and dependence plots for the XGBoost machine learning model. (**A**) The SHAP summary plot illustrates the mean absolute SHAP values for the top 10 predictors of Bacterial Vaginosis (BV). RDW-CV emerged as the most significant predictor, with a mean absolute SHAP value of 0.0297, followed by Uric acid (0.0136) and Percentage of neutrophils (0.0083). (**B**) The SHAP dependence plot shows the marginal effect of RDW-CV on the model's prediction. Each dot represents an individual participant. The positive slope indicates that as the RDW-CV value increases, its contribution to the predicted likelihood of BV also increases, suggesting a strong positive association.

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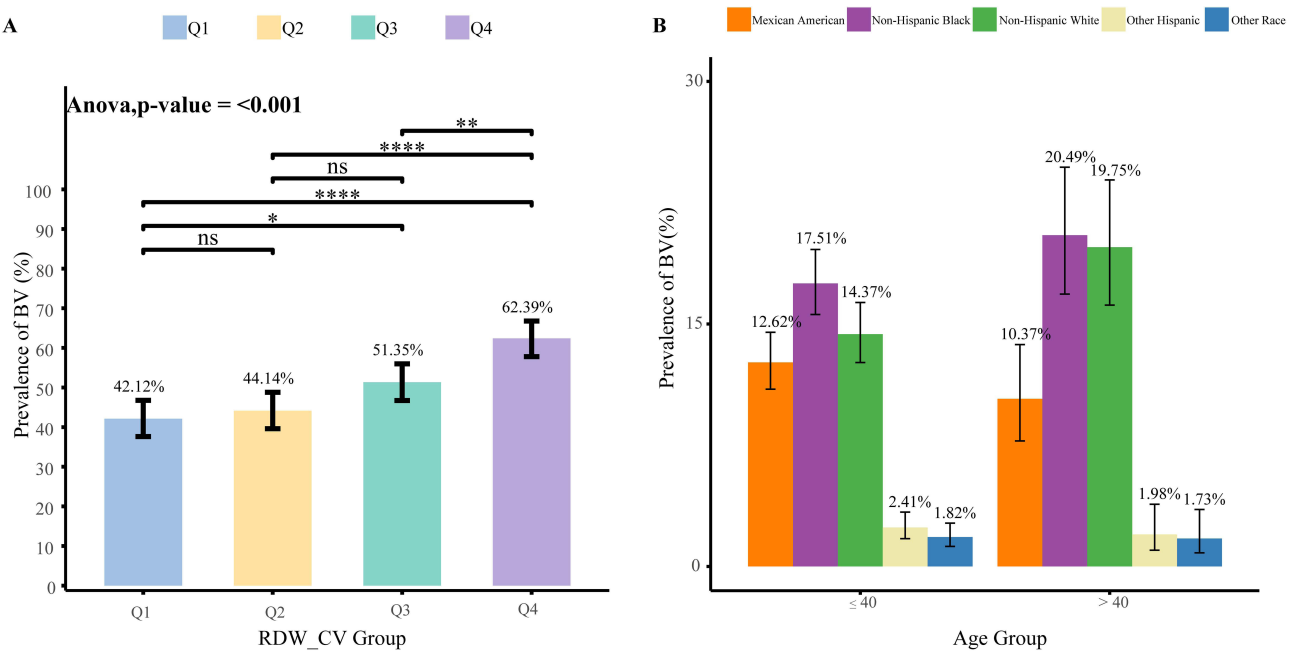

Figure 4 Prevalence of Bacterial Vaginosis (BV) stratified by RDW-CV quartiles, age groups, and race. (**A**) Prevalence of BV across RDW-CV quartiles (Q1–Q4). The prevalence significantly increases from Q1 to Q4 (ANOVA, P < 0.001), indicating a strong positive association. (**B**) Prevalence of BV categorized by age groups ($\le$ 40 and $>$ 40 years) and race/ethnicity. Error bars represent the standard error. Statistical significance is indicated as follows: ns, P ≥ 0.05; *P < 0.05; **P < 0.01; ****P < 0.0001.

Consistency Analysis Using the MIMIC-IV Database

To assess whether the observed association between RDW-CV and bacterial vaginosis (BV) extends to broader vaginal inflammatory conditions, we performed a consistency analysis using the MIMIC-IV 3.1 database. This analysis focused on patients diagnosed with vaginitis—a clinical entity that encompasses BV—thereby providing an opportunity to evaluate the generalizability of RDW-CV as a potential marker across related gynecological disorders.

Data Source and Study Population

Data Sources

MIMIC-IV is a publicly available database containing de-identified electronic health records from Beth Israel Deaconess Medical Center, spanning 2008 to 2019.[13] It includes demographic details, physiological monitoring data, laboratory test results, and disease diagnoses (ICD-9 and ICD-10). Since the data is de-identified, patient consent and ethical review were not required for this study. Yang Feng, one of the authors, accessed the MIMIC-IV database after completing the necessary training and passing the "Protecting Human Research Participants" exam (Record ID: 71589555). The study adhered strictly to the STROBE reporting guidelines.[14]

Study Population

From the MIMIC database, we initially identified 117,737 patients who met the criteria for vaginitis. After excluding entries with missing key data, such as RDW-CV, and removing extreme values, we included 789 subjects in the study. Among these, 87 were diagnosed with vaginitis, while 702 comprised the control group (Figure S2).

Covariate Assessment and Statistical Methods

In this study, we utilized PostgreSQL software (version 13.7.2) and Navicat Premium software (version 16) to extract and analyze potential confounding factors from the MIMIC-IV database using SQL. These factors included age, race, blood potassium, chloride, hyperlipidemia, total calcium, and total cholesterol. Additionally, we gathered relevant data on patients' basic information, laboratory test results, and clinical outcomes.

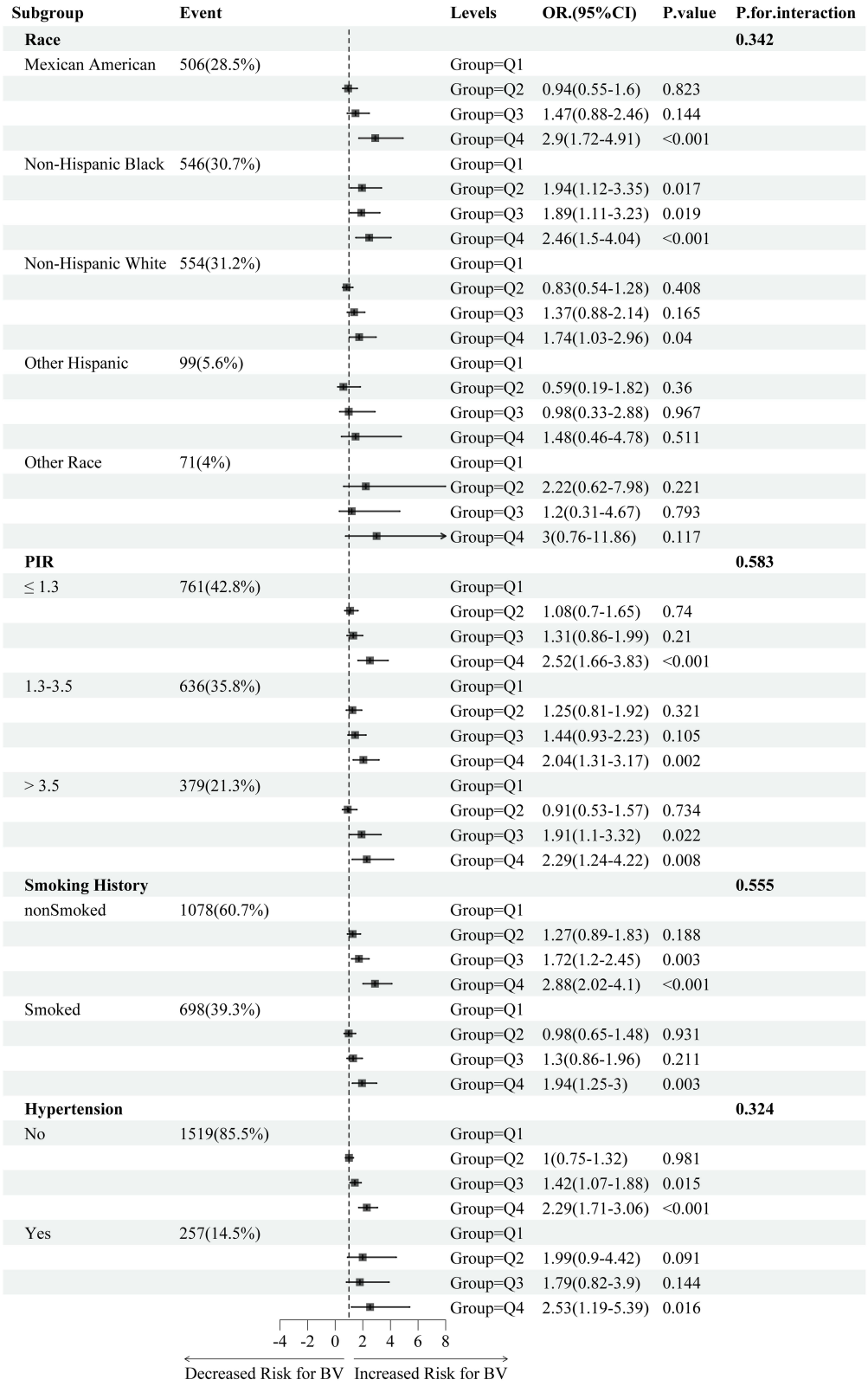

Figure 5 Subgroup analysis of the association between RDW-CV quartiles and the prevalence of Bacterial Vaginosis (BV). The forest plot displays the odds ratios (ORs) and 95% confidence intervals (CIs) for BV across RDW-CV quartiles (Q1–Q4) stratified by race, poverty income ratio (PIR), and other key demographic factors. Each subgroup analysis was adjusted for age, race, BMI, PIR, smoking history, C-reactive protein, globulin, lymphocyte count, percentage of neutrophils, red blood cell count, total protein, and uric acid (except for the stratification variable itself). The P for interaction indicates the consistency of the association across different strata. A P for interaction > 0.05 suggests that the relationship between RDW-CV and BV is stable and not significantly modified by these factors.

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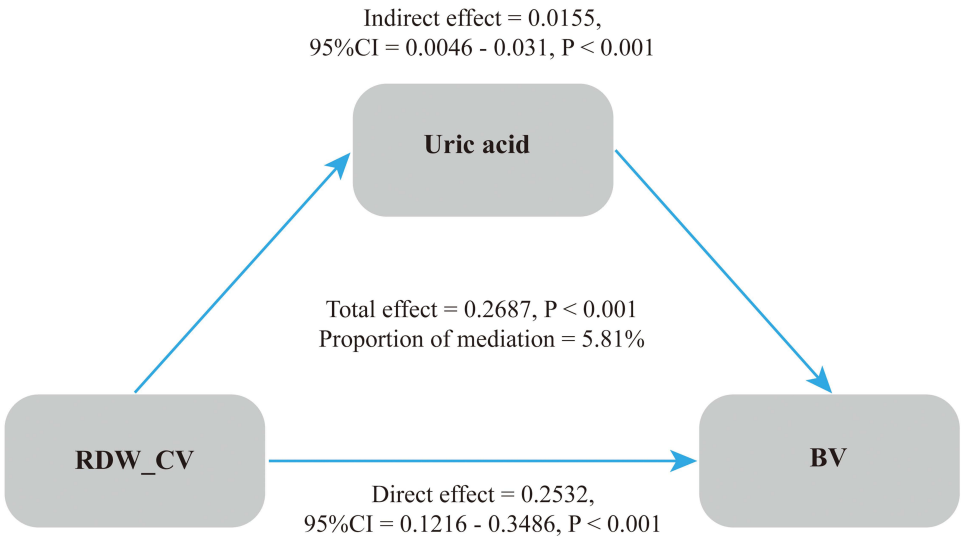

Figure 6 Mediation analysis of Uric acid in the association between RDW-CV and Bacterial Vaginosis (BV). The mediation model illustrates the indirect effect of RDW-CV on the prevalence of BV through Uric acid. The total effect of RDW-CV on BV was 0.2687 (P < 0.001). The direct effect was 0.2532 (95% CI: 0.1216–0.3486, P < 0.001), and the indirect effect mediated by Uric acid was 0.0155 (95% CI: 0.0046–0.031, P < 0.001). Uric acid accounted for 5.81% of the total association between RDW-CV and BV, suggesting that the impact of RDW-CV on BV is partially mediated by serum Uric acid levels.

MIMIC-IV Cohort: Analytical Findings

Baseline Characteristics of the Research Subjects

Multiple imputation was employed to address missing values, ensuring consistent data distribution (Table S9). After propensity score matching (PSM), 174 participants were included, with 87 individuals in both the vaginitis and control groups. The average age was 45±18 years, with 64% identifying as white, 91% speaking English, and 61% being single or divorced. In the vaginitis group, levels of blood potassium (4.0 vs. 3.84), blood glucose (119 vs. 115), total cholesterol (185 vs. 165), and RDW-CV (1.62 vs. 1.52) were higher compared to the control group. Post-PSM, no significant differences were observed in age, race, insurance type, or language between groups. Notably, RDW-CV remained significantly higher in the vaginitis group after matching (P=0.010), as detailed in Tables S8, S10, and S11. Due to the small sample size (n=87) and the broad outcome definition in this cohort, these results are exploratory and should be interpreted with caution.

Relationship Between Vaginitis and RDW-CV

Conditional logistic regression suggested a positive association between RDW-CV and vaginitis. In the unadjusted model, participants in the highest RDW-CV quartile (≥1.61) appeared to have higher odds of vaginitis compared to those in the lowest quartile (<1.39) (OR=2.903, 95% CI: 1.222–6.899, P=0.0158). This trend remained suggestive after adjustment (Model 1: OR=2.55, 95% CI: 1.015–6.406, P=0.0463; Model 2: OR=4.265, 95% CI: 1.129–16.117, P=0.0325). The relatively wide confidence intervals, particularly in Model 2, may reflect the modest number of vaginitis cases (n=87) and warrant prudent interpretation. Trend tests across models were consistent (all P<0.05; Table S12), and RCS analysis indicated a generally linear pattern (Figure S3A–C). Of note, vaginitis encompasses a broader clinical spectrum that includes bacterial vaginosis. The consistent direction of association observed across both specific (BV) and broader (vaginitis) outcome definitions raises the possibility that RDW-CV may serve as a general indicator of vaginal inflammatory conditions, potentially extending its relevance beyond BV to related gynecological health contexts.

RDW-CV Distribution Across Cohorts

As illustrated in the box plots (Figure S1), patients with BV (NHANES) and vaginitis (MIMIC-IV) exhibited consistently higher median RDW-CV levels compared to their respective controls (P < 0.001 for both). This parallel pattern across two distinct populations, despite differences in outcome definitions and clinical settings,suggests that elevated RDW-CV may be a common feature of vaginal inflammatory conditions. The broader definition of vaginitis, which encompasses

BV, further supports the potential relevance of RDW-CV as a general marker in this context, though the exploratory nature of the MIMIC analysis should be acknowledged.

Discussion

Bacterial vaginosis (BV) is the most prevalent reproductive tract infection among women of childbearing age,significantly increasing the risk of sexually transmitted infections, postoperative infections, and adverse pregnancy outcomes. While previous studies have identified associations between systemic factors, such as folic acid levels, and BV,[17] the link between conventional hematological parameters and BV remains underexplored. Using nationally representative NHANES data,this study demonstrates that RDW-CV is independently and positively associated with an increased risk of BV.

After adjusting for demographic and metabolic parameters, we found that individuals in the highest quartile of RDW-CV (≥ 1.51) had a 56.5% higher prevalence of BV compared to those in the lowest quartile (< 1.32) (OR = 1.565, 95% CI: 1.128–2.173, P = 0.007). This association was confirmed using restricted cubic splines (RCS) and the XGBoost machine learning model. Exploratory mediation analysis suggested that serum uric acid partially mediated this relationship. Additionally, consistency analysis using the MIMIC-IV database further supported these findings.

The biological plausibility of this association rests on the current understanding of BV as a disorder characterized by interactions between local dysbiosis and systemic host factors. Inflammation plays a crucial role in BV pathogenesis, marked by significant changes in pro-inflammatory cytokines and chemokines.[5] However, the mere presence of BV-associated bacteria does not consistently lead to symptomatic disease. Instead, host factors, particularly genetic and immune determinants, significantly influence clinical outcomes.[6] In this context, elevated RDW-CV, a recognized marker of chronic inflammation and oxidative stress,[18] may indicate the host's inflammatory status, predisposing individuals to clinically manifest BV.

The mechanistic connection between RDW-CV and inflammation is established through well-known pathways. Pro-inflammatory cytokines, such as TNF-α and IL-6, hinder erythrocyte maturation in the bone marrow, resulting in the early release of immature reticulocytes and increased heterogeneity in red blood cell size.[19,20] These cytokines also destabilize red blood cell membranes and reduce erythrocyte lifespan.[19,21,22] Simultaneously, oxidative stress damages red blood cell membranes and disrupts hematopoietic stem cell function.[23] Consequently, elevated RDW-CV indicates a state of chronic low-grade inflammation and oxidative stress.[24,25] This systemic condition is relevant to BV pathogenesis due to its potential impact on vaginal ecology: systemic inflammatory mediators may alter local immune responses, hinder lactobacillus growth, and create conditions favorable for anaerobic pathogens.[6] This aligns with clinical findings that BV recurrence exceeds 50% within months of treatment, partly due to persistent biofilm and the failure to restore protective lactobacilli.[26]

Our study revealed that serum uric acid partially mediated 5.81% of the relationship between RDW-CV and BV, offering preliminary mechanistic insights that warrant further investigation. Uric acid has a dual role in immune regulation: it acts as an antioxidant intracellularly, but under oxidative stress, its extracellular release functions as a danger-associated molecular pattern.[27,28] This danger signal activates the NLRP3 inflammasome in macrophages, leading to the release of pro-inflammatory cytokines.[29,30] These results suggest that oxidative stress, reflected by elevated RDW-CV, may contribute to BV development through uric acid-mediated enhancement of inflammatory responses. This finding illuminates a specific pathway linking host physiology to vaginal dysbiosis: "RDW-CV → systemic inflammation → BV."

Beyond the immediate diagnosis of BV, the systemic inflammatory state indicated by RDW-CV may have broader clinical implications. BV is linked to significant reproductive issues, such as infertility, endometritis, and pelvic inflammatory disease, primarily due to ascending infections, persistent inflammation, and bacterial toxin-induced tissue damage.[31] This observation resonates with the multifactorial framework proposed by Gilbert et al,[6] which emphasizes that BV outcomes result from complex interactions among microbial factors, such as virulence and biofilm formation, host determinants like genetic and immune status, and social influences, including nutrition. In this broader context, elevated RDW-CV, as an indicator of host inflammatory status, may represent a measurable component of this intricate puzzle, contributing alongside microbial and social factors to the diverse clinical manifestations of BV.

Based on this understanding, we propose a conceptual model: the systemic pathological state, as indicated by RDW-CV, is linked to an imbalance in the vaginal microenvironment. In this model,the systemic inflammatory environment may "pre-activate" the vaginal mucosa's immune system through inflammatory factors. When BV-related pathogens, such as lipopolysaccharides from Gram-negative bacteria, are present, they interact with the sensitized local immune system, activating the NF-κB pathway and releasing large amounts of pro-inflammatory factors, including IL-1β, IL-6, and TNF-α.[32] This local inflammatory response not only fails to eliminate pathogens effectively but also damages the epithelial barrier, worsening microecological disorders.[33–35] The resulting local inflammation exacerbates the systemic inflammatory burden, establishing a potential self-perpetuating cycle. This proposed cycle may offer a plausible explanation for the high recurrence rates observed in BV, though direct experimental validation is needed.

A healthy vaginal microenvironment relies on the hydrogen peroxide (H_2O_2) and acidic conditions produced by lactic acid bacteria.[36,37] Systemic oxidative stress can cause oxidative damage to vaginal epithelial cells[38,39] and inhibit lactic acid bacteria,[40] which are sensitive to such stress. This creates favorable conditions for the proliferation of more tolerant BV pathogens, such as Gardnerella.[41]

This study has several limitations. Firstly, using two independent databases, NHANES and MIMIC, enhances the generalizability of the study, yet these cohorts exhibit significant differences. The MIMIC database employs a broader definition of "vaginitis" based on ICD codes, while NHANES relies on the Nugent score, the gold standard for diagnosing BV. Moreover, MIMIC includes hospitalized patients, whereas NHANES reflects a community-dwelling population. These distinctions, along with the small number of vaginitis cases (n=87) in MIMIC, suggest that the findings should be considered exploratory evidence rather than a formal validation of NHANES results. Secondly,the cross-sectional design allows us to establish only a statistical association between RDW-CV and BV, without inferring causality. Thus, when discussing potential mechanistic pathways, they should be considered as generating hypotheses rather than providing conclusive evidence. Thirdly, the database lacks key information, such as BV clinical classification, microbiome data, and antibiotic use history, which restricts deeper mechanistic analysis. Lastly, despite controlling for multiple confounding factors using rigorous statistical methods, the influence of residual confounding from unknown variables may persist. Nevertheless, we confirmed the robustness of our main findings through propensity score matching and multiple sensitivity analyses. Overall, this study indicates that RDW-CV could be a potential cost-effective marker for stratifying BV risk, underscoring the significance of systemic inflammation in BV pathogenesis. The proposed conceptual model—linking systemic inflammation through uric acid-mediated pathways to vaginal dysbiosis—provides a framework for future research. Prospective cohort studies and experimental investigations are necessary to validate these findings and assess their clinical applicability.

Conclusion

This cross-sectional study found a significant positive association between RDW-CV and BV risk in the NHANES cohort, with serum uric acid mediating 5.81% of this effect. External validation using the MIMIC-IV dataset revealed a consistent trend, although the broader definition of vaginitis posed limitations. RDW-CV could potentially serve as a cost-effective marker for BV risk stratification, suggesting a link between BV pathogenesis and systemic inflammation. However, causality cannot be established, and prospective studies are necessary to confirm these findings.

Abbreviations

BV, Bacterial Vaginosis; RDW-CV, Red Blood Cell Distribution Width - Coefficient of Variation; NHANES, National Health and Nutrition Examination Survey; MIMIC, Medical Information Mart for Intensive Care; CART, Classification and Regression Tree; MICE, Multiple Imputation by Chained Equations; XGBoost, Extreme Gradient Boosting; CRP, C-Reactive Protein; BMI, Body Mass Index.

Data Sharing Statement

The data supporting the results reported in this manuscript are available from the following public databases: the National Health and Nutrition Examination Survey (NHANES) and the MIMIC-IV database. The datasets can be accessed through

their respective websites: (https://www.cdc.gov/nchs/nhanes/) and (https://mimic.mit.edu/). Any additional unpublished data from this study are available upon reasonable request from the corresponding author.

Ethics Approval and Informed Consent

This study employs de-identified data from the publicly accessible National Health and Nutrition Examination Survey (NHANES). It received an ethical review exemption with the opinion number of 2026005801 from the Ethics Committee of The Affiliated Yongchuan Hospital of Chongqing Medical University. This exemption strictly adheres to Item 1 of Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects (2023), issued by the National Health Commission of the People's Republic of China on February 18, 2023. The regulation allows for an exemption when research utilizes legally obtained public data or data generated through non-intrusive observation of public behaviors.

Data for this study were sourced from the MIMIC-IV database, approved by the institutional review boards of Beth Israel Deaconess Medical Center (IRB No. 2001-P-001699/14) and the Massachusetts Institute of Technology (IRB No. 0403000206). Team member Yang Feng completed the Collaborative Institutional Training Initiative (CITI) course to access the MIMIC-IV database (Certificate No. 71589555). Following the same national regulation, this study received an ethical review exemption (Opinion No. 2026005801) from the Ethics Committee of The Affiliated Yongchuan Hospital of Chongqing Medical University for utilizing the MIMIC-IV database. This exemption was granted because the MIMIC-IV database is a legally obtained public database containing de-identified electronic health records, and the research involved only data analysis without affecting public behavior. Since all identifying information has been removed from the databases, further ethical review is not required. Patients or the public did not participate in the design, conduct, reporting, or dissemination of this research.

Consent for Publication

All authors have consented to the publication of this manuscript. The details of any images, videos, recordings, etc., included in the manuscript can be published, and all persons providing consent have been shown the article contents to be published.

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Author Contributions

All authors significantly contributed to the reported work, whether in conception, study design, execution, data acquisition, analysis, interpretation, or all these areas. They participated in drafting, revising, or critically reviewing the article, gave final approval for the version to be published, agreed on the journal for submission, and accepted accountability for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests related to this study.

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