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Association Between the Hemoglobin-to-Red Cell Distribution Width Ratio and Risk of Type 2 Diabetic Kidney Disease: A Machine Learning Study

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Abstract

Background

Hemoglobin (Hb) and red cell distribution width (RDW) are well-established risk factors for the onset and progression of diabetic kidney disease (DKD). Consequently, this study investigated the clinical association between the hemoglobin-to-RDW ratio (HRR) and the risk of incident DKD in patients with type 2 diabetes mellitus (T2DM).

Methods

This study utilized the MIMIC-IV3.2 database and, through rigorous inclusion and exclusion criteria, ultimately identified 8,201 patients diagnosed with T2DM during their ICU stay. Using random sampling, the dataset was divided into a training set (5,741 cases) and a validation set (2,460 cases) in a 70:30 ratio. Through receiver operating characteristic (ROC) curve analysis, the consistency of the predictive performance of HRR, Hb, and RDW for assessing DKD risk was compared between the training and validation sets. Restricted cubic splines (RCS) were used to explore nonlinear dose-response relationships and determine the optimal risk thresholds for HRR in both the training and validation sets. Finally, by constructing various machine learning models and integrating multi-indicator information, we comprehensively validated the clinical significance of HRR in assessing the risk of DKD.

Results

We confirmed through multivariate logistic regression analysis that elevated HRR is significantly negatively correlated with the risk of DKD ($P < 0.05$). ROC curve analysis indicated that, in both the training and validation sets, the correlation between HRR and the risk of DKD was stronger than that of the individual markers Hb and RDW ($P < 0.05$).

Furthermore, in the multivariate risk assessment model based on HRR, the LightGBM learning algorithm demonstrated superior overall performance compared to other models. The ROC values in the training and validation sets were 0.7774 (0.7621–0.7927) and 0.6560 (0.6261–0.686), respectively. SHAP analysis indicated that HRR had the highest importance in the model, further validating its strong association with the risk of DKD. The SHAP dependency plot revealed a nonlinear relationship between HRR and DKD risk, with an optimal risk threshold of 6.9492.

Conclusions

Our findings indicate that elevated HRR is negatively correlated with the risk of developing DKD. Compared to measuring Hb or RDW alone, HRR offers higher sensitivity and accuracy, making it more clinically useful for early screening.

Keywords: Hemoglobin-to-Red Cell Distribution Width Ratio, Type 2 Diabetes Mellitus, Diabetic Kidney Disease, Machine Learning, MIMIC-IV

1. Introduction

Diabetes mellitus (DM) is a systemic metabolic disorder; prolonged chronic hyperglycemia significantly increases the risk of various microvascular and macrovascular complications^[1]. Epidemiological data indicate that there were approximately 529 million people with diabetes worldwide in 2021, and the prevalence is projected to rise further, with the total number of cases expected to reach 783 million by 2045^[2]. Diabetic kidney disease (DKD), as the primary type of chronic kidney disease (CKD) and the leading cause of end-stage kidney disease (ESKD) worldwide, poses risks that extend far beyond the kidneys themselves^[3]. Studies indicate that DKD can further increase the risk of cardiovascular disease (CVD), significantly raising the risk of adverse outcomes and mortality^[4]. Furthermore, the incidence of DKD is higher among patients with type 2 diabetes mellitus (T2DM) than among those with type 1 diabetes mellitus (T1DM)^[2]. Given current medical capabilities, diabetic microvascular complications cannot yet be completely cured^[5]. This results in not only poorer clinical outcomes for diabetic patients with renal complications but also a significantly increased disease-related economic burden.

In recent years, to effectively address the challenges posed by diabetic kidney disease (DKD), there has been a growing emphasis on identifying novel biomarkers, with the aim of gaining a clearer understanding of the pathogenesis of DKD and better predicting its progression^[6]. An increasing number of studies have demonstrated that routine blood tests not only hold the potential to provide effective biomarkers but also aid in the stratification of disease risk^[7, 8]. Both RDW and hemoglobin (Hb) have demonstrated clinical predictive value for complications such as nephropathy in diabetic patients when used individually^[9-12]. However, an elevated RDW alone can be caused by non-renal factors such as infection

or iron deficiency, while nutritional or hematological issues may lead to reduced Hb levels^[13, 14]. Therefore, when used in isolation, these two markers are inevitably subject to interference from various confounding factors. HRR effectively addresses this limitation, as an elevated HRR value requires the simultaneous fulfillment of two conditions: reduced Hb and elevated RDW. It directly reflects the damage caused by diabetes itself to the kidneys, more closely capturing the essence of DKD pathogenesis.

Given the clinical utility of hematological parameters in the field of diabetic kidney disease (DKD), the objective of this study is to utilize the MIMIC-IV database to further validate the practical efficacy of HRR in assessing DKD pathogenesis. This research aims to provide practical tools and theoretical support for implementing optimized prevention and treatment strategies and improving patient outcomes in future clinical practice.

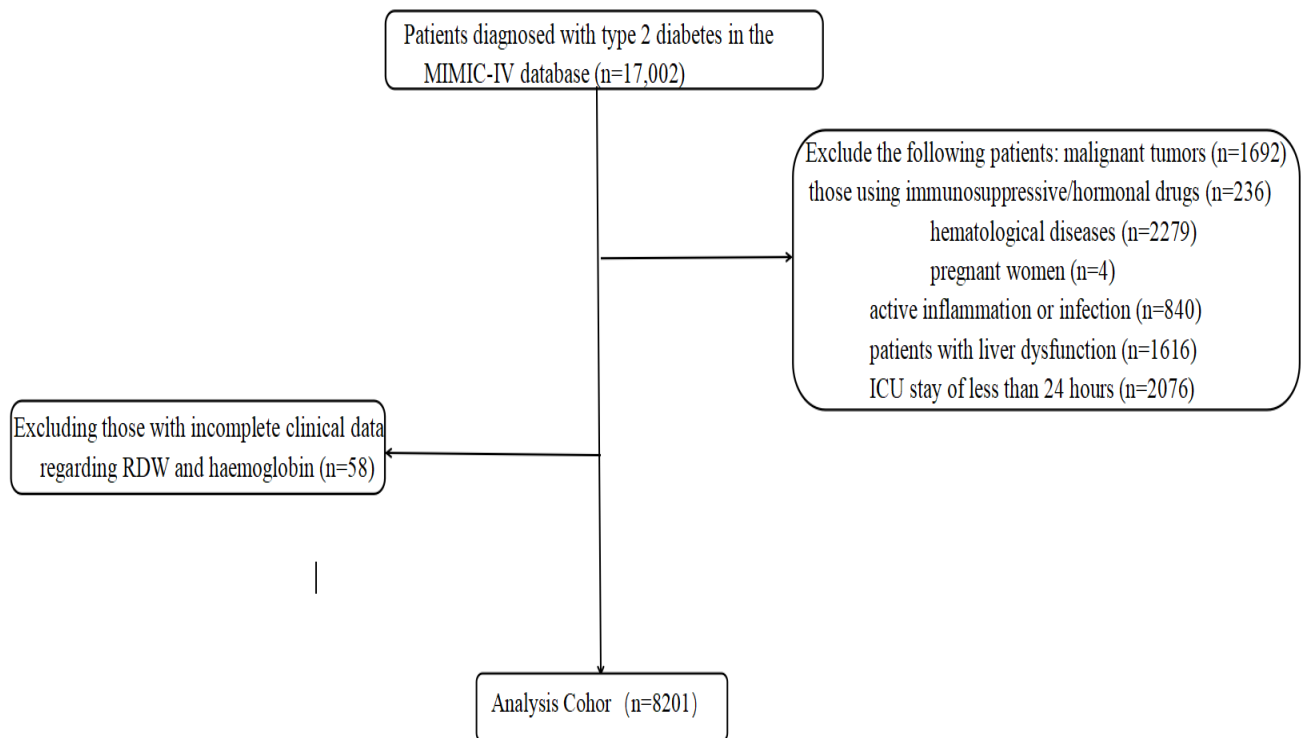
2.Methods

2.1.Data source

The data for this retrospective cohort study were obtained from the MIMIC-IV 3.2 database, which contains de-identified clinical records of all intensive care unit (ICU) patients admitted to Beth Israel Deaconess Medical Center (BIDMC) in Boston, USA, between 2008 and 2019. These records include demographic information, laboratory results, medication records, and vital signs. The researcher, Feng Li, has completed CITI research ethics training (certification number: 73796363) and obtained legal authorization to use this database.

The specific inclusion and exclusion criteria are as follows: 1. Patients diagnosed with T2DM based on the coding of the International Classification of Diseases, Ninth Edition (ICD-9) (250.x0/x2) and Tenth Edition (ICD-10) (E11.xx). 2. Exclude individuals with hematological disorders, malignant tumors, long-term use of immunosuppressants or high-dose hormones, active inflammation or infection, severe liver dysfunction, pregnant or lactating women, etc. Finally, cases with missing or incomplete RDW and Hb data were excluded to ensure the accuracy of the statistical analysis. In total, 8,201 patients were included (**Figure 1**).

Figure1.



Flowchart of Patient Inclusion and Exclusion.

2.2.Data collection

This study used Structured Query Language (SQL) to extract patients' baseline demographic data from a PostgreSQL 14.2 database. I. Demographic and General Clinical Characteristics: age, sex, race, weight, smoking history, and alcohol consumption history. II. Vital Signs: systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, and respiratory rate. III. Laboratory Test Results: 1. Complete blood count and related parameters: white blood cell count, hemoglobin (Hb), red blood cell distribution width (RDW); 2. Renal function and electrolytes: serum creatinine (Scr), blood urea nitrogen (BUN), estimated glomerular filtration rate (eGFR), potassium, calcium, chloride, phosphorus, bicarbonate, anion gap; 3. Glucose and lipid metabolism: Blood glucose; IV. Comorbidities: Hyperlipidemia, coronary heart disease (CHD), myocardial infarction (MI), congestive heart failure (CHF), atrial fibrillation, stroke. V. Treatment and Interventions: Insulin use, vasoactive agents, renal replacement therapy (RRT); VI. Disease Severity and Scores: Systemic Inflammatory Response Syndrome (SIRS), Acute Physiology Score III (APS III), Sequential Organ Failure Assessment (SOFA) score; VII. Hospitalization Outcomes: Length of hospital stay (Los_hospital), length of ICU stay (Los_ICU). Glycated hemoglobin (HbA1c), triglycerides, total cholesterol, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) were excluded from the analysis because the missing data rate exceeded 70%, failing to meet the inclusion criteria.

2.3.Exposure variable

The HRR (hemoglobin-red blood cell distribution width ratio) is calculated as the ratio of hemoglobin (Hb, g/L) to red blood cell distribution width (RDW, %), using the following formula:

$$\text{HRR} = \frac{(\text{Hb, g/L})}{(\text{RDW, \%})}$$

2.4. Outcome variable

The primary outcome measure of this study was diabetic kidney disease (DKD). eGFR was calculated using the 2021 CKD-EPI creatinine-based equation, which does not include racial coefficients[15].

$$\text{eGFR} = 142 \times \min\left(\frac{(\text{Scr})}{(\kappa)}, 1\right)^\alpha \times \max\left(\frac{(\text{Scr})}{(\kappa)}, 1\right)^{-1.2} \times 0.9938^{\text{Age}} \times [1.012 \text{ if female}]$$

Scr refers to serum creatinine (mg/dL), and Age refers to age (years).

The parameters are set as follows:

Females: $\kappa = 0.7$, $\alpha = -0.241$, gender coefficient = 1.012.

Males: $\kappa = 0.9$, $\alpha = -0.302$, gender coefficient = 1.

2.5.Statistical Analysis

In this study, the data were randomly divided into a training set and an internal validation set in a 7:3 ratio, used for model development and performance validation, respectively. For continuous variables, statistical descriptions were presented as the median (interquartile range), and intergroup comparisons were performed using the Mann-Whitney U test. Categorical variables were described in terms of frequency (percentage). Intergroup comparisons were analyzed using either the chi-square test or Fisher's exact test, depending on the distribution characteristics. Multivariate logistic regression analysis was further conducted to identify the independent association between HRR and the occurrence of DKD, with results expressed as odds ratios (OR) and their 95% confidence intervals. To account for confounding factors, three analytical models were established: Model 1: HRR; Model 2: HRR, age, sex, race, body weight, smoking history, and alcohol consumption history; Model 3: Model 2, white blood cell count, glucose, atrial fibrillation, stroke, hyperlipidemia, CHD, MI, CHF, and insulin. The restricted cubic spline (RCS) method was used to assess the trend of association between HRR and the risk of DKD. Significant variables from the multivariate regression analysis were selected to further construct a risk model using a risk plot. The clinical utility of HRR in the training and validation cohorts was evaluated via decision curve analysis (DCA). The statistical value of HRR, RDW, and

Hb was compared using the area under the receiver operating characteristic curve (AUC). To enhance the model's discriminatory power and applicability, we incorporated four representative machine learning methods. We compared the statistical performance of logistic regression (LR), XGBoost, LightGBM, and random forest (RF) in predicting the risk of DKD.

All statistical analyses of the data in this study were performed using R software; a p-value of <0.05 was considered statistically significant.

3.Results

3.1.Baseline Characteristics of the Patients

This study included a total of 8,201 cases, with the data randomly divided into a training set (5,741 cases, accounting for 70%) and a validation set (2,460 cases, accounting for 30%). The results showed that the distributions of all baseline variables were balanced between the two groups, and no statistically significant differences were observed in the comparisons between them. In the training cohort, 15.60% of patients had concomitant DKD, and the proportion was the same in the validation cohort([Table 1](#)).

Table 1.

Comparison of Baseline Characteristics between Training and Validation Sets.

Characteristic	Training set (n=5741)	Validation set (n=2460)	p-value
Age	70.00 (61.00,79.00)	70.00 (61.00,79.00)	0.571
Gender			0.283
Female	2357 (41.10%)	978 (39.80%)	
Male	3384 (58.90%)	1482 (60.20%)	
Race			0.542
WHITE	3453 (60.10%)	1498 (60.90%)	
OTHER	2288 (39.90%)	962 (39.10%)	
Weight	87.00 (73.40,102.65)	87.30 (74.00,102.53)	0.761
Drinking			0.176
No	5487 (95.60%)	2368 (96.30%)	
Yes	254 (4.40%)	92 (3.70%)	
Smoking			0.775
No	4515 (78.60%)	1927 (78.30%)	
Yes	1226 (21.40%)	533 (21.70%)	
WBC (10 ⁹ /L)	10.70 (8.10,14.10)	10.70 (8.00,14.00)	0.522
Anion_gap(mmol/L)	14.00 (11.00,16.00)	13.00 (11.00, 16.00)	0.358
Calcium (mmol/L)	8.50 (8.10,8.90)	8.50 (8.10,9.00)	0.579
Chloride (mmol/L)	105.00 (101.00,108.00)	105.00 (101.00,108.00)	0.904
Glucose (mg/dL)	144.00 (115.00, 194.00)	144.00 (114.00,195.00)	0.572

Potassium (mmol/L)	4.20 (3.80, 4.60)	4.20 (3.90,4.60)	0.869
Scr.(mmol/L)	1.00 (0.80, 1.40)	1.00 (0.80,1.40)	0.605
BUN (mg/dL)	20.00 (14.00,31.00)	20.00 (14.00,31.00)	0.967
Bicarbonate(mmol/L)	23.00 (21.00, 26.00)	23.00 (21.00, 26.00)	0.698
Phosphate(mg/dL)	3.50 (2.90, 4.20)	3.50 (2.98, 4.20)	0.814
Heart_rate(beats/min)	82.00(73.00, 94.00)	82.00 (73.00, 94.00)	0.744
Respiratory_rate (breaths/min)	17.00 (14.00,21.00)	17.00 (14.00, 21.00)	0.263
SBP (mmHg)	125.00 (109.00,143.00)	124.00 (109.00, 142.00)	0.432
DBP (mmHg)	66.00 (55.00,78.00)	66.00 (55.00, 78.00)	0.691
eGFR(mL/min/1.73 m ²)	72.96 (44.89, 94.17)	72.03 (46.75, 94.60)	0.409
SOFA.	4.00 (2.00,6.00)	4.00 (2.00,6.00)	0.297
APSI	39.00 (30.00, 51.00)	39.00 (30.00, 49.00)	0.186
SIRS	2.00 (2.00,3.00)	3.00 (2.00,3.00)	0.788
Hb (g/dL)	10.50 (9.1,12.1)	10.60 (9.10,12.30)	0.235
RDW	14.10 (13.30, 15.20)	14.10 (13.20, 15.20)	0.646
HRR	7.40 (6.10, 8.78)	7.40 (6.31, 8.91)	0.219
RRT			0.281
No	5618 (97.90%)	2417 (98.30%)	
Yes	123 (2.10%)	43 (1.70%)	
Insulin			0.849
No	553 (9.60%)	241 (9.80%)	
Yes	5188 (90.40%)	2219 (90.20%)	
Vasoactive_agents			0.766
No	3056(53.20%)	1319 (53.60%)	
Yes	2685(46.80%)	1141 (46.40%)	
Atrial_fibrillation.			0.833
No	3882 (67.60%)	1670 (67.90%)	
Yes	1859 (32.40%)	790 (32.10%)	
Stroke			1.000
No	4532 (78.90%)	1942 (78.90%)	
Yes	1209 (21.10%)	518 (21.10%)	
hypertension			
No	2657 (46.30%)	1162 (47.20%)	0.441
Yes	3084 (53.70%)	1298 (52.80%)	
Hyperlipidemia.			0.490
No	2359 (41.10%)	990 (40.20%)	
Yes	3382 (58.90%)	1470 (59.80%)	
CHF			0.514
No	3797 (66.10%)	1646 (66.90%)	
Yes	1944 (33.90%)	814 (33.10%)	
MI			0.893

No	5130 (89.40%)	2195 (89.20%)	
Yes	611 (10.60%)	265 (10.80%)	
CHD.			0.336
No	2593 (45.20%)	1082 (44.00%)	
Yes	3148 (54.80%)	1378 (56.00%)	
hosp_day	7.19 (4.74,11.13)	7.06 (4.66, 11.17)	0.470
icu_day	2.23 (1.43, 3.97)	2.21 (1.41, 3.96)	0.670

Continuous variables are presented as median (interquartile range), and categorical variables are presented as n (%). HRR: hemoglobin-to-red blood cell distribution width ratio; Hb: hemoglobin; RDW: red blood cell distribution width; SOFA: Sequential Organ Failure Assessment; APS III: Acute Physiology Score III; SIRS: Systemic Inflammatory Response Syndrome; eGFR: Estimated glomerular filtration rate; WBC: White blood cell count; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; CHF: Congestive heart failure; MI: Myocardial infarction; CHD: Coronary heart disease; RRT: Renal replacement therapy; Scr: Serum creatinine; BUN: Blood urea nitrogen.

The training dataset for this study included a total of 5,741 subjects, of whom 896 (15.6%) had DKD. As shown in **Table 2**, compared with the non-DKD group, patients in the DKD group had elevated serum creatinine (Scr) and blood urea nitrogen (BUN) levels, as well as a significantly lower estimated glomerular filtration rate (eGFR) ($P < 0.05$). Regarding hematological parameters, the RDW level in the DKD group was significantly higher than that in the non-DKD group, while Hb and HRR were lower ($P < 0.05$). Additionally, the anion gap, serum potassium, and serum phosphorus levels in the DKD group were elevated compared to those in the non-DKD group ($P < 0.05$).

Table 2.

Baseline Characteristics of Patients with DKD and Non-DKD.

	Non-DKD(n=4845)	DKD(n=896)	P-value
Age.	70.00(61.00, 78.00)	73.00 (64.00, 80.00)	<0.001
Gender.			0.005
Female	2028(41.90%)	329(36.70%)	
male	2817(58.10%)	567(63.30%)	
Race			0.002
WHITE	2957(61.00%)	496(55.40%)	
OTHER	1888(39.00%)	400 (44.60%)	
Weight	87.00(73.40, 102.75)	86.03(73.07, 102.03)	0.331
Smoking			<0.001
No	3749(77.40%)	766(85.50%)	
Yes	1096(22.60%)	130(14.50%)	
Drinking			0.032
No	4618(95.30%)	869(97.00%)	
Yes	22(4.70%)	27(3.00%)	

WBC	10.80(8.10, 14.20)	10.30(8.00, 13.83)	0.064
Anion_gap	13.00(11.00, 16.00)	15.00(12.00, 18.00)	<0.001
Calcium	8.50(8.10, 8.90)	8.60(8.20, 9.00)	<0.001
Chloride.	105.00(101.00, 108.00)	103.00(98.00, 107.00)	<0.001
Glucose	143.00(115.00, 193.00)	150.00(116.00, 199.00)	0.074
Potassium	4.20(3.80, 4.60)	4.50(4.00, 4.90)	<0.001
Sodium	139.00(136.00, 141.00)	138.00(135.00, 141.00)	<0.001
Scr	0.90(0.70, 1.20)	1.80(1.30, 3.40)	<0.001
BUN	18.00(13.00, 27.00)	34.00(23.00, 55.00)	<0.001
Bicarbonate	24.00(21.00, 26.00)	22.00(20.00, 25.00)	<0.001
Phosphate	3.50(2.90, 4.10)	4.00(3.30, 4.90)	<0.001
Heart_rate	82.00(73.00, 94.00)	80.00(72.00, 92.25)	0.035
Respiratory_rate	17.00(14.00, 21.00)	18.00(15.00, 22.00)	<0.001
SBP.	125.00(109.00, 142.00)	125.00(109.00, 145.00)	0.517
DBP	66.00(55.00, 78.00)	65.00(54.00, 78.00)	0.503
Hb	10.70(9.20, 12.30)	9.70(8.40, 11.22)	<0.001
RDW	14.00(13.20, 15.10)	14.60(13.60, 15.90)	<0.001
HRR	7.56(6.24, 8.92)	6.50 (5.52, 7.85)	<0.001
SIRS	3.00(2.00, 3.00)	2.00(2.00, 3.00)	<0.001
APSO	38.00(29.00, 49.00)	46.00(38.00, 57.00)	<0.001
SOFA	4.00(2.00, 5.00)	5.00(3.00, 7.00)	<0.001
eGFR	79.45(54.86, 96.48)	35.35(16.11, 53.31)	<0.001
RRT			<0.001
No	4789(98.80%)	829(92.50%)	
Yes	56(1.20%)	67(7.50%)	
Insulin			<0.001
No	503(10.40%)	50(5.60%)	
Yes	4342(89.60%)	846(94.40%)	
Vasoactive_agents			0.404
No	2591(53.50%)	465(51.90%)	
Yes	2254(46.50%)	431(48.10%)	
Atrial_fibrillation			0.040
No	3303 (68.20%)	579 (64.60%)	
Yes	1542 (31.80%)	317 (35.40%)	
Stroke			0.017
No	3852 (79.50%)	680 (75.90%)	
Yes	993 (20.50%)	216 (24.10%)	
hypertension			
No	1834 (37.90%)	823 (91.90%)	<0.001
Yes	3011 (62.10%)	73 (8.10%)	
Hyperlipidemia			<0.001
No	2040 (42.10%)	319 (35.60%)	
Yes	2805 (57.90%)	577 (64.40%)	
CHD			<0.001

No	2287 (47.20%)	306 (34.20%)	
Yes	2558 (52.80%)	590 (65.80%)	
MI			<0.001
No	4401 (90.80%)	729 (81.40%)	
Yes	444 (9.20%)	167 (18.60%)	
CHF			<0.001
No	3354 (69.20%)	443 (49.40%)	
Yes	1491 (30.80%)	453 (50.60%)	
hosp_day	6.98 (4.66, 10.90)	8.64 (5.57, 12.74)	<0.001
icu_day	2.21 (1.41, 3.90)	2.32 (1.53, 4.25)	0.029

3.2.Association between HRR and Risk of DKD.

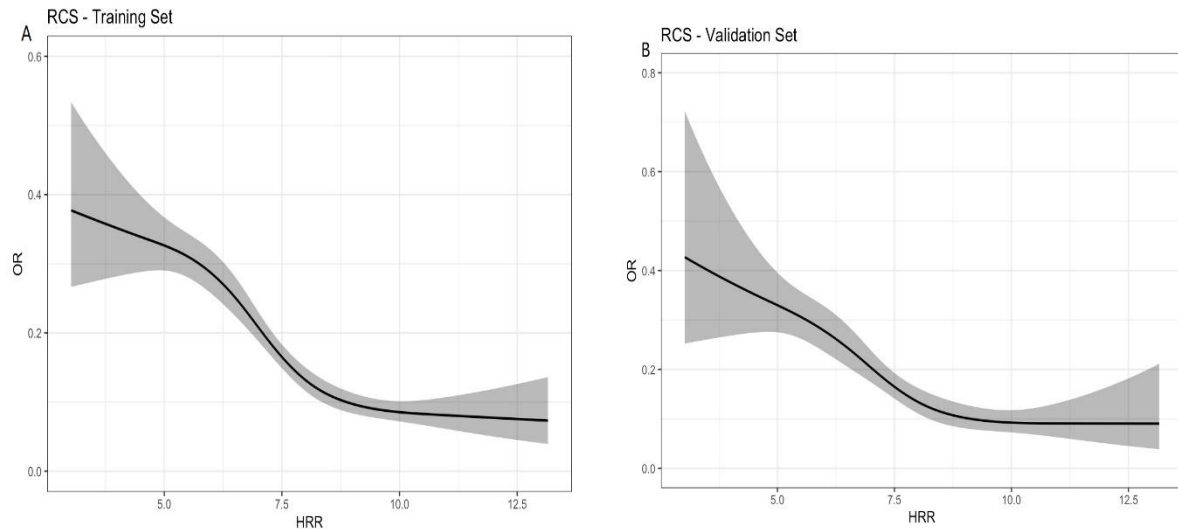
Multivariate logistic regression analysis was performed on the training set data, as shown in (**Table 3**), With HRR treated as a continuous variable, HRR was significantly associated with the risk of DKD in both Model 1 and Model 2 (both $p < 0.05$). In Model 3, which fully adjusted for confounding factors, it was found that for every 1-unit increase in HRR, the risk of DKD decreased by 23%. Considering the possibility of a nonlinear relationship between HRR and DKD risk, we performed an RCS analysis (**Figure 2**), which identified the optimal HRR cutoff value in the training set as 6.9492. Using this value as the cutoff, we divided both the training and validation sets into low HRR (< 6.9492) and high HRR (≥ 6.9492) groups and performed multivariate regression analysis again. The results showed that in training set model 3, compared with the low HRR group (< 6.9492), the high HRR group (≥ 6.9492) had a reduced risk of DKD (OR = 0.38, 95% CI: 0.33–0.45, $P < 0.001$). Similarly favorable validation results were observed in the validation set (OR = 0.44, 95% CI: 0.34–0.56, $P < 0.001$).

Table 3.

Variable	Model I OR(95%CI)	P-value	Model II OR(95%CI)	P-value	Model III OR(95%CI)	P-value
HRR	0.77(0.74, 0.80)	<0.001	0.76(0.73, 0.80)	<0.001	0.77(0.73, 0.80)	<0.001
Training						
Low-HRR	1 Reference		1 Reference		1 Reference	
High-HRR	0.39(0.34, 0.45)	<0.001	0.38(0.33, 0.45)	<0.001	0.38(0.33, 0.45)	<0.001
Validation						
Low-HRR	1 Reference		1 Reference		1 Reference	
High-HRR	0.43(0.34, 0.53)	<0.001	0.41(0.33, 0.52)	<0.001	0.44(0.34, 0.56)	<0.001

Model 1: HRR. Model 2: Based on HRR, age, sex, race, weight, smoking history, alcohol consumption history. Model 3: Model 2 adjusted for white blood cell count, glucose, atrial fibrillation, stroke, hyperlipidemia, CHD, MI, CHF, and insulin.

Figure2.

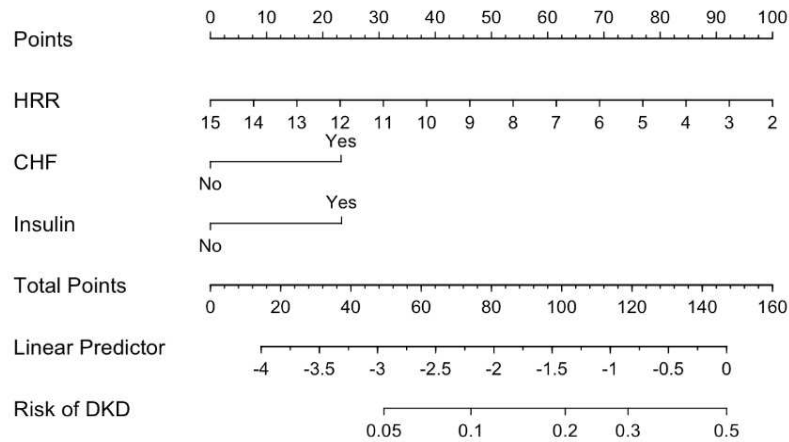


Restrained cubic spline (RCS) analysis of the training set (A) and validation set (B).

3.3. Nomogram

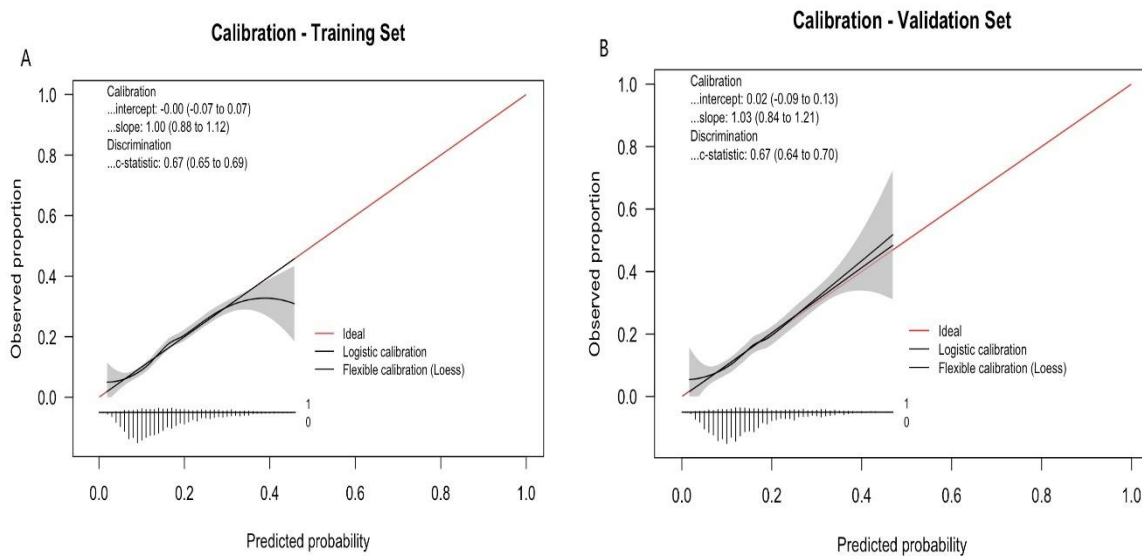
The results of multivariate logistic regression analysis in the training set showed that multiple clinical indicators were significantly associated with the risk of DKD ($p < 0.05$). To ensure the model's simplicity and accuracy, we conducted further iterative testing of the C-index results. Ultimately, we identified HRR, heart failure, and insulin use as key variables for the risk of DKD and used them to construct a nomogram model (**Figure 3**). The results showed that the C-index of the model in the training set was 0.6725 (95% CI: 0.6536–0.6913). The C-index of the validation set was 0.6749 (95% CI: 0.6453–0.7045), demonstrating high consistency with the performance of the training set. Receiver operating characteristic (ROC) curve analysis further confirmed the model's reliability; the predicted probabilities for both the training set (**Figure 4A**) and the validation set (**Figure 4B**) were generally consistent with the observed values, with no significant overestimation or underestimation.

Figure 3



This study included three predictive variables in the nomogram: HRR, insulin, and CHF.

Figure 4.



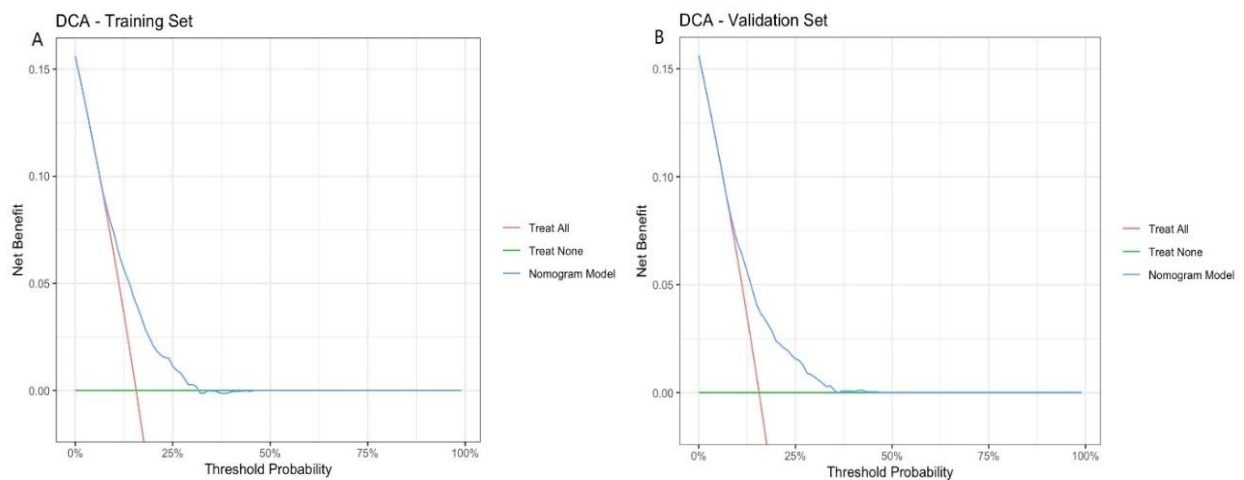
The calibration curves for the training set (A) and validation set (B) show good agreement between the model-predicted probabilities and the observed probabilities.

3.4. Decision Curve Analysis

As shown in **Figure 5A**, in the training set, when the risk threshold ranges from 10% to 40%, patients derive significant benefits from clinical interventions guided by the HRR-based prediction model, indicating that the model exhibits good discriminatory performance. In the validation set, the risk threshold remains largely consistent, and the model continues to perform stably and reliably (**Figure 5B**), which is of great significance

for the early risk stratification and management of DKD.

Figure 5.

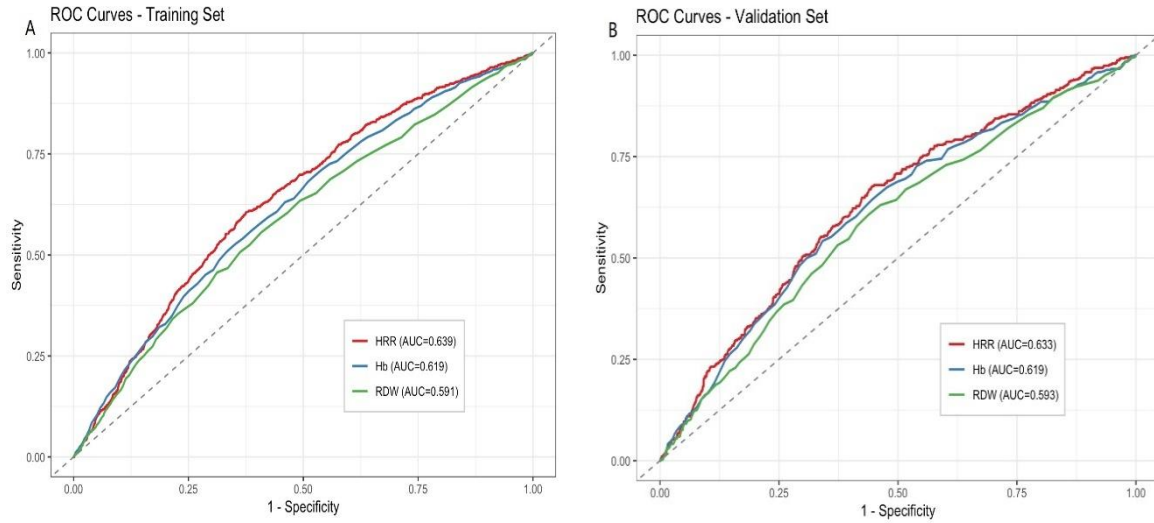


Receiver operating characteristic (ROC) curve analysis for DKD in the training set (A) and test set (B). The threshold probability (0%–100%) on the x-axis represents the cutoff value at which clinicians would consider intervention. The y-axis shows net benefit, which measures the net gain (benefit from true positives minus the loss from false positives) of using the model for decision-making at that threshold.

3.5. ROC curve analysis

We evaluated the predictive performance of HRR, Hb, and RDW for the risk of DKD in both the training and validation sets. As shown in **Figure 6A**, in the training set, the area under the curve (AUC) for HRR, Hb, and RDW were 0.639, 0.619, and 0.591, respectively. In the validation set, the AUCs for HRR, Hb, and RDW were 0.633, 0.619, and 0.593, respectively (**Figure 6B**). The AUC of HRR in the training set was significantly higher than that of Hb and RDW ($P < 0.001$). In the validation set, the differences in AUC between HRR and Hb ($P = 0.039$) and between HRR and RDW ($P = 0.004$) remained statistically significant. HRR demonstrated consistent discriminatory performance across both cohorts.

Figure 6.

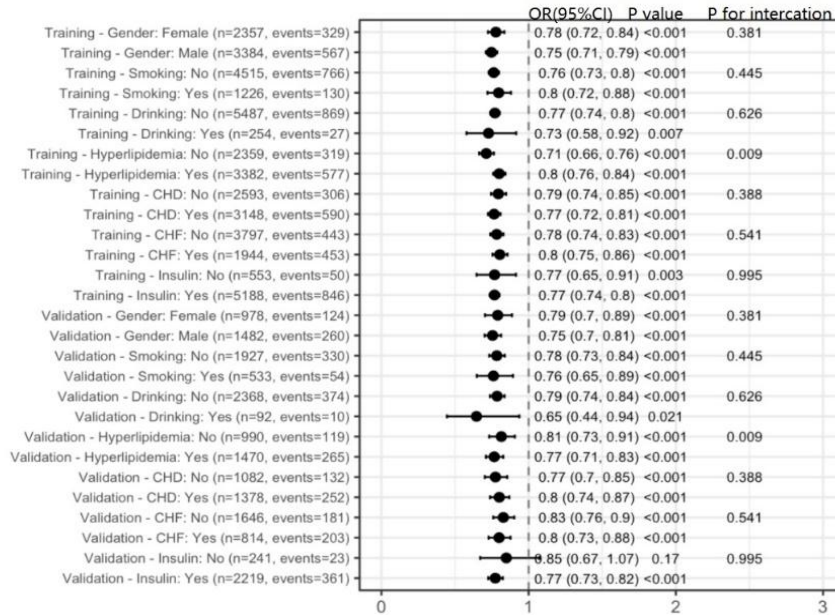


Comparative analysis of ROC curves for HRR, Hb, and RDW in predicting the onset of DKD in the training set (A) and validation set (B).

3.6. Subgroup analysis

We further examined the association between HRR and the risk of developing DKD through subgroup analysis. As shown in [Figure 7](#), Gender ($P=0.381$), Smoking ($P=0.445$), Drinking ($P=0.626$), CHD ($P=0.388$), CHF ($P=0.541$), and Insulin ($P=0.995$) showed no significant interactions in the training set. Both the training and validation sets showed an interaction between HRR and the presence or absence of hyperlipidemia (P for interaction < 0.05). It is worth noting that in the training set, HRR had a lower OR of 0.71 (95% CI: 0.66, 0.76) in the non-hyperlipidemic subgroup, indicating a more significant protective effect compared to the hyperlipidemic subgroup (OR= 0.80, 95% CI: 0.76, 0.84). In contrast, the validation set showed the opposite trend, with the OR in the hyperlipidemia subgroup (OR=0.77, 95% CI: 0.71, 0.83) being lower than that in the non-hyperlipidemia group (OR=0.81, 95% CI: 0.73, 0.91). Except for hyperlipidemia, the analysis results for the remaining subgroups were consistent across both cohorts.

Figure 7.



3.7. Machine learning model

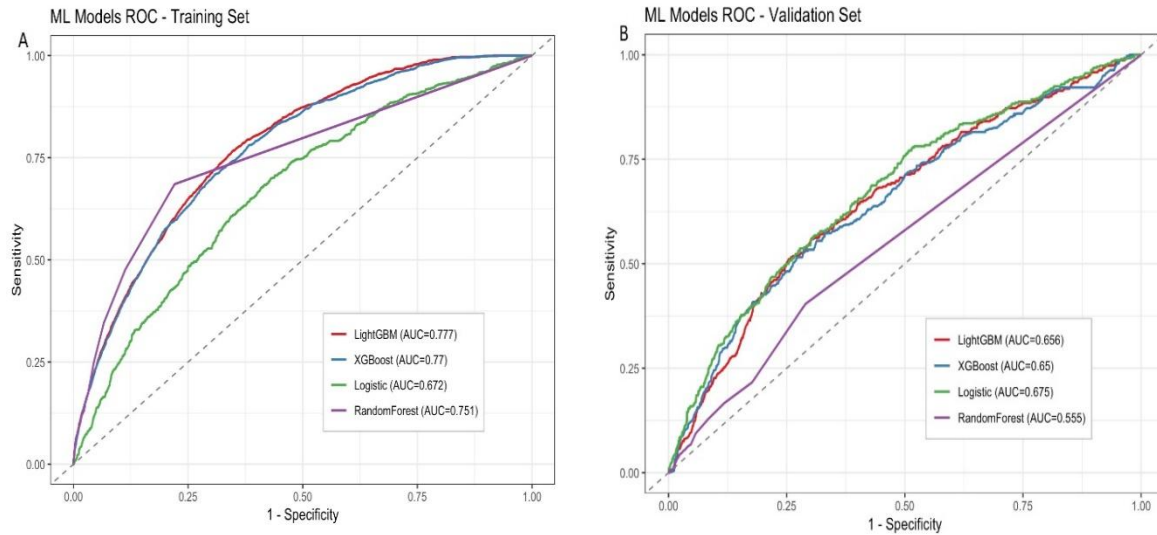
3.7.1 Model Construction and Evaluation

To more accurately assess the association between HRR and the risk of developing DKD, we selected HRR, CHF, and insulin levels based on the results obtained from multivariate regression analysis to construct a model. We then compared four classic machine learning prediction models: LightGBM, XGBoost, Logistic Regression, and Random Forest (RF). We evaluated the performance of the machine learning models using accuracy, specificity, sensitivity, positive predictive value (PPV), negative predictive value (NPV), and AUC. As shown in **Figure 8A**, the LightGBM method achieved the highest prediction accuracy in the training set, with an AUC of 0.7774 (0.7621, 0.7927), a sensitivity of 0.7656, and a specificity of 0.6535. In the validation set, although the NPV remained at a high level (>0.86), the PPV was low (0.20–0.26). Overall, the LightGBM model performed better than the other models (**Table 4**).

	Sensitivity	Specificity	NPV	PPV	Accuracy	AUC
Training						
LightGBM	0.7656	0.6535	0.9378	0.2901	0.6710	0.7774
XGBoost	0.7087	0.6918	0.9278	0.2984	0.6945	0.7699
Logistic	0.6998	0.5692	0.9111	0.2310	0.5896	0.6725
RandomForest	0.6853	0.7796	0.9305	0.3650	0.7648	0.7510
Validation						
LightGBM	0.5599	0.6980	0.8956	0.2553	0.6764	0.6560
XGBoost	0.5312	0.7139	0.8917	0.2556	0.6854	0.6502
Logistic	0.7786	0.4836	0.9219	0.2181	0.5297	0.6749

RandomForest	0.4036	0.7105	0.8656	0.2050	0.6626	0.5554
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Figure 8.

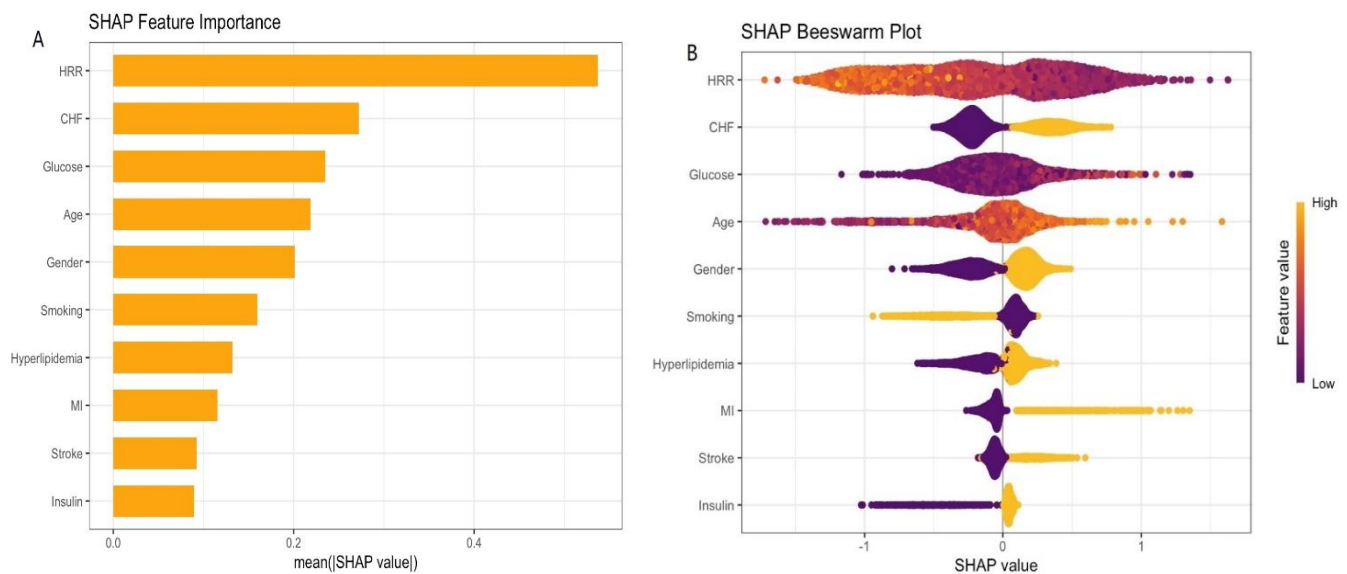


Area under the curve for the training set (Group A) and the validation set (Group B). The model includes a total of three variables: HRR, insulin, and CHF.

3.7.2. SHAP feature analysis of the DKD risk factor assessment

To further enhance the model's clinical utility, we used the SHAP method to identify the variables most closely associated with the onset of DKD. The results are shown in **Figure 9A**, HRR contributed the most to the model's output, with an average absolute SHAP value of 0.5308, which was significantly higher than that of CHF, blood glucose, age, and gender. As shown in the SHAP heatmap in **Figure 9B**, purple dots represent low feature values, while yellow dots represent high values. From the results, we can see that elevated HRR exhibits a strong negative SHAP value, indicating a negative correlation with DKD risk. Conversely, increases in the values of features such as CHF, Glucose, Age, Hyperlipidemia, MI, and Stroke correspond to positive SHAP values, indicating that they contribute to an increased risk of DKD. Insulin use exhibits a positive SHAP value in the model, which may reflect the fact that T2DM patients using insulin typically have a longer disease duration and more severe disease.

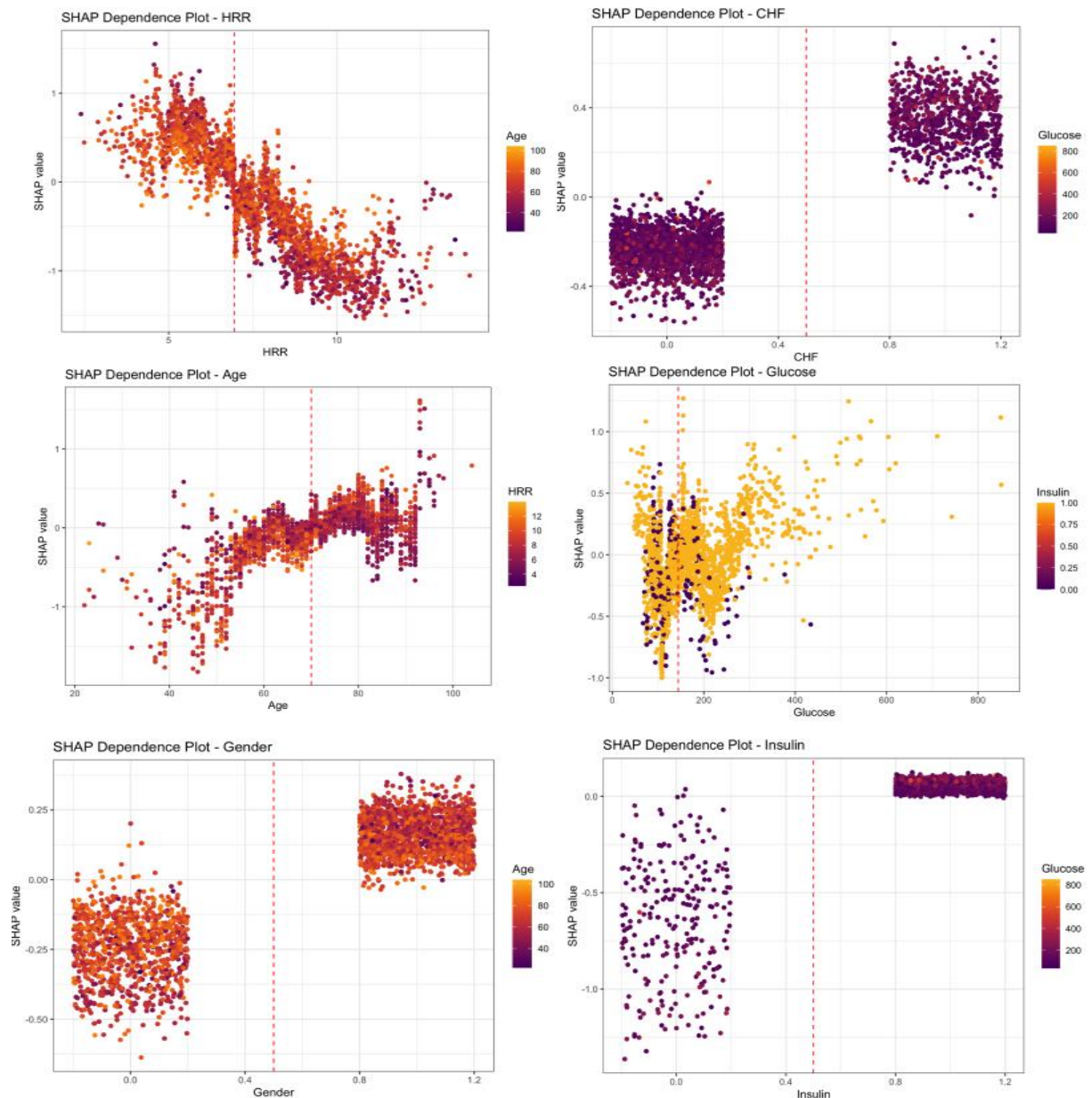
Figure 9.



3.7.3. SHAP dependency graph

As shown in **Figure 10**, the SHAP dependency plot reveals the dynamic relationship between each feature and the risk of DKD. The optimal protective threshold for HRR is 6.9492; below this value, the SHAP score decreases rapidly as HRR increases. However, when HRR exceeds 0.8–1.0, the SHAP score tends to stabilize, and the risk of DKD remains at a low level. Furthermore, characteristics such as blood glucose >144 mg/dL, age >70 years, concomitant heart failure, and male gender are all associated with positive SHAP values, leading to an increased risk of DKD. We also identified an interaction between HRR and age. For elderly patients aged >70 years, if HRR is below 0.7, the risk of DKD is significantly higher compared to those with normal HRR. The interaction between hyperglycemia and heart failure, as well as insulin use, demonstrates that the concurrent presence of all three factors leads to a significantly increased risk of DKD.

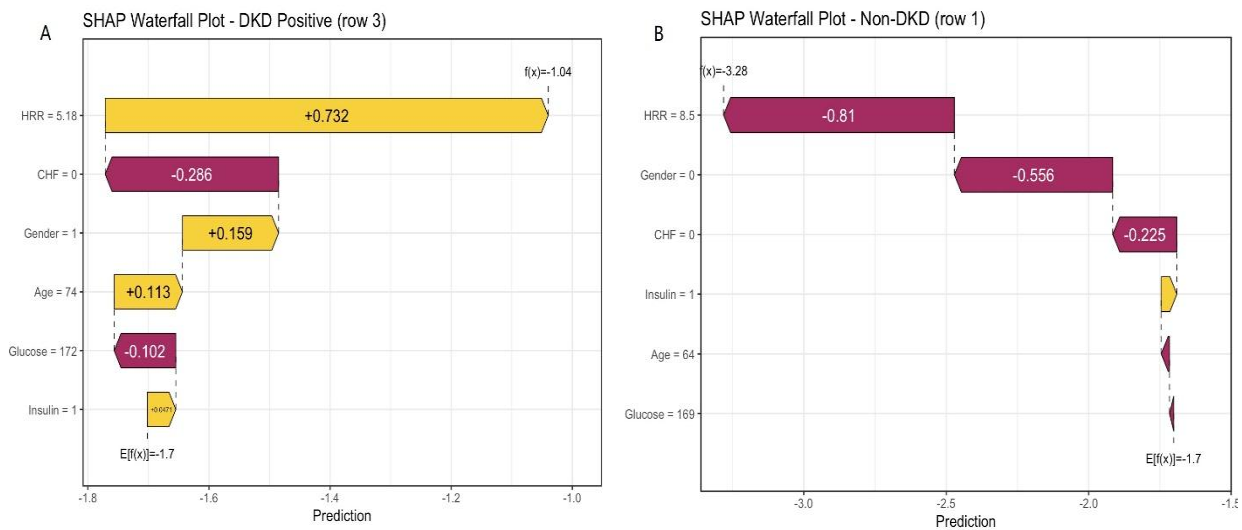
Figure 10.



3.7.4.SHAP plot

To elucidate the model's predictive mechanisms for individual patients, we constructed a SHAP waterfall plot. As shown in **Figure 11A**, a low HRR (5.18) was the primary factor contributing to an increased risk of DKD (+0.732), while male gender (+0.159) and advanced age (+0.113) also increased the risk of developing the condition. The absence of heart failure (-0.286) partially mitigates this risk. As shown in **Figure 11B**, among patients without DKD, a high HRR (8.50) provides the strongest protective effect (-0.81), keeping the risk of DKD at a low level.

Figure 11.



Two representative case examples illustrating local interpretations of DKD risk assessments using SHAP waterfall plots. (A) Type 2 diabetes patients predicted to develop diabetic kidney disease (DKD); (B) Type 2 diabetes patients predicted not to develop diabetic kidney disease (Non-DKD). Factors that increase the predicted score (elevating DKD risk) are shown in yellow, while factors that decrease the predicted score (reducing DKD risk) are shown in purple.

4. Discussion

Based on the MIMIC-IV database, this study evaluated the clinical association between HRR and the risk of developing DKD through a large-scale retrospective cohort analysis. Multivariate regression analysis in this study revealed that elevated HRR is significantly associated with a reduced risk of DKD and serves as an independent protective factor against DKD. RCS and SHAP analyses jointly identified an optimal risk threshold of 0.6949 for HRR, providing a quantifiable reference standard for clinical risk stratification of DKD.

Previous reports have primarily focused on studying the relationship between Hb or RDW and the development of DKD in isolation^[16, 17]. However, HRR incorporates both Hb and RDW, reflecting multiple pathophysiological mechanisms such as inflammation and hypoxia simultaneously, thereby enhancing the ability to stratify the risk of DKD. As a novel predictive biomarker, HRR has been shown to correlate with the onset and progression of various diseases, including diabetic retinopathy (DR), cardiovascular disease, and acute kidney injury^[18-21]. Data analysis in this study indicates that the AUC values for HRR in the training and validation sets were 0.699 and 0.633, respectively, which are significantly higher than those for RDW and Hb alone. In patients with T2DM, elevated blood glucose levels can disrupt erythrocyte homeostasis through multiple mechanisms, leading to reduced erythrocyte deformability and increased adhesion, which

in turn causes a further decrease in hemoglobin concentration and an increase in RDW^[22]. Elevated RDW typically indicates the presence of oxidative stress and chronic inflammatory responses in the body^[23]. Existing studies have confirmed that inflammatory responses can lead to a persistent decline in hemoglobin levels by further exacerbating oxidative stress^[24, 25], hereby creating a vicious cycle. Once anemia develops, capillary perfusion and cellular oxygen supply are significantly reduced. The body compensates by increasing cardiac output, which in turn leads to increased renal blood flow and induces glomerular hyperfiltration, ultimately causing renal injury^[26].

In recent years, machine learning methods have demonstrated significant potential in DKD risk assessment, offering new insights for clinical decision-making^[27, 28]. To validate the performance of HRR in DKD risk stratification, we compared four representative machine learning algorithms: LightGBM, XGBoost, logistic regression, and random forest (RF). The results showed that LightGBM demonstrated the best discriminatory performance, with an AUC value of 0.7774 (0.7621–0.7927). These findings are consistent with the conclusions of studies by Zou^[29] and Deng et al.^[30] which also confirmed that LightGBM has superior discriminatory performance for DKD risk stratification. Feature importance analysis based on SHAP values revealed that HRR ranked first among all variables. Previous studies on DKD risk prediction models built using machine learning have also shown that hemoglobin and RDW were confirmed as important predictive variables in SHAP analysis^[16, 31]. CHF was the second most critical predictive variable in the SHAP analysis, following HRR. Our dependency graph interaction analysis showed that patients with CHF combined with hyperglycemia had higher positive SHAP values. This demonstrates that the renal perfusion insufficiency caused by CHF and the inflammatory stress mediated by hyperglycemia produce a synergistic effect, with hyperglycemia further exacerbating the damaging effects of CHF on the kidneys, consistent with the pathophysiological mechanism of “cardiorenal syndrome”^[32]. The advantage of SHAP analysis lies in its ability to effectively uncover the internal mechanisms of predictive models, providing a clearer and more intuitive demonstration of how each variable influences the predictive outcome. The decision tree model constructed in this study based on HRR, CHF, and insulin use can be integrated with SHAP interpretability analysis. This not only facilitates rapid clinical application but also enhances the transparency and credibility of the risk prediction process, providing a reliable basis for the precise assessment and personalized prevention and treatment of DKD.

This study did not include renal function indicators such as eGFR in the model analysis because the diagnostic criteria for DKD already incorporate these variables, which could lead to data leakage. In our preliminary statistical analysis, we also found that including

eGFR not only overestimates the actual predictive value but also interferes with the predictive effect of HRR. Of course, this study still has some limitations: First, as a retrospective cohort study, it may not establish a causal relationship between HRR and the onset of DKD, but only confirm a clear correlation between the two. Second, the MIMIC-IV database lacks important clinical information regarding patients' lifestyles, long-term glycemic control trends, and medication regimens, making it impossible to completely rule out the potential confounding effects of these factors. Finally, we did not explore the specific molecular mechanisms by which HRR influences the development of DKD, and the relationship between dynamic changes in HRR and disease progression remains unclear. To truly translate HRR into clinical practice, future efforts should involve large-scale, multicenter prospective cohort studies and external validation to further assess the robustness of its predictive performance and its generalizability across populations, thereby providing more reliable evidence for clinical application.

Despite certain limitations, the findings of this study still provide practical guidance for the early prevention, control, and management of DKD from a clinical perspective. In clinical practice, approximately 20%–30% of DKD patients exhibit normal protein levels in routine urine tests. Serum creatinine and estimated eGFR do not show significant abnormalities until glomerular filtration rate (GFR) has decreased by $\geq 50\%$ ^[33-35]. In contrast, HRR can become abnormal even before significant renal damage occurs. This may stem from hyperglycemia-induced inflammatory responses and tissue damage, which in turn affect erythropoiesis and cause renal tissue hypoxia^[36, 37], ultimately leading to the early onset of HRR. Calculated using the clinically common and cost-effective Hb and RDW, HRR can serve as a supplementary screening tool for DKD. By incorporating HRR into traditional assessment metrics such as glycated hemoglobin, urine albumin-to-creatinine ratio (UACR), and duration of diabetes, it may be possible to further optimize the DKD risk assessment system. This could facilitate earlier clinical prevention and intervention, improve survival outcomes for patients with end-stage renal disease, and significantly reduce subsequent healthcare costs.

Conclusion

Our findings confirm that HRR is significantly more effective than Hb and RDW in assessing the risk of DKD and shows promise as a novel biomarker for predicting the onset and progression of DKD. By incorporating HRR into machine learning models, we can more accurately assess the risk of DKD onset and progression in patients with T2DM, thereby providing a more intuitive tool to support early clinical intervention and personalized management.

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Author contributions

FL: Software, methodology, writing—original draft. YL: Methodology, writing—original draft; writing—review & editing. LM: Data organization, supervision, writing—review & editing. HR: Data organization, funding acquisition, investigation, writing—review & editing. JZ: Investigation, supervision, validation, writing—review & editing.

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Data availability

This study analyzed the data from the public database. The data can be obtained through the following link: <https://mimic.physionet.org/>.

Declarations

Ethical approval

This study was conducted using the publicly available, anonymized MIMIC-IV database, and all data usage strictly adhered to the database access agreement. The establishment of this database was approved by the Institutional Review Boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center. As this study is a retrospective analysis and the data have been fully de-identified, individual informed consent from patients was not required.

Consent for publication

Not applicable.

Conflict of Interest

Author declares no conflict of interest.

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