Association Between Hematological Parameters and Generalized Severe Periodontitis Among Young Adults in the United States

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Research Article

Keywords: Periodontitis, Risk factors, Public health, Statistics, Retrospective study

Posted Date: July 26th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1872033/v1

Abstract

Background: Generalized severe periodontitis (GSP), a common oral inflammatory disease associated with systemic circulatory disease, can result in tooth loss and chewing dysfunction.

Objective: This study aims to investigate the relationship between GSP and systemic circulation-related hematological parameters in young adults aged 30 to 40.

Methods: A total of 212 participants were enrolled in the National Health and Nutrition Examination Surveys (NHANES) during 2009 to 2014. The generalized severe periodontitis was identified as 30% of teeth with ≥ 5mm attachment loss. Restricted cubic splines were used to investigate the nonlinearity among variables. Logistic regression analysis was utilized to study the hematological parameters correlated with GSP. Stepwise regression and receiver operating characteristic curve were applied to generate and assess the predictive models for GSP occurrence.

Results: Based on the indicators of 212 subjects, we found that generalized severe periodontitis tended to occur in males and was accompanied by higher Hemoglobin (HB), Hematocrit (HCT), Red cell distribution width (RDW), Red blood cell count (RBC), as well as less Poverty-income ratio (PIR). Restricted cubic splines confirmed the relationships between GSP and HB or HCT were nonlinear. Logistic regression showed that RDW was a potential indicator of GSP. Compared with HCT (AUC = 0.702), HB (AUC = 0.697), RBC (AUC = 0.684), RDW (AUC = 0.585), and other single variable, multi-variables regression (including gender, PIR, RDW, education levels, and BMI) (AUC = 0.913) demonstrated better predictive effects on generalized severe periodontitis.

Conclusion:

Hematological parameters can predict generalized severe periodontitis, for which RDW is a potential indicator.

1. Introduction

As a chronic inflammatory disease, generalized severe periodontitis (GSP) commonly leads to tooth loss and affects the adult population in the United States[1]. Otherwise, GSP requires complex treatment and expensive expenses. Besides impairing chewing function and causing aesthetic troubles, severe periodontitis has a high correlation with obesity[2], cardiovascular disease[3], diabetes[4], etc. Therefore, it is imperative to explore GSP-related predictive factors, not only to but also reduce the potential consequences of GSP.

Current studies have presented the systemic circulation mechanisms of GSP occurrence. In which, periodontal pathogens and bacterial components spread systemically through bacterial invasion of host cells[5, 6], and inflammatory mediators originate from periodontal lesions into the systemic circulation[7, 8]. Additionally, periodontitis affects hematological parameters[10] as well as the proportion and function of circulating inflammatory cells[9]. In previous studies, chronic periodontitis and related treatment cause the alteration of Hemoglobin (HB) and Hematocrit (HCT) levels[11,12]. However, the potential and predictive factors of GSP were not reported.

Logistic regression analysis is used to explore correlations and potential key factors[13]. Non-linear relationships among variables are often efficiently modeled with restricted cubic splines (RCS)[14]. Stepwise regression can

effectively exclude covariance problems and screen out key factors[15]. The receiver operating characteristic (ROC) curve can be used as a prediction model and determine an appropriate cut-off point with the highest sensitivity and specificity[16]. . We are currently unaware of any research on multivariate regression analysis of hematological markers and generalized severe periodontitis/ There has not yet existed any research on multivariate regression analysis of hematological markers and generalized severe periodontitis .

This study aims to explore the association between GSP and hematological parameters based on the National Health and Nutrition Examination Survey (NHANES) database.

2. Materials And Methods

2.1 Study population

This study collected publicly available data from the NHANES during 2009 to 2014. After excluding participants with missing data (n = 16400) on the periodontal examination at baseline, 14071 participants were available. Further excluding participants over 40 years old (n = 10847) or had an attachment loss of 2-5 mm (n = 3012). Finally, 212 participants were enrolled for the analysis (Figure 1). All participants provided written informed consent and the protocol was approved by the NCHS Research Ethics Review Board.

2.2 Periodontitis indicators

The stage of periodontitis was identified by attachment loss conducted by dental examiners, who were dentists (D.D.S./D.M.D.) licensed in at least one U.S. state. All oral health assessments occurred in a designated room at the mobile examination center (MEC). According to the new definition of periodontitis in 2018, stage I was defined as the attachment loss (AL) ≤ 2 mm and ≥ 1mm. Stage II was AL ≤ 4 mm and ≥ 3mm. Stage III or IV were AL ≥ 5mm. A periodontitis that involves more than 30% of teeth with attachment loss is described as generalized periodontitis [17]. In this study, the severe periodontitis group consisted of generalized stage III and stage IV periodontitis. Mild periodontitis was stage I periodontitis.

2.3 Covariates

Based on the NHANES database, information on age, gender, education level (< 9th grade, 9-11th grade, high school, college, graduate), race/ethnicity (Mexican American, Hispanic, non-Hispanic White, non-Hispanic Black, and other race), PIR (poverty income ratio), Body Mass Index (BMI) were acquired from the demographics data. Hematological parameters (including HB, HCT, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, red cell distribution width, platelet count, mean platelet volume, and red blood cell count) and Direct HDL-Cholesterol (HDL) had been obtained from laboratory data. PIR was stratified as < 1, 1-3, and >3[18]. BMI was stratified as normal weight (18.5 - 24.9 kg/m^2), overweight (25 - 29.9 kg/m^2), and obesity (> 30 kg/m^2)[19].

2.4 Statistical analysis

After obtaining data from NHANES, the continuous variables were tested by Statistical Product Service Solutions (SPSS) for normality. The continuous variables conforming to a normal distribution were presented as the mean (standard deviation), while continuous variables not conforming to a normal distribution were presented as the mean (quartiles). The categorical variables were presented as the number (percentage). Linear relationships were verified for all factors, and nonlinear factors were presented in restricted cubic splines. R 4.1.2 was used to

calculate the cut-off point in the single factor analysis. Logistic regression models were used to perform each factor correlation. Model 1 was not adjusted. Model 2 was adjusted for gender and PIR. Model 3 was further adjusted for age and race. P-value < 0.05 was considered statistically significant. The stepwise regression method was used to exclude covariance problems and generate the best model. ROC curves was drawn by GraphPad Prism 6 to describe the prediction of various covariables and comprehensive variables in generalized severe periodontitis.

3. Results

3.1 Characteristics of the study population.

The baseline characteristics of the population are shown in Table 1. 212 participants were made up of 114 males (53.78%) and 94 females (46.2%). Male prevalence of severe periodontitis (64.9%) was higher than female (22.4%). Participants with severe periodontitis tend to have higher RBC, HB, HCT, RDW, and MPV, as well as less HDL and PIR. Mexican Americans and non-Hispanic Blacks were more likely to suffer from severe periodontitis. The highly educated population has a lower rate of severe periodontal disease.

3.2 Non-linear regression

Restricted cubic splines suggested that HB (P for nonlinearity = 0.005) and HCT (P for nonlinearity = 0.0288) were nonlinearly associated with severe periodontitis (Figure 2). HB exceeded 14.42 g/dL or HCT over 42.03% was the risk range for severe periodontitis, while HB below 14.42 g/dL or HCT below 42.03% was the protective range for mild periodontitis.

3.3 Logistic regression

BMI was associated with severe periodontitis in the unadjusted model 1(OR 0.66, 95% CI [0.43-1.00]; p = 0.047), partly-adjusted Model 2 (OR 0.42, 95% CI [0.24-0.73]; p = 0.002) and fully-adjusted Model 3 (OR 0.42, 95% CI [0.24-0.73]; p = 0.002) respectively (Table 2). Besides, RDW was also associated with severe periodontitis in the unadjusted model 1(OR 1.96, 95% CI [1.29-2.96]; p = 0.002), partly-adjusted Model 2 (OR 1.81, 95% CI [1.05-3.10]; p = 0.033) and fully-adjusted Model 3 (OR 1.80, 95% CI [1.04-3.09]; p = 0.034).

3.4 ROC curve prediction

Based on the consequence of correlation analysis, we generated the multi-variables regression model (including gender, PIR, RDW, education levels, and BMI) (AUC = 0.913) with best sensitivity and specificity by stepwise regression method, followed by HCT (AUC = 0.702), HB (AUC = 0.697), RBC (AUC = 0.684), HDL (AUC = 0.626), MPV (AUC = 0.593), RDW (AUC = 0.585) (Figure 3). The cutoff value of the multi-variable regression model was 0.688, while the corresponding sensitivity and specificity were 93.8% and 75%, respectively. The sensitivity and specificity of each model at the optimal cutoff point were listed in Table 3.

4. Discussion

Current epidemiological data describe the association between generalized severe periodontitis and systemic circulation disease[20]. Additionally, periodontitis is associated with a variety of hematological parameters (including blood glucose[21], Vitamin D[22], high-density lipoprotein cholesterol[23], etc.). Previous studies on

periodontitis and hematological parameters have focused on the relationship between healthy and periodontitis populations[10, 24], while there was no mention of the variations in hematological markers between severe and mild periodontitis.. This study used restricted cubic splines and logistic regression to demonstrate the hematological parameters related predictors (including HB, HCT, and RDW) in generalized severe periodontitis, for identifying the relationship between hematological parameters and generalized severe periodontitis in young adults,.

Previous studies have shown that periodontitis alters the levels of HB and HCT[11, 20-23]. By releasing proinflammatory cytokines from host cells in localized periodontal lesions, periodontitis affects the production and differentiation of erythrocytes[25-27]. Meanwhile, HB and HCT were indicators of blood viscosity[28]. High hemoglobin levels increase the risk of arterial thrombosis, and males with high hemoglobin levels (14.5-15.9 g/dl) had 1.7 times the risk of myocardial infarction than males with low hemoglobin levels (13.0-14.4 g/dl)[29]. In addition, Males with high HCT (> 49%) had a 1.4-fold increased risk of myocardial infarction compared to males with low HCT (< 44%). On account of previous research, our results showed that HB (> 14.42 g/dl) or HCT (> 42.03%) are contributing factors to GSP and can serve for clinical prevention and treatment.

Sufficient evidence showed that periodontal pathogens involve the body circulation[3], and periodontitis alters the iron status of the serum. Periodontitis pathogens obtain iron by breaking down ferritin and impairing the interference with HB production ultimately resulting in iron deficiency anemia[30]. As a diagnostic indicator of anemia[31], RDW reflects the disease occurrence[32] as well as indicates the development of severe periodontitis as a potential factor in the study.

Although the current study has demonstrated the accuracy of the regression model in predicting severe periodontitis, some limitations exist in our study. Further studies with larger sample sizes using more relevant variables (such as microbiome data, smoking habits) may discover more precise factors and better ROC performance in generalized severe periodontitis. Additionally, leukocytes, platelets, lymphocytes, monocytes, and other hematological parameters associated with generalized severe periodontitis will be added in follow-up studies.

5. Conclusion

Hematologic parameters can predict generalized severe periodontitis and can be defined as risk indicators. In addition, RDW is a potential factor in severe periodontitis.

Declarations

Data Availability

Publicly available datasets were analyzed in this study. Data used for this study are available on the NHANES website: https://wwwn.cdc.gov/nchs/nhanes/.

Ethics Statement

The studies involving human participants were approved by the institutional review board of the National Center for Health Statistics, CDC, and were conducted in accordance with the Helsinki Declaration of 1975, as revised in 2013. The patients/participants provided their written informed consent to participate in this study.

Consent for publication

Not applicable.

Funding

This work was supported by the Basic and Clinical Cooperative Research Promotion Program of Anhui Medical University (2021xkjT038).

Author Contributions

H.M. collected the data and wrote the manuscript; Z.W., S.Z., D.B., and L.X. assisted H.M. with data analyses. H.M, Z.W., S.Z., and C.X. performed statistical analyses. W.Y. conceived of this study. Z.H. analyzed the data and revised the manuscript. All authors read and approved the final manuscript.

Acknowledgement

We acknowledge Zishuo Wang for the invaluable contributions of manuscript revision (Shanghai Jiaotong University).

Conflict of interest

The authors declare that they have no conflict of interest

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Tables

Table 1 Characteristics of the study population (NHANES, 2009–2014).

	Total	Mild periodontitis	Severe periodontitis	P-value
participants n	212	116	96	-
Age(n%)	36(34-39)	36 35-38	36.5 34-39	0.469
gender n%				0.00
male	114[53.78]	40[34.4]	74[77]	
female	98[46.2]	76[65.5]	22[22.9]	
Race				0.00
Mexican American	27[12.74]	6[5.17]	21[21.88]	
Other Hispanic	19[8.96]	11[9.48]	8[8.33]	
Non-Hispanic White	102[48.11]	68[58.62]	34[35.42]	
Non-Hispanic Black	36[16.98]	15[12.93]	21[21.88]	
Other Race - Including Multi-Racial	28[13.21]	16[13.79]	12[12.5]	
Person Education Level				0.00
Less Than 9th Grade	16[7.55]	3[2.59]	13[13.54]	
9-11th Grade	32[15.09]	4[13.79]	28[28.13]	
High School Grad/GED or equivalent	43[20.28]	16[13.79]	27[28.13]	
Some College or AA degree	57[26.89]	36[31.03]	21[21.88]	
College Graduate or above	64[30.19]	57[49.14]	7[7.29]	
PIR	2.465 1.13-4.95	3.53 2.25-5	1.245 0.69-2.44	0.00
RBC (million cells/uL)	4.7±0.49	4.56±0.44	4.87±0.51	0
HB (g / dL)	14.4 13.3-15.4	13.7 12.9-15	15 14-15.8	0.00
HCT (%)	42.4 38.75-44.9	40.2(38.03-43.55)	43.95(41.05-46.05)	0.00
MCV (fL)	89.65 86.4-92	89.5(86.33-91.85)	89.7(86.68-92.18)	0.89
MCH (pg)	30.8 29.3-32	30.75(29.1-31.95)	30.85(29.53-32.08)	0.525
RDW %	12.9 12.4-13.4	12.7(12.3-13.18)	13(12.4-13.78)	0.034
PLT (1000 cells/uL)	233.5 201-275.5	240.5(202.75-290)	223.5(193-262.75)	0.057
MPV (fL)	8.35±1.05	8.22±1.13	8.52±0.93	0.038
BMI (kg/m^2)				0.873
Normal weight	64[30.19]	36[31.03]	28[29.17]	
Overweight	69[32.55]	36[31.03]	33[34.38]	

Obesity	79[37.26]	44[37.93]	35[36.46]	
HDL mg/dL	48 39-58	50.5 41-60	44(35.25-53.75)	0.002

PIR, poverty income ratio; RBC, red blood cell count; HB, hemoglobin; HCT, hematocrit; MCV, mean cell volume; MCH, Mean cell hemoglobin; RDW, red blood cell distribution width; PLT, platelet count; MPV, mean platelet volume; BMI, body mass index; HDL, high density lipoprotein.

Table 2 Relationship between generalized severe periodontitis and hematological parameters in adolescents.

	Model 1			Model 2			Model 3		
	OR	[95%CI]	P	OR	[95%CI]	P	OR	[95%CI]	P
RBC	14.51	0.01-23940.99	0.479	42.76	0.02-111589.62	0.349	56.92	0.02-187813.1	0.328
HB	1.03	0.01-83.46	0.991	0.37	0.00-64.49	0.704	0.40	0.00-74.88	0.729
HCT	0.91	0.15-5.63	0.919	0.99	0.13-7.81	0.996	0.93	0.11-7.73	0.950
MCV	1.09	0.45-2.61	0.850	1.05	0.39-2.84	0.918	1.09	0.39-3.00	0.874
MCH	1.23	0.15-10.29	0.846	1.48	0.12-17.74	0.756	1.42	0.11-17.57	0.786
RDW	1.96	1.29-2.96	0.002	1.81	1.05-3.10	0.033	1.80	1.04-3.09	0.034
PLT	1.00	0.99-1.01	0.758	1.00	0.99-1.01	0.973	1.00	0.99-1.01	0.962
MPV	1.31	0.92-1.85	0.135	1.56	0.98-2.49	0.062	1.56	0.97-2.50	0.062
BMI	0.66	0.43-1.00	0.047	0.42	0.24-0.73	0.002	0.42	0.24-0.73	0.002
HDL	0.97	0.94-1.00	0.021	0.99	0.96-1.02	0.462	0.99	0.96-1.02	0.455

Model 1 was not adjusted.

Model 2 was adjusted for gender, PIR.

Model 3 was adjusted for age, race, gender, PIR.

Table 3 Sensitivity, specificity, and other conventional parameters of each model at optimal cutoff point

Model	Sensitivity	Specificity	Optimal cutoff of probability
Multivariate	93.80%	75.00%	0.688
HCT	62.50%	73.30%	0.358
HB	82.30%	54.30%	0.366
RBC	76.00%	53.40%	0.295
HDL	74.10%	46.90%	0.21
MPV	71.90%	45.70%	0.176
RDW	41.70%	75.00%	0.167

The optimal cutoff was considered as the point maximizing the sum of sensitivity and specificity.

Figures

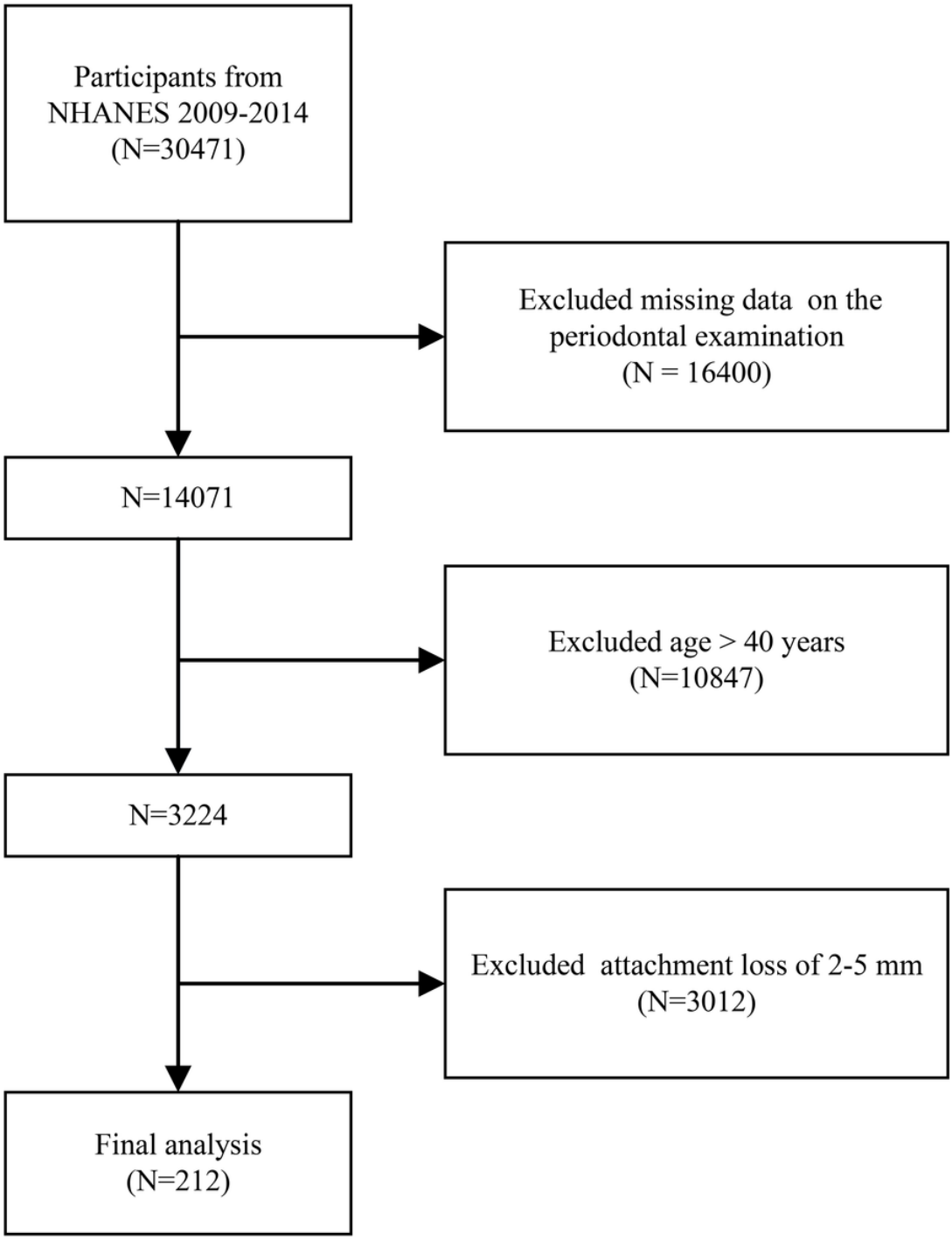

Figure 1

Selection process of participant sample.

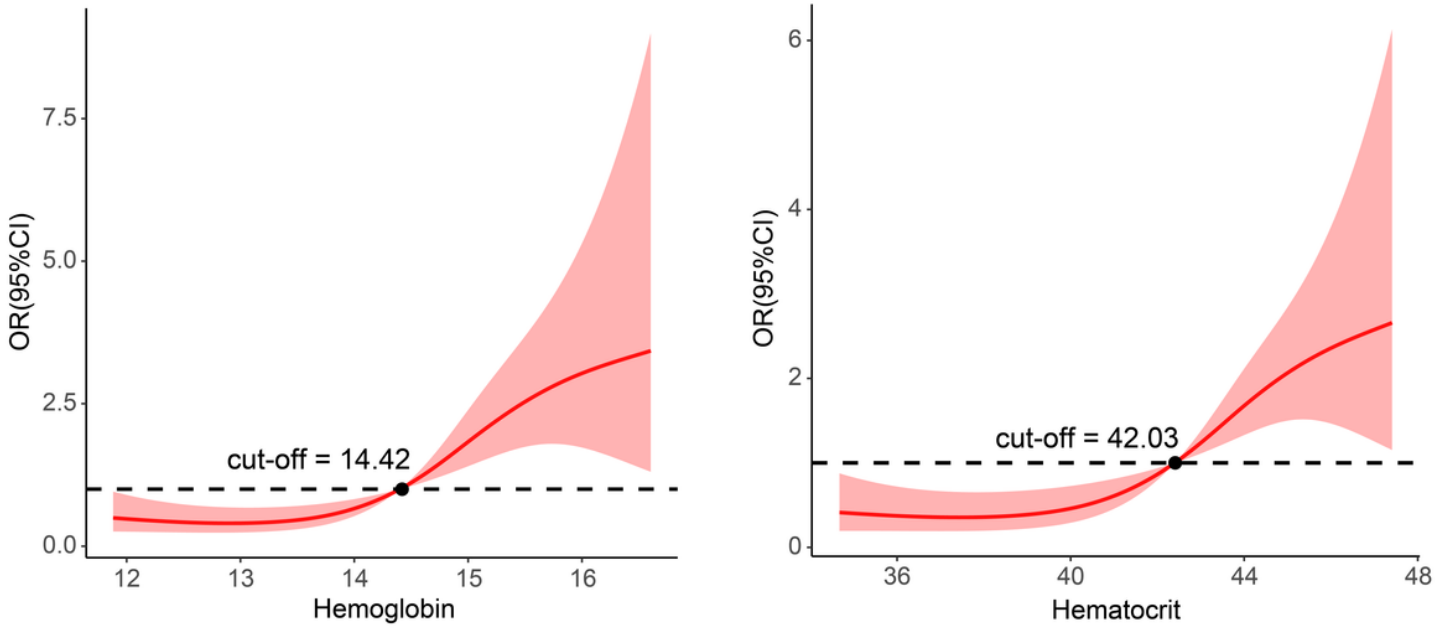

Figure 2

The restricted cubic splines between generalized severe periodontitis with Hemoglobin and Hematocrit.

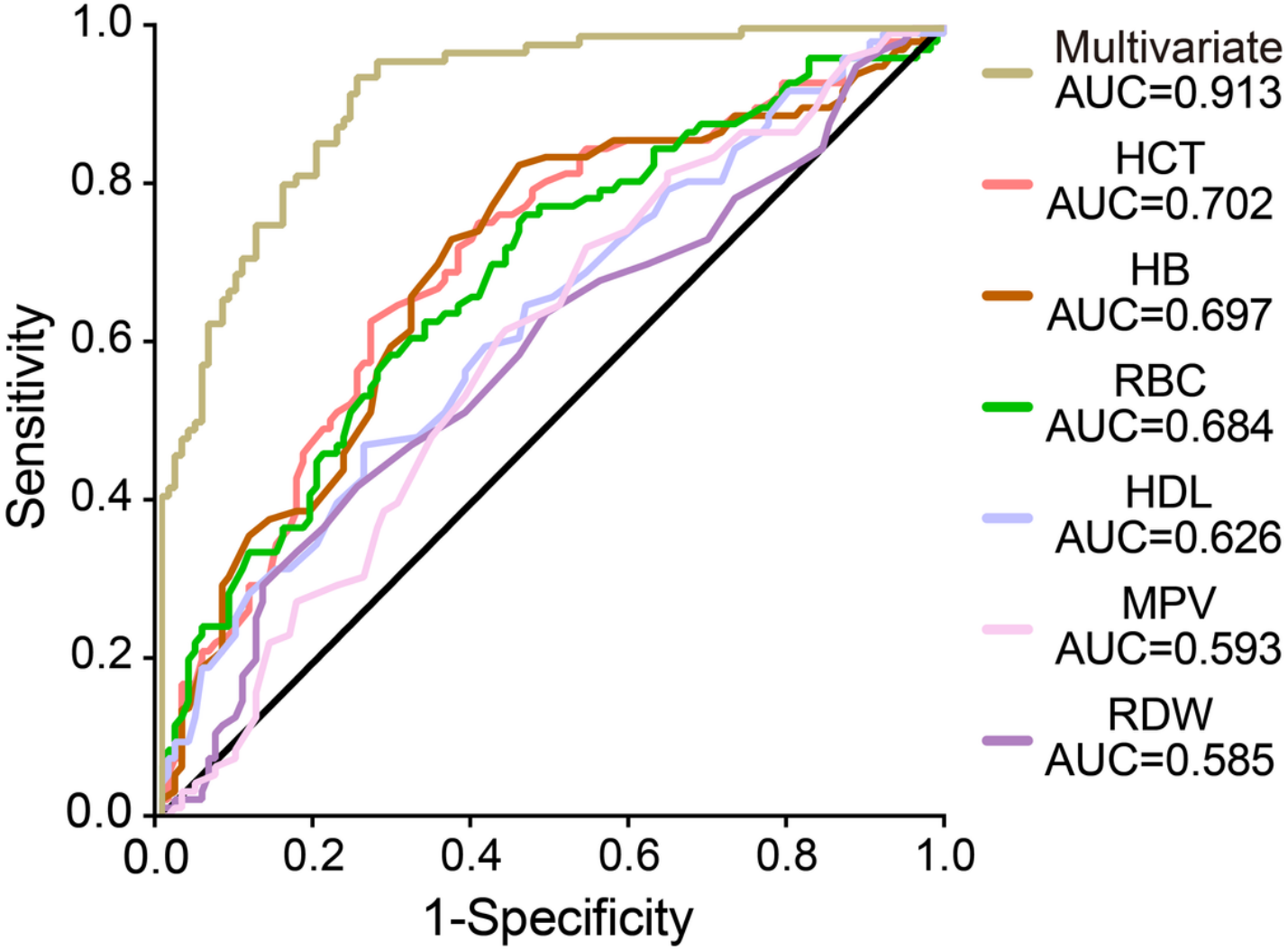

Figure 3

ROC & AUC of prediction models.

The sensitivity and specificity of multivariate, the best performing model, were 93.80% and 75.00%, respectively, at its optimal cutoff.