Predictive Value of Non-Traditional Lipid Parameters NHHR and the TyG Index for Rapid Kidney Function Decline in Diabetic Patients: A Longitudinal Cohort Study Based on CHARLS

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Abstract. Objective: The objective of this study was to investigate the predictive value of the non-high-density lipoprotein cholesterol (nonHDL-C)/high-density lipoprotein cholesterol (HDL-C) ratio (NHHR) and the triglyceride–glucose (TyG) index for rapid kidney function decline (RKFD) in Chinese patients with diabetes. Methods: This study used data from the China Health and Retirement Longitudinal Study (CHARLS) 2011–2015. A total of 1051 patients with diabetes were analyzed with rapid kidney function decline (RKFD) as the primary endpoint. Associations between NHHR and the TyG index with renal outcomes were examined using logistic regression models. Restricted cubic splines and subgroup analyses were performed to investigate potential linear relationships and consistency across population strata. Receiver operating characteristic (ROC) curves were used to assess the predictive performance of NHHR and the TyG index. Results: The study included 1051 participants. During a median follow-up of four years, 189 individuals (17.98%) developed RKFD. After full adjustment for confounding factors, both NHHR and the TyG index showed significant positive correlations with RKFD risk. Restricted cubic spline (RCS) analysis revealed linear relationships between both metrics and RKFD risk. ROC analysis demonstrated that adding the NHHR to the baseline model significantly improved predictive ability, whereas adding the TyG index did not result in a statistically significant improvement. Subgroup analyses indicated that the predictive role of the NHHR was more pronounced in women and non-smokers. Conclusion: In patients with diabetes, elevated levels of NHHR and the TyG index represent independent risk factors for RKFD, with NHHR exhibiting a more stable incremental predictive value.

1 Introduction

Diabetes is a major cause of chronic kidney disease (CKD), with a global prevalence of approximately 10.5% and a rapid rise in low- and middle-income countries, thus posing a major global health challenge. China's diabetes prevalence is about 11.2%, affecting over 140.9 million people[1].The risk of developing end-stage renal disease (ESRD) due to diabetes is also significantly increased[2]. Patients with diabetic nephropathy have higher risks of dialysis, kidney transplantation and all-cause mortality than diabetic patients without kidney disease[3]. Therefore, early identification of diabetic patients at high risk of rapid kidney function decline (RKFD) is critical to delay ESRD progression and improve patient outcomes.

Current clinical risk prediction for RKFD relies primarily on traditional indicators: baseline estimated glomerular filtration rate (eGFR) and urinary albumin-to-creatinine ratio (UACR)[4]. These markers are indispensable but show limited sensitivity for predicting dynamic renal function trajectories. In some patients, UACR may present at a late stage of the disease, failing to satisfy clinical demands for early detection and intervention[5]. Therefore, identification of novel biomarkers has become an urgent clinical research priority. These biomarkers should integrate multiple metabolic dysregulation features of diabetes, be readily accessible, and enable earlier warning of RKFD. In diabetic patients, lipid metabolism imbalance and insulin resistance play significant roles in renal impairment. The non-high-density lipoprotein cholesterol (non-HDL-C)/highdensity lipoprotein cholesterol (HDL-C) ratio (NHHR), which integrates levels of atherogenic and protective lipoproteins, has been associated with endothelial dysfunction and inflammation. These are key pathways in renal impairment progression[6]. NHHR is also strongly associated with atherosclerotic cardiovascular disease and metabolic disorders[7]. The triglyceride–glucose (TyG) index, exhibiting strong correlation with insulin resistance, serves as a reliable indicator for assessing insulin resistance[8, 9]. Previous data indicate that insulin resistance accelerates renal function decline by affecting renal hemodynamics, podocyte viability, and tubular function[10]. Cross-sectional studies or cohort analyses in general populations have suggested associations between NHHR or the TyG index and renal impairment[11, 12], but these findings have limitations. Most studies have not focused on diabetic

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patients, who are at high risk of RKFD. Few studies have systematically compared the predictive efficacy of NHHR and the TyG index for RKFD in the same cohort. These two indices reflect metabolic abnormalities in lipid metabolism and insulin resistance. Their independent contributions, dose-response relationships, and predictive value for RKFD in diabetic populations remain unclear.

This study, based on the China Health and Retirement Longitudinal Study (CHARLS) cohort, aims to systematically investigate the predictive role of baseline NHHR and the TyG index for rapid kidney function decline in diabetic patients. It seeks to clarify their dose-response relationship and evaluate their incremental predictive value. This could provide new evidence-based support for early identification of high-risk patients and optimization of clinical management strategies.

2 Materials and methods

2.1 Data source and study populations

This study is based on publicly available data from CHARLS, a nationally representative prospective cohort covering 28 provinces and municipalities. The baseline survey began in 2011, with follow up assessments conducted every two years thereafter. The second follow-up wave was completed in 2015, and duplicate fasting blood samples were collected during this period. The study protocol was approved by the Ethics Committee of Peking University (IRB00001052-11015), and all participants provided written informed consent[13]. Figure 1 illustrates the detailed flowchart of the inclusion and exclusion process. This study included participants aged ≥ 40 years with a baseline eGFR ≥15 $mL/min/1.73m^2$ and complete follow-up eGFR data. After excluding individuals with malignancy, missing key variables, no diabetes diagnosis, insufficient data to confirm diabetes, or extreme values, 1051 eligible participants were included in the final analysis.

2.2 Study variables and clinical definitions

Non-traditional lipid parameters are calculated as follows:

$$NHHR = [TC - (HDL\text{-}C)]/(HDL\text{-}C) \quad (1)$$

$$TyG = \ln[TG \times FPG/2] \quad (2)$$

In the Eq.(1), TC refers to the content of total cholesterol and HDL-C denotes the content of high-density lipoprotein cholesterol. In the Eq.(2), TG represents the content of triglyceride and FPG stands for fasting plasma glucose, which was measured by the glucose oxidase method. In the dataset, the levels of total cholesterol, triglyceride, and high-density lipoprotein cholesterol were all determined by the enzymatic colorimetric method. The unit of all the above variables is mg/dL.

Both indicators were quartile-stratified based on 2011 baseline values: Q1 (lowest) to Q4 (highest). Diabetes was defined as self-reported history of "being diagnosed with diabetes or hyperglycemia by a physician" or current use of antidiabetic medications (oral hypoglycemic agents or insulin). If no such self-reported diagnosis or medication history existed, diabetes was diagnosed if either fasting plasma glucose ≥ 7.0 $mmol/L$ and/or glycated hemoglobin ≥ 6.5% was present.

2.3 Definition of endpoint event

In this study, the endpoint event was RKFD, defined as an annual eGFR decline rate of ≥3 $mL/min/1.73m^2$[14, 15]. eGFR was calculated using the CKD EPI 2021 creatinine equation. Participants' eGFR values in 2011 and 2015 were used as the baseline and endpoint measures of renal function, respectively.

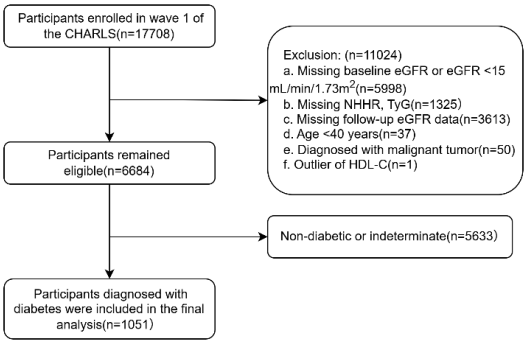

Figure 1. Flowchart of participant selection.

2.4 Statistical analysis

Normality of continuous variables was assessed using the AndersonDarling test and Q-Q plots. Normally distributed variables are presented as mean ± standard deviation and compared between groups using t-tests. Non-normally distributed variables are presented as median (interquartile range) and compared between groups using the Mann-Whitney U test. Categorical variables are presented as frequency (percentage) and analyzed using χ^2 tests. Multivariate logistic regression was used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) of NHHR and the TyG index for RKFD, with a three-stage model constructed. Model 1: Unadjusted model; Model 2: Adjusted for sociodemographic variables; Model 3: Further adjusted for behavioral factors, disease status, medication use, and laboratory indicators. Linear trend tests were conducted at the quartile median level. Restricted cubic splines (RCS) were used to generate dose-response curves, with 5 nodes and the 50th percentile (P50) as the reference value. Receiver operating characteristic (ROC) curves were constructed to compare the area under the curve (AUC) between the basic model and the models incorporating NHHR or the TyG index. DeLong's test was applied to assess significant differences in AUC values. Additionally, subgroup analyses and interaction tests were conducted stratified by age, gender, smoking status, drinking status, hypertension, dyslipidemia, body mass index (BMI), antidiabetic medication use, lipid-lowering medication use, and glycated hemoglobin levels. A two-sided $p < 0.05$ was considered statistically significant.

3 Results

3.1 Baseline characteristics of the study population

The baseline characteristics of the participants were summarized in Table 1. A total of 1051 participants were included in the final analysis. Among these participants, 189 (17.98%) developed RKFD, while 862 (82.02%) did not. No significant differences were observed between the two groups in terms of age, sex, education level, marital status, residence, smoking status, alcohol consumption, hypertension, dyslipidemia, heart disease, liver disease, or medication use (all p > 0.05). However, compared with the non-RKFD group, the RKFD group had significantly higher levels of hemoglobin (Hb) (14.64 vs. 14.18 g/dL, p = 0.007), as well as significantly lower baseline eGFR (89.76 vs. 95.48 mL/min/1.73m2, $p < 0.001$), and high-density lipoprotein cholesterol (HDL-C) (45.04 vs. 48.93 mg/dL, $p = 0.003$). Two novel composite indices, NHHR (3.39 vs. 3.64, $p = 0.013$) and the TyG index (9.15 vs. 9.35, $p = 0.032$), were significantly higher in the RKFD group than in the non-RKFD group ($p < 0.001$ for all). These results suggest that both NHHR and the TyG index are closely associated with the occurrence of RKFD (Table 1).

Table 1. Baseline characteristics of the study population.

Variables	Overall	RKFD	Non-RKFD	p-value
Sample size	1051 (100.0%)	189 (17.98%)	862 (82.02%)	-
Age (years)	60.08 ± 8.60	59.85 ± 8.56	61.12 ± 8.71	0.072
Sex				0.959
Male	480 (45.67%)	86 (45.50%)	394 (45.71%)	
Female	571 (54.33%)	103 (54.50%)	468 (54.29%)	
Education level				0.813
College or above	15 (1.43%)	2 (1.06%)	13 (1.51%)	
High school	80 (7.61%)	13 (6.88%)	67 (7.77%)	
Elementary school and below	956 (90.96%)	174 (92.06%)	782 (90.72%)	
Marital status				0.125
Married	879 (83.63%)	151 (79.89%)	728 (84.45%)	
Others	172 (16.37%)	38 (20.11%)	134 (15.55%)	
Residence				0.402
Rural	422 (40.15%)	81 (42.86%)	341 (39.56%)	
Urban	629 (59.85%)	108 (57.14%)	521 (60.44%)	
Smoking status	403 (38.34%)	69 (36.51%)	334 (38.75%)	0.566
Alcohol consumption	416 (39.58%)	71 (37.57%)	345 (40.02%)	0.532
Hypertension	595 (56.61%)	112 (59.26%)	483 (56.03%)	0.418
Dyslipidemia	235 (22.36%)	41 (21.69%)	194 (22.51%)	0.808
Heart disease	183 (17.41%)	39 (20.63%)	144 (16.71%)	0.197
Liver disease	50 (4.76%)	12 (6.35%)	38 (4.41%)	0.256
Antidiabetic medication use	254 (24.17%)	43 (22.75%)	211 (24.48%)	0.616
Lipid-lowering medication use	137 (13.04%)	23 (12.17%)	114 (13.23%)	0.696
SBP (mmHg)	133.94 ± 21.17	133.71 ± 21.12	135.03 ± 21.43	0.442
DBP (mmHg)	76.88 ± 11.62	76.86 ± 11.48	76.96 ± 12.28	0.919
BMI (kg/m^2)	24.51 (5.17)	24.46 (5.12)	24.84 (5.51)	0.359
Waist circumference (cm)	89.40 (14.40)	89.35 (14.00)	89.60 (14.90)	0.921
Height (m)	1.58 ± 0.09	1.58 ± 0.09	1.57 ± 0.13	0.444
Weight (kg)	60.90 (15.90)	61.10 (16.00)	59.70 (14.80)	0.601
WBC (×109/L)	6.20 (2.30)	6.11 (2.38)	6.40 (2.00)	0.520
PLT (×109/L)	202.00 (92.00)	203.50 (91.00)	198.00 (92.00)	0.122
MCV (fl)	90.17 ± 8.18	90.11 ± 8.08	90.43 ± 8.63	0.639
HCT (%)	42.11 ± 5.93	42.21 ± 5.73	41.65 ± 6.78	0.291
Hb (g/dL)	14.56 ± 2.15	14.64 ± 2.15	14.18 ± 2.13	0.007
FPG (mg/dL)	139.14 (46.80)	139.59 (46.26)	137.70 (56.52)	0.185
HbA1c (%)	5.70 (1.60)	5.70 (1.60)	5.70 (1.70)	0.634
Serum Creatinine (mg/dL)	0.76 (0.23)	0.76 (0.23)	0.76 (0.24)	0.664
BUN (mg/dL)	15.41 (5.61)	15.38 (5.55)	15.57 (6.11)	0.926
UA (mg/dL)	4.34 (1.68)	4.35 (1.72)	4.26 (1.70)	0.160
Cystatin C (mg/L)	0.95 (0.27)	0.95 (0.27)	0.97 (0.28)	0.050
$eGFR$2011 (ml/min/1.73m^2)	90.79 ± 15.68	89.76 ± 15.30	95.48 ± 16.57	< 0.001
TC (mg/dL)	200.33 ± 42.26	199.92 ± 42.88	202.21 ± 39.34	0.478
TG (mg/dL)	137.18 (129.22)	138.95 (129.21)	127.44 (123.02)	0.465
HDL-C (mg/dL)	45.74 ± 15.39	45.04 ± 15.15	48.93 ± 16.07	0.003
LDL-C (mg/dL)	114.39 ± 40.58	113.73 ± 40.21	117.44 ± 42.22	0.271
CRP (mg/L)	1.32 (1.98)	1.29 (1.91)	1.39 (2.02)	0.498
NHHR	3.45 (2.23)	3.39 (2.12)	3.64 (2.74)	0.013
TyG	9.17 (1.10)	9.15 (1.10)	9.35 (1.17)	0.032

Notes: Data are presented as mean ± standard deviation for normally distributed continuous variables, median (interquartile range) for non-normally distributed continuous variables, and number (percentage) for categorical variables. RKFD: Rapid kidney function decline; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; BMI: Body mass index; WBC: White blood cell count; PLT: Platelet count; MCV: Mean corpuscular volume; HCT: Hematocrit; Hb: Hemoglobin; FPG: Fasting plasma glucose; HbA1c: Hemoglobin A1c; SCr: Serum creatinine; BUN: Blood urea nitrogen; UA: Uric acid; eGFR: Estimated glomerular filtration rate; TC: Total cholesterol; TG: Triglycerides; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; CRP: C-reactive protein; NHHR: Non-HDL to HDL cholesterol Ratio; TyG: Triglyceride-glucose ratio. p <0.05 was considered statistically significant.

3.2 Association of NHHR and TyG with the risk of RKFD

Multivariate logistic regression analysis with different adjustments, summarized in Table 2, were conducted to evaluate the associations between NHHR, the TyG index, and the risk of RKFD. In Model 2, adjustments were made for sociodemographic factors. In Model 3, additional adjustments included lifestyle factors, disease history, and key laboratory indicators. Specifically, each unit increase in NHHR was associated with a 15% higher risk of RKFD (OR = 1.15, 95% CI: 1.07–1.24, $p < 0.001$), while each unit increase in the TyG index correspondingly increased the risk of RKFD by 35% (OR = 1.35, 95% CI: 1.11–1.65, $p = 0.003$). Analysis by quartile further revealed risk trends: compared with the lowest quartile (Q1) of NHHR, the highest quartile (Q4) was associated with an 86% increased risk of RKFD (OR = 1.86, 95% CI: 1.16–3.00, $p = 0.010$), and the trend test was significant (p for trend = 0.012). A similar increasing trend was observed for the TyG index (p for trend = 0.038). These results remained robust after fully adjusting for known confounders, indicating that both NHHR and the TyG index are independent risk factors for RKFD.

3.3 Dose-response relationship between baseline NHHR and TyG with RKFD risk

Figure 2 illustrates the dose-response relationships between the NHHR, the TyG index, and RKFD, as derived from RCS analysis. Figure 2a-2c showed that NHHR was linearly and positively correlated with RKFD risk after full adjustment for confounding factors (nonlinear test, $p > 0.05$). Figure 2d-2f illustrates a positive association between the TyG index and RKFD risk. The dose-response curve suggested that RKFD risk increased with elevated TyG levels. Trend tests based on quartile grouping for both variables further supported the presence of significant dose-response relationships (NHHR: p for trend = 0.012; TyG: p for trend = 0.038).

3.4 Predictive role of baseline NHHR and TyG in RKFD risk among diabetic patients

Figure 3 presents the ROC curve analysis, which was used to evaluate the discriminative ability of three different models in predicting the risk of RKFD.

ROC curve analysis showed that the AUC of the basic model (including age, gender, education, residence, marital status, BMI, hypertension, dyslipidemia, alcohol consumption, HbA1c, uric acid, and blood urea nitrogen) was 0.562. The inclusion of NHHR (AUC = 0.603) and the TyG index (AUC = 0.594) shifted the ROC curves upward and to the left, significantly enhancing the models' discriminatory power. The addition of NHHR yielded the most pronounced improvement, indicating its superior effectiveness in boosting model discrimination. Table 3 further compares the AUC values of the three models using the DeLong test, confirming that the model incorporating NHHR had a significantly higher AUC than the basic model (p =0.045). Conversely, the AUC of the TyG index model showed no significant difference from the basic model (p =0.109).

Table 2. Association of the NHHR and TyG with RKFD.

	Model 1		Model 2		Model 3	
Character	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
NHHR	**1.15 (1.08-1.23)**	**<0.001**	**1.16 (1.09–1.24)**	**<0.001**	**1.15 (1.07–1.24)**	**<0.001**
Q1	ref		ref		ref	
Q2	1.06 (0.66–1.69)	0.812	1.08 (0.67–1.73)	0.749	1.13 (0.70–1.84)	0.617
Q3	1.03 (0.64–1.65)	0.905	1.05 (0.65–1.69)	0.840	1.14 (0.69–1.87)	0.603
Q4	1.68 (1.09–2.62)	0.020	1.79 (1.15–2.81)	0.011	1.86 (1.16–3.00)	0.010
p for trend		0.023		0.013		0.012
TyG	**1.34 (1.11–1.61)**	**0.002**	**1.38 (1.14–1.67)**	**0.001**	**1.35 (1.11–1.65)**	**0.003**
Q1	ref		ref		ref	
Q2	1.23 (0.64–1.65)	0.905	1.01 (0.62–1.62)	0.983	1.05 (0.64–1.72)	0.839
Q3	1.27 (0.81–2.01)	0.300	1.27 (0.81–2.02)	0.304	1.41 (0.88–2.27)	0.157
Q4	1.44 (0.93–2.26)	0.106	1.52 (0.97–2.40)	0.071	1.54 (0.96–2.48)	0.073
p for trend		0.066		0.040		0.038

Notes: Model 1, unadjusted crude representation; Model 2, adjusted for sociodemographic variables such as age, gender, educational level, location, and marital status; and Model 3, further adjusted for confounding factors including smoking status, drinking status, hypertension, dyslipidemia, antidiabetic medication use, lipid-lowering medication use, estimated glomerular filtration rate, and Hemoglobin A1c.

Table 3. Comparison of AUCs Between the Basic Model and Models Incorporating NHHR or TyG Using DeLong's Test.

Comparison	AUC of Basic Model	AUC of Marker	Z Statistic (DeLong Test)	p-value
+NHHR vs. Basic Model	0.562	0.603	-2.004	0.0450
+TyG vs. Basic Model	0.562	0.594	-1.603	0.1090

Notes: Basic model adjusted for age, sex, marital status, residence, education level, BMI, hypertension, dyslipidemia, drinking status, hemoglobin A1c, uric acid, and blood urea nitroge

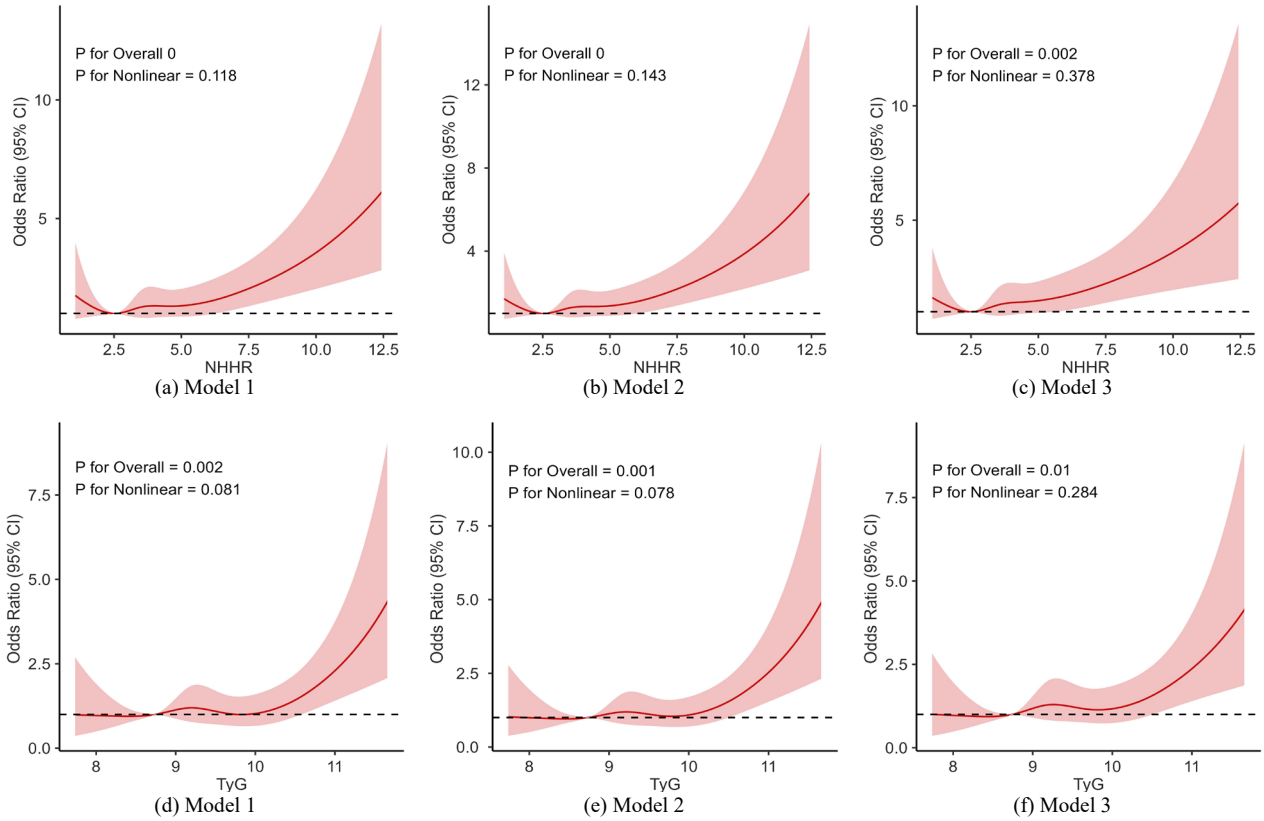

Figure 2. Restricted cubic spline analysis of the relationship between NHHR, TyG and RKFD. Notes: X-axis: Represents the levels of NHHR or TyG. Y-axis: Represents the odds ratios for RKFD, indicating the relative likelihood of RKFD presence associated with NHHR or TyG. Solid lines depict fitted curves illustrating the association between NHHR or TyG and RKFD. Dotted horizontal lines denote an OR of 1, representing no association. Red areas surrounding fitted curves indicate 95% CIs for predicted ORs. Model 1: unadjusted crude representation; Model 2, adjusted for sociodemographic variables such as age, gender, educational level, location, and marital status; and Model 3, further adjusted for confounding factors including smoking status, drinking status, hypertension, dyslipidemia, antidiabetic medication use, lipid-lowering medication use, eGFR, and HbA1c.

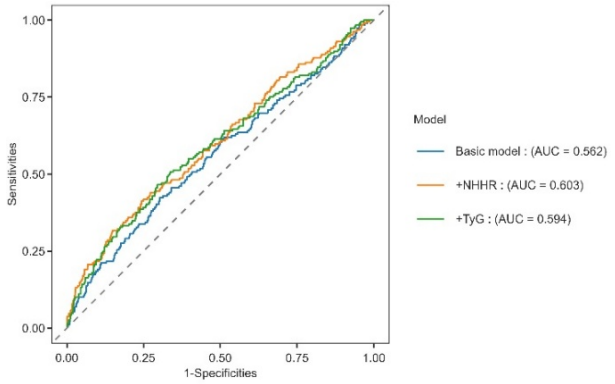

Figure 3. ROC curves for the association between basic model, NHHR and the TyG index with RKFD.

3.5 Subgroup analysis and interaction

Table 4 presents the results of stratified analyses of the associations between NHHR, the TyG index and the risk of RKFD, along with tests for interaction (p for interaction) to determine whether the predictive value of these indices is consistent across different populations. Subgroup analysis revealed that NHHR and the TyG index were significantly associated with RKFD risk in most subgroups ($p < 0.05$), suggesting their broad applicability as RKFD predictors.

Table 4. Subgroup analysis of NHHR and TyG associations with RKFD.

Subgroup	NHHR			TyG		
	OR (95%CI)	p-value	p for interaction	OR (95%CI)	p-value	p for interaction
Sex			0.056			0.004
Female	1.22 (1.11-1.33)	<0.001		1.75 (1.35-2.27)	<0.001	
Male	1.07 (0.98-1.18)	0.125		0.99 (0.75-1.32)	0.966	
Age (years)			0.435			0.496
<65	1.14 (1.06-1.22)	<0.001		1.3 (1.05-1.62)	0.018	
≥65	1.21 (1.06-1.39)	0.006		1.51 (1.05-2.18)	0.027	
Hypertension			0.976			0.883

No	1.15 (1.03-1.28)	0.012		1.31 (0.97-1.76)	0.079	
Yes	1.15 (1.06-1.24)	<0.001		1.34 (1.06-1.71)	0.016	
Dyslipidemia			0.783			0.587
No	1.16 (1.08-1.25)	<0.001		1.3 (1.05-1.62)	0.016	
Yes	1.14 (1-1.29)	0.045		1.47 (1-2.17)	0.048	
Drinking status			0.237			0.135
No	1.19 (1.09-1.29)	<0.001		1.51 (1.18-1.9)	0.001	
Yes	1.1 (1-1.21)	0.046		1.13 (0.85-1.51)	0.391	
Smoking status			0.032			0.11
No	1.22 (1.12-1.32)	<0.001		1.5 (1.18-1.9)	0.001	
Yes	1.05 (0.95-1.16)	0.31		1.09 (0.79-1.49)	0.601	
BMI (kg/m^2)			0.721			0.711
<24	1.14 (1.03-1.26)	0.011		1.41 (1.06-1.87)	0.018	
≥24	1.17 (1.08-1.27)	<0.001		1.31 (1.02-1.69)	0.036	
Antidiabetic medication use			0.317			0.517
No	1.17 (1.09-1.25)	<0.001		1.38 (1.12-1.71)	0.003	
Yes	1.07 (0.91-1.25)	0.437		1.19 (0.8-1.77)	0.389	
Lipid-lowering medication use			0.748			0.844
No	1.16 (1.08-1.24)	<0.001		1.35 (1.11-1.65)	0.003	
Yes	1.12 (0.94-1.34)	0.189		1.27 (0.74-2.2)	0.386	
HbAlc (%)			0.494			0.562
<7.0	1.15 (1.07-1.23)	<0.001		1.28 (1.04-1.59)	0.023	
7.0–8.0	1.08 (0.9-1.29)	0.405		1.31 (0.76-2.27)	0.329	
≥8.0	1.27 (1.03-1.57)	0.027		1.76 (1.02-3.03)	0.041	

Interaction tests indicated that smoking status potentially modified the association between NHHR and RKFD (p for interaction = 0.032), with a stronger association observed among non-smokers. while gender significantly modified the association between the TyG index and RKFD (p for interaction = 0.004), with the TyG index exhibiting stronger predictive power for RKFD in female populations. No significant interactions were observed in other subgroups ($p > 0.05$).

4 Discussion

This study, based on data from CHARLS, examined the association between two non-traditional lipid parameters, namely NHHR and the TyG index, and the risk of RKFD in middle-aged and elderly individuals with diabetes. Analyzing 1051 participants, the study found that after fully adjusting for multiple confounders, higher baseline NHHR and the TyG index levels were both independent risk factors for RKFD, with significant dose-response relationships with RKFD risk. Further analysis revealed that NHHR provided incremental predictive value for RKFD risk, with its association being more pronounced in specific subgroups (e.g., women, non-smokers). These findings suggest that NHHR and the TyG index have potential as biomarkers for assessing RKFD risk in middle-aged and elderly individuals with diabetes.

Previous domestic and international studies have consistently indicated that dyslipidemia and insulin resistance are closely associated with the risk of renal function decline. A study based on the Chinese Stroke Primary Prevention Trial (CSPPT) found that among hypertensive patients with normal renal function, a higher triglyceride-to-high-density lipoprotein cholesterol ratio (TG/HDLC) was significantly associated with the risk of RKFD[16]. Another analysis of CHARLS data also reported associations between nontraditional lipid parameters, such as residual cholesterol, and the risk of renal function progression[17]. Furthermore, extensive research confirms that insulin resistance (primarily reflected by the the TyG index is a key driver of renal decline in both diabetic and non-diabetic populations[18]. Collectively, these studies indicate that dyslipidemia and insulin resistance represent critical pathophysiological pathways in renal impairment.

NHHR reflects the atherogenic lipid profile and mediates renal lipotoxic injury. Elevated NHHR indicates a relative increase in atherogenic lipoproteins and a relative deficiency in renoprotective high-density lipoproteins. Excessive non-HDL-C and its remnant particles can deposit in the glomerular mesangial region and tubulointerstitial space. Resident renal cells, such as mesangial cells, podocytes and tubular epithelial cells, can phagocytose these lipids. This phagocytosis triggers intracellular lipid overload. Intracellular lipid overload causes endoplasmic reticulum stress and mitochondrial dysfunction. These changes ultimately induce apoptosis or epithelial-mesenchymal transition and directly damages the renal structure[19–21]. For instance, in diabetic nephropathy models, free fatty acids can activate NLRP3 inflammasomes via CD36 receptors, causing podocyte injury and proteinuria[22]. These lipid particles readily undergo oxidative modification to form oxidized lipoproteins, exacerbating renal inflammation and oxidative stress. Oxidized low-density lipoprotein (ox-LDL) activates signaling pathways such as nuclear factor κB (NF-κB) in the kidney by binding scavenger receptors (e.g., LOX-1). This promotes the expression of multiple inflammatory cytokines (e.g., TNF-α, IL-6) and chemokines while generating reactive oxygen species clusters. These processes cause oxidative damage, disrupting the glomerular filtration barrier and tubular function[23].

The TyG index reflects insulin resistance, driving renal overload and metabolic dysfunction. Elevated the TyG index reliably reflects decreased peripheral tissue

insulin sensitivity. In diabetic patients, insulin resistance causes relative over-dilatation of afferent glomerular arterioles, increasing glomerular pressure and filtration fraction (glomerular hyperfiltration). Prolonged excessive mechanical stress directly damages podocytes and endothelial cells, accelerating glomerulosclerosis. Furthermore, in the context of insulin resistance, even when glycemic control is adequate, associated metabolic disorders (e.g., increased free fatty acid concentrations) continue to exert adverse effects on renal cells via disrupted insulin signaling pathways, such as inhibition of the PI3K/Akt pathway. Podocytes and renal tubular epithelial cells possess insulin sensitivity; compromised insulin signaling in these cells induces cytoskeletal structural disorders, impaired autophagy, and disrupted energy metabolism, thereby enhancing their susceptibility to various damaging factors[24]. In addition, insulin resistance and hyperinsulinemia promote sodium reabsorption in renal tubules, which increases volume load and synergistically activates the renin-angiotensinaldosterone system (RAAS). This further raises blood pressure and aggravates renal burden[25, 26].

In diabetic patients, insulin resistance and lipid metabolism disorders often coexist and mutually exacerbate each other. Insulin resistance promotes lipolysis, worsening dyslipidemia; conversely, lipotoxicity further impairs insulin signaling. Their combined action forms a vicious cycle characterized by chronic inflammation, oxidative stress, cellular metabolic dysfunction, and hemodynamic alterations, ultimately leading to rapid decline in glomerular filtration rate. Thus, NHHR and TyG integrate information from these key pathological processes, enabling more sensitive identification of diabetic patients in the accelerated phase of this vicious cycle and predicting RKFD risk.

The findings of this study hold significant potential for clinical translation. Compared to traditional single lipid or glucose markers, NHHR and the TyG index, as composite indices, integrate multifaceted metabolic abnormality information and may more sensitively identify diabetic patients in the accelerated phase of metabolic kidney injury. Notably, the TyG index, calculated solely from triglycerides and fasting blood glucose obtained during routine physical examinations, offers exceptional clinical convenience and scalability. Incorporating such indicators into routine management and risk assessment systems for diabetic patients could facilitate earlier identification of high-risk individuals for kidney disease. This would enable the initiation of enhanced lifestyle interventions or consideration of hypoglycemic and lipid-lowering medications with renal protective effects, thereby achieving early prevention and treatment of kidney disease.

Some study limitations need to be acknowledged. First, the observational nature of the CHARLS cohort means that our findings reflect statistical associations rather than causal relationships between NHHR, the TyG index, and RKFD. Further studies using causal inference approaches or interventional designs are needed to validate these relationships. Second, RKFD was defined based on eGFR measurements at two time points (2011 and 2015), which may not fully account for short-term variability in renal function and could potentially influence the assessment of long-term decline. Future research with more frequent eGFR assessments would help to reduce this uncertainty. Third, despite adjusting for multiple important confounders, unmeasured residual confounding may still exist. Finally, the CHARLS cohort primarily comprises middle-aged and elderly individuals, necessitating caution when extrapolating findings to younger diabetic patients.

5 Conclusions

This study systematically evaluated the predictive role of nontraditional lipid parameters NHHR and the TyG index for RKFD in diabetic populations using CHARLS cohort data. Results indicate that elevated NHHR and the TyG index levels are both independent risk factors for RKFD, exhibiting a doseresponse relationship. Regarding predictive performance, NHHR demonstrated stable incremental value, significantly enhancing risk discrimination, whereas improvements in the TyG index did not reach statistical significance.

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