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ORIGINAL RESEARCH

Triglyceride-Glucose Index and Neutrophil-to-Lymphocyte Ratio: A Metabolic-Inflammatory Signature for Mortality Prediction in a Multicenter Retrospective Cohort of 1249 Dialysis Patients with Coronary Artery Disease

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Introduction: Hyperlipidemia, impaired glucose tolerance, and inflammatory status are critical contributors to the progression of coronary artery disease (CAD). Biomarkers associated with these pathways may predict clinical outcomes in dialysis-dependent CAD patients. This study aims to compare conventional lipid profiles, inflammatory markers, and insulin resistance-related indicators to evaluate their associations with mortality and prognostic performance in this high-risk population.

Methods: This multicenter retrospective cohort study included 1249 patients from January 2015 to June 2021. 864 patients were finally included in the analysis. Baseline lipid profiles, inflammatory markers, and insulin resistance-related indicator (the triglyceride-glucose [TyG] index) were analyzed.

Results: Among 864 patients, 252 deaths (29.2%) occurred over three years. Both the TyG index (hazard ratio [95% confidence interval]: 1.22 [1.03–1.44], p=0.024) and inflammatory marker (neutrophil-to-lymphocyte ratio [NLR]: 1.02 [1.00–1.04], p=0.038) were independently associated with mortality, whereas lipid profiles showed no significant association. Adding the TyG index or NLR to the Global Registry of Acute Coronary Events (GRACE) score (TyG c-index: 0.644 [0.609–0.679]; NLR c-index: 0.642 [0.607–0.677]) or baseline model (TyG c-index: 0.707 [0.676–0.738]; NLR c-index: 0.705 [0.672–0.738]) improved predictive performance. The combined model integrating TyG index and NLR demonstrated the highest discriminative ability for mortality prediction (GRACE score c-index: 0.660 [0.625–0.695]; Baseline model c-index: 0.713 [0.682–0.744]).

Conclusion: The findings indicate that systemic inflammation and insulin resistance are more significant risk factors for three-year mortality in dialysis-dependent CAD patients than dyslipidemia. This suggests that targeted anti-inflammatory therapies and regulation of glucose-lipid metabolism may offer greater benefits compared to conventional lipid-lowering strategies in this high-risk cohort.

Keywords: dialysis, coronary artery disease, inflammation, triglyceride-glucose index, all-cause mortality

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Introduction

Patients undergoing dialysis experience an exceptionally high burden of cardiovascular mortality, with a risk that is 7 to 8 times greater than that of individuals with normal renal function.[1] Risk evaluation tools, including the Global Registry of

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Acute Coronary Events (GRACE) score, are broadly applied in coronary artery disease (CAD) cohorts, yet they often fail to accurately predict the risks of heart attack and mortality in CAD patients on dialysis.[2] This limitation highlights the pressing need for novel biomarkers that are specifically tailored to the unique pathophysiology of dialysis-dependent CAD.

Emerging evidence indicates a deviation from traditional cardiovascular risk paradigms in end-stage renal disease (ESRD). Chronic inflammation, driven by the accumulation of uremic toxins and repeated immune activation related to vascular access, accelerates atherosclerosis through endothelial injury and increased plaque vulnerability.[3,4] Furthermore, dialysis patients exhibit a "reverse epidemiology" of lipid metabolism, where lower levels of low-density lipoprotein cholesterol (LDLC) paradoxically correlate with increased mortality. This term describes a common paradox in ESRD where the association of traditional risk factors with outcomes is reversed. This phenomenon likely reflects the malnutrition-inflammation complex syndrome rather than providing cardiovascular protection.[5,6] Additionally, insulin resistance, as quantified by the triglyceride-glucose (TyG) index, has recently been associated with cardiovascular events in dialysis cohorts, suggesting a role for glucose-lipid dysregulation that is independent of traditional diabetes metrics.[7]

Current evidence lacks direct comparisons of lipid profiles, inflammatory markers, and the TyG index in predicting mortality among dialysis patients who have CAD, and their interactions under uremic conditions remain inadequately understood. Our multicenter cohort study aims to fill this knowledge gap by examining these biomarkers to improve risk stratification and guide targeted interventions in this high-risk group.

Method

Study Population

Data utilized in this study were derived from the Coronary Revascularization in Patients on Dialysis in China-Retrospective Registry (CRUISE-R, ClinicalTrials.gov entry: NCT05841082). Supplementary Table 1 provides details on the CRUISE-R study design. This national multicenter retrospective study was conducted across 30 medical centers in 12 provinces of China. It involved a total of 1,249 patients who were undergoing regular dialysis and had been diagnosed with CAD through coronary angiography. The study period extended from January 2015 to June 2021. Ethical approval was obtained from the Ethics Committee of the China-Japan Friendship Hospital (2020–112-K71). The ethics committee explicitly waived the requirement for informed consent due to the retrospective analysis. All data were handled in a strictly confidential and anonymized manner. In this particular analysis, we omitted 23 patients with tumors, 136 patients with active infections or autoimmune diseases, 21 patients with abnormal liver function (defined as liver enzyme levels more than three times the normal upper limit), 45 patients lacking routine blood indices, and 50 patients with triglyceride (TG) deficiency. 22 patients with blood glucose deficiency, 28 cases of suspected familial hypertriglyceridemia, with TG levels at or above 5.65 mmol/L (suspected familial hypertriglyceridemia), and 60 patients who were lost to follow-up (Figure 1). The final analysis included 864 participants. Researchers adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement guidelines during the observational study.

Study Definition

In this investigation, trained study coordinators assembled data by examining the medical files of participants, which covered basic information, existing health conditions, heart-related background, heart performance, details of coronary artery disease, therapeutic measures, and significant medical occurrences. Experienced nursing professionals administered outpatient consultations and conducted telephone interviews using standardized forms to evaluate patient survival and clinical outcomes. Standardized follow-up procedure and consistent definitions for clinical endpoints were implemented to ensure uniform assessment of outcome events. In this context, dialysis patients were defined as those undergoing blood or peritoneal dialysis for a minimum of three months. Using values gathered within 24 hours of admission, the TyG index is calculated by first multiplying fasting triglyceride and fasting glucose levels, then dividing the result by 2, and finally taking the natural logarithm of that quotient.

Five inflammatory scores were calculated as follows: The neutrophil-to-lymphocyte ratio (NLR) was determined by dividing the neutrophil count by the lymphocyte count; The platelet-to-lymphocyte ratio (PLR) was calculated by

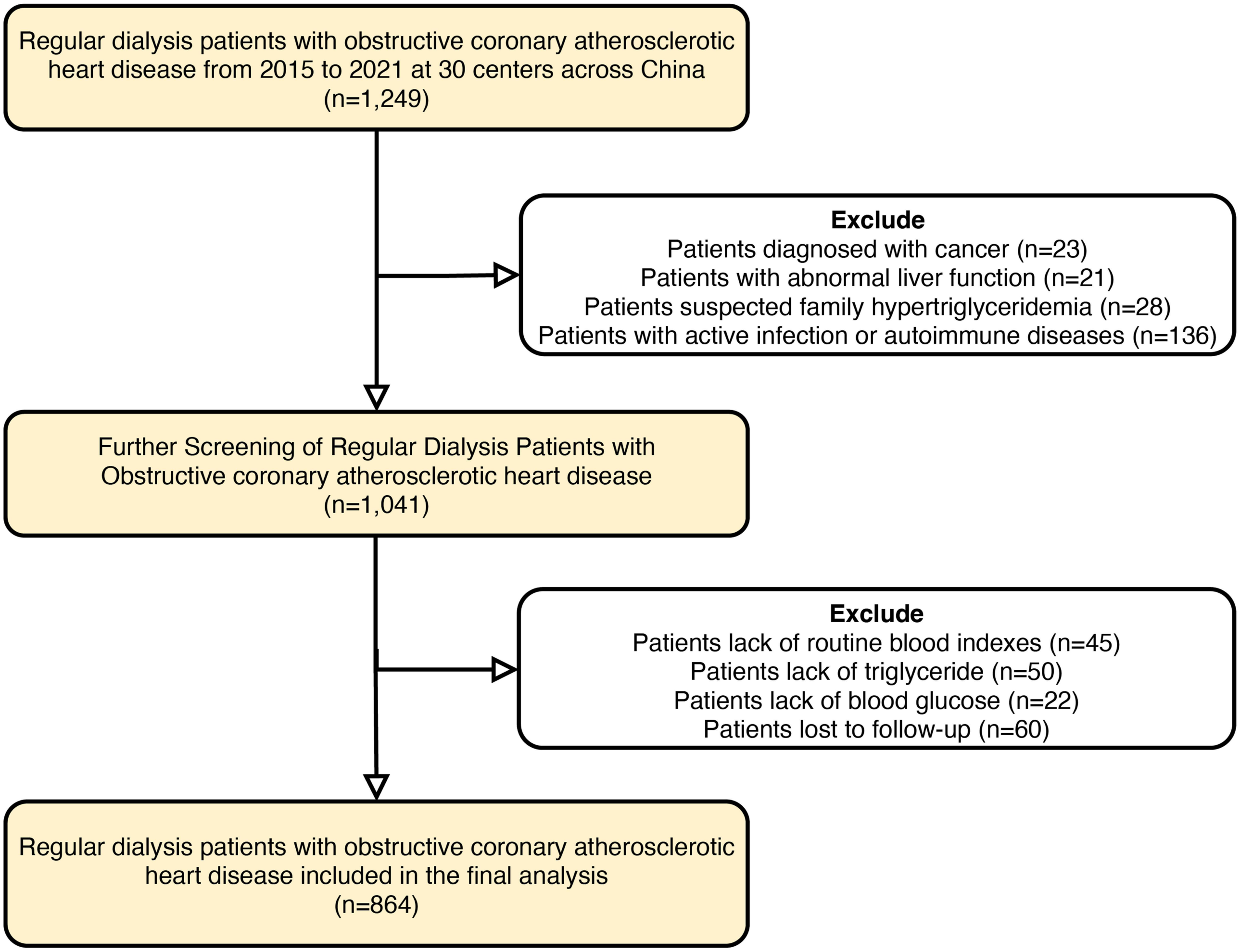

Figure 1 Flowchart of the patient inclusion and exclusion.

dividing the platelet count by the lymphocyte count; The monocyte-to-lymphocyte ratio (MLR) was obtained by dividing the monocyte count by the lymphocyte count; The systemic immune-inflammation index (SII) was computed as the product of the platelet count and neutrophil count, divided by the lymphocyte count; The systemic immune-inflammation response index (SIIRI) was defined as the product of the neutrophil count, monocyte count, and platelet count, divided by the lymphocyte count.

The following calculations were made for five lipid-derived indices using lipid profiles, including total cholesterol (TC), TG, high-density lipoprotein cholesterol (HDLC), and LDLC collected within the first 24 hours of hospital admission. The atherogenic index of plasma (AIP) was calculated as the logarithm of the ratio of TG to HDLC; The lipoprotein combine index (LCI) was determined by multiplying TC, TG, and LDLC, and then dividing the product by HDLC; Castelli's index-II (CRIII) was obtained by dividing LDLC by HDLC; The atherogenic index (AI) was calculated as the difference between TC and HDLC, divided by HDLC; The atherogenic combined index (ACI) was computed by multiplying TG by the difference between TC and HDLC, and then dividing the result by HDLC.

Outcomes

The endpoint was defined as mortality from any cause within a three-year period, with follow-up conducted via telephone by trained nursing staff.

Statistical Analysis

To compare the baseline characteristics between the two groups, the Mann–Whitney *U*-test was utilized for variables with non-normal distributions. For continuous variables that followed a normal distribution, the independent samples *t*-test was applied. Categorical variables were analyzed using the chi-square test (χ^2). A significance level of $P < 0.05$ was set for two-tailed tests.

To examine the correlation between various scores and endpoint events, the scores were segmented into three tiers according to their tertile distribution, with each tier labeled as T1, T2, and T3. The Log rank test was subsequently utilized to compare the incidence of events among these three groups. Additionally, Cox regression models were employed, with the score initially treated as a continuous variable and subsequently as a categorical variable. The following variables were adjusted in the adjusted multivariate Cox model: age, sex, manifestations of coronary heart disease, systolic and diastolic blood pressure, hypertension, diabetes, atrial fibrillation, cerebrovascular disease, admission treatment method, left main CAD, three-vessel disease, heart rate, active smoking and pharmacological therapies including beta-blocker, statin, dual antiplatelet therapy, angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB). The relationship between various scores and outcome events was further examined using a restricted cubic spline plot. The model's precision and optimal cut-off point were assessed using the receiver-operating characteristic (ROC) curves. Calibration curves and Decision Curve Analysis (DCA) were also employed to assess the model's predictive accuracy. To compare the discrimination of different scores for 3-year all-cause deaths, three metrics were calculated: Harrell' concordance index, continuous net reclassification improvement (NRI) and integrated discrimination improvement (IDI). All statistical analyses were performed using R software (version 4.5.0).

Results

Characteristics of the Study Population

The study cohort comprised 864 participants, whose mean age was 61.8 years, and the majority (75.2%) were men. Of these, 58.3% were diagnosed with myocardial infarction, 93.5% had hypertension, and 53.8% had diabetes mellitus. Over the three-year follow-up period, 252 patients died from any cause, resulting in an all-cause mortality rate of 29.2%. Compared to survivors, those who experienced outcome events were older and had a higher incidence of myocardial infarction, atrial fibrillation, valvular disease, diabetes, and left main and three-vessel coronary artery disease. Lab tests showed that patients who died from any cause had higher blood glucose, white blood cell, and neutrophil counts when admitted, with no notable differences in blood lipid levels (Table 1).

Insulin Resistance, Lipid-Derived Index and Inflammation Score with All-Cause Death

The AUC was calculated to assess the prognostic value of 9 lipid-related indices and 9 inflammatory scores concerning all-cause mortality, with the results displayed in supplementary Figure 1. Notably, the inflammation score (NLR) and the lipid-

Table 1 Population Baseline

	Overall	Survivors	Mortality	p-value
N	864	612	252	
Demographics				
Age, years	61.8 (10.4)	60.7 (10.3)	64.6 (10.1)	<0.001
Sex				0.219
Male	650 (75.2)	468 (76.5)	182 (72.2)	
Female	214 (24.8)	144 (23.5)	70 (27.8)	
Physical examination				
SBP, mmHg	141.9 (25.0)	142.9 (25.2)	139.3 (24.4)	0.058
DBP, mmHg	78.9 (13.3)	79.6 (13.2)	77.2 (13.5)	0.016
HR, beats per min	79.9 (14.4)	79.3 (14.3)	81.3 (14.6)	0.060

(*Continued*)

Table 1 (Continued).

	Overall	Survivors	Mortality	p-value
Cardiovascular risk factors, n (%)				
Hypertension	808 (93.5)	570 (93.1)	238 (94.4)	0.577
Diabetes	465 (53.8)	312 (51.0)	153 (60.7)	0.011
Atrial fibrillation	72 (8.3)	43 (7.0)	29 (11.5)	0.042
Valvular heart disease	27 (3.1)	14 (2.3)	13 (5.2)	0.047
Cerebrovascular disease	157 (18.2)	101 (16.5)	56 (22.2)	0.060
Hyperglycaemia	694 (80.3)	493 (80.6)	201 (79.8)	0.863
Current smoking	167 (19.3)	128 (20.9)	39 (15.5)	0.081
Anemia	744 (86.1)	523 (85.5)	221 (87.7)	0.449
Pheripheral artery disease	84 (9.7)	60 (9.8)	24 (9.5)	1.000
COPD	10 (1.2)	8 (1.3)	2 (0.8)	0.775
Dialysis modality and duration				
Hemodialysis	800 (92.6)	570 (93.1)	230 (91.3)	0.472
Peritoneal dialysis	64 (7.4)	42 (6.9)	22 (8.7)	0.418
Dialysis time, month	51.3 (46.9)	51.9 (48.3)	49.9 (43.5)	0.582
Laboratory test				
White blood cell, 10^9/L	7.2 (2.7)	7.0 (2.5)	7.6 (3.1)	0.001
Neutrophil, 10^9/L	5.2 (2.4)	4.9 (2.2)	5.7 (2.7)	<0.001
Monocyte, 10^9/L	0.7 (0.9)	0.7 (1.0)	0.7 (0.6)	1.000
Lymphocyte, 10^9/L	1.2 (0.6)	1.2 (0.6)	1.1 (0.8)	0.467
Hemoglobin, g/L	106.1 (19.7)	106.6 (19.9)	104.8 (19.3)	0.220
Platelet, 10^9/L	189.0 (70.2)	188.5 (66.8)	190.2 (77.8)	0.742
Glucose, mmol/L	7.6 (4.2)	7.1 (3.8)	8.8 (5.0)	<0.001
Total cholesterol, mmol/L	3.91 (1.10)	3.91 (1.14)	3.91 (1.00)	0.956
Triglyceride, mmol/L	1.85 (1.00)	1.88 (1.04)	1.78 (0.90)	0.188
HDLC, mmol/L	0.96 (0.33)	0.96 (0.30)	0.97 (0.40)	0.451
LDLC, mmol/L	2.28 (0.85)	2.28 (0.89)	2.27 (0.77)	0.822
Cardiac catheterization, n (%)				
Left main CAD	94 (10.9)	51 (8.3)	43 (17.1)	<0.001
Two vessel CAD	243 (28.1)	174 (28.4)	69 (27.4)	0.819
Three vessel CAD	482 (55.8)	321 (52.5)	161 (63.9)	0.003
PCI	606 (70.1)	444 (72.5)	162 (64.3)	0.020
CABG	19 (2.2)	15 (2.5)	4 (1.6)	0.595
Manifestations of CAD, n (%)				<0.001
Stable angina pectoris	57 (6.6)	51 (8.3)	6 (2.4)	
Unstable angina pectoris	303 (35.1)	226 (36.9)	77 (30.6)	
Non-ST elevation MI	408 (47.2)	278 (45.4)	130 (51.6)	
ST elevation MI	96 (11.1)	57 (9.3)	39 (15.5)	
Medications, n (%)				
Aspirin	795 (92.0)	562 (91.8)	233 (92.5)	0.863
Clopidogrel	716 (82.9)	501 (81.9)	215 (85.3)	0.260
Ticagrelor	93 (10.8)	67 (10.9)	26 (10.3)	0.880
DAPT	754 (87.3)	528 (86.3)	226 (89.7)	0.210
ACEI/ARB	396 (45.8)	294 (48.0)	102 (40.5)	0.051
ARNI	68 (7.9)	45 (7.4)	23 (9.1)	0.459
Beta-blocker	697 (80.7)	493 (80.6)	204 (81.0)	0.969
Statin	814 (94.2)	578 (94.4)	236 (93.7)	0.769

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; COPD, chronic obstructive pulmonary disease; HDLC, high density lipoprotein cholesterol; LDLC, low density lipoprotein cholesterol; CAD, coronary artery disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; MI, myocardial infarction; DAPT, dual anti-platelet therapy; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor.

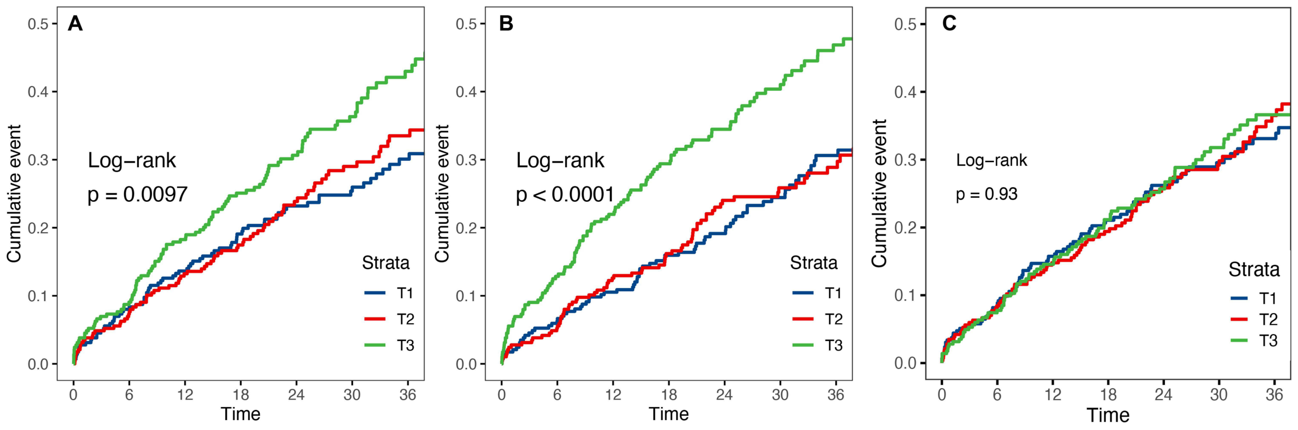

Figure 2 Cumulative event rate curves for mortality based on TyG index, NLR, and LDLC. (**A**) Cumulative event rate curves of TyG index. (**B**) Cumulative event rate curves of NLR. (**C**) Cumulative event rate curves of LDLC.

Abbreviations: TyG index, triglyceride-glucose index; NLR, neutrophil - lymphocyte ratio; LDLC, low-density lipoprotein cholesterol.

related index (LDLC) demonstrated superior predictive performance for all-cause mortality (NLR: 0.601; LDLC: 0.521). Subsequently, participants were divided into three strata according to the tertiles of the TyG index, NLR, and LDLC, labeled as T1, T2, and T3. A notable variation in all-cause mortality was detected among individuals classified by the TyG index and NLR, whereas no significant prognostic difference was detected among patients grouped by LDLC levels (Figure 2).

Correlation of TyG Index and NLR with Three-year Mortality

The results from the Cox proportional hazards models demonstrated that the TyG index is a significant independent risk factor for all-cause mortality (hazard ratio [HR]=1.22, 95% confidence interval [95% CI]:1.03–1.44, *p*=0.024), after accounting for multiple covariates (Table 2). As a categorical variable, the third tertile had a 40% greater risk of death relative to those in the lowest tertile (HR=1.40, 95% CI:1.01–1.93, *p*=0.041). NLR also emerged as a significant independent predictor of mortality (when evaluated continuously, HR=1.02, 95% CI:1.00–1.04, *p*=0.038; when categorized, T3 vs T1, HR=1.57, 95% CI:1.14–2.16, *p*=0.005). Figure 3 shows the dose-response relationships of TyG and NLR, both as continuous and categorical variables, with all-cause mortality over a 3-year span. The analysis revealed a notable

Table 2 Association of TyG Index, LDLC and NLR with 3-year All-Cause Mortality

Variables	Unadjusted		Model I		Model II	
	HR (95% CI)	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
TyG index, continuous	1.31 (1.11, 1.54)	0.001	1.32 (1.13, 1.55)	<0.001	1.22 (1.03, 1.44)	0.024
TyG index, category						
T1	reference		reference		reference	
T2	1.08 (0.78, 1.49)	0.641	1.19 (0.86, 1.64)	0.303	1.13 (0.81, 1.58)	0.470
T3	1.50 (1.11, 2.03)	0.008	1.52 (1.13, 2.06)	0.006	1.40 (1.01, 1.93)	0.041
p for trend		0.007		0.006		0.037
LDLC, continuous	0.98 (0.84, 1.13)	0.739	0.98 (0.84, 1.13)	0.737	0.96 (0.83, 1.11)	0.624
LDLC, category						
T1	reference					
T2	1.03 (0.76, 1.40)	0.840	1.04 (0.77, 1.41)	0.799	1.19 (0.87, 1.62)	0.287
T3	1.07 (0.79, 1.45)	0.660	1.07 (0.79, 1.46)	0.650	1.08 (0.79, 1.48)	0.618
p for trend		0.659		0.653		0.686

(*Continued*)

Table 2 (Continued).

Variables	Unadjusted		Model I		Model II	
	HR (95% CI)	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
NLR, continuous	1.03 (1.01, 1.05)	<0.001	1.03 (1.01, 1.05)	0.002	1.02 (1.00, 1.04)	0.038
NLR, category						
T1	reference		reference		reference	
T2	1.00 (0.72, 1.40)	0.981	1.03 (0.74, 1.44)	0.854	1.03 (0.73, 1.44)	0.883
T3	1.87 (1.39, 2.52)	<0.001	1.91 (1.41, 2.57)	<0.001	1.57 (1.14, 2.16)	0.005
p for trend		<0.001		<0.001		0.002

Notes: Model I: adjusted for age and sex. Model II: further adjusted for manifestations of coronary heart disease, hypertension, diabetes, atrial fibrillation, cerebrovascular disease, admission treatment method, left main coronary disease, three-vessel disease, systolic blood pressure, diastolic blood pressure, heart rate, current smoking and medications including ACEI/ARB, beta-blocker, statin, dual anti-platelet.
Abbreviations: HR, hazard ratio; CI, confidence interval; TyG index, triglyceride-glucose index; NLR, neutrophil-lymphocyte ratio; LDLC, low density lipoprotein cholesterol.

dose-response link between the TyG index and NLR with overall mortality. Notably, the hazard of all-cause mortality escalated significantly once the TyG index exceeded 8.141. A comparable increase in mortality risk was also detected when the NLR value went above 2.207.

Predictive Performance of the TyG Index Combined with NLR

Since the TyG index and NLR are both linked to mortality risk, a correlation analysis was conducted, revealing a weak correlation between the two indices (correlation coefficient = 0.080, p = 0.021, Supplementary Figure 2). This weak correlation suggests that the TyG index and NLR likely capture distinct yet complementary pathophysiological pathways, and may have a synergistic effect in predicting prognosis in dialysis patients with CAD. Given these findings, we investigated whether combining the TyG index with NLR could provide superior predictive power for all-cause mortality compared to using each index separately. To determine the most effective thresholds for the TyG index and NLR in predicting all-cause mortality, we utilized ROC curve analysis (see Supplementary Figure 3). The TyG index was found to have an optimal threshold of 8.981, which corresponded to a 66.1% sensitivity and a 52.6% specificity. In the case of

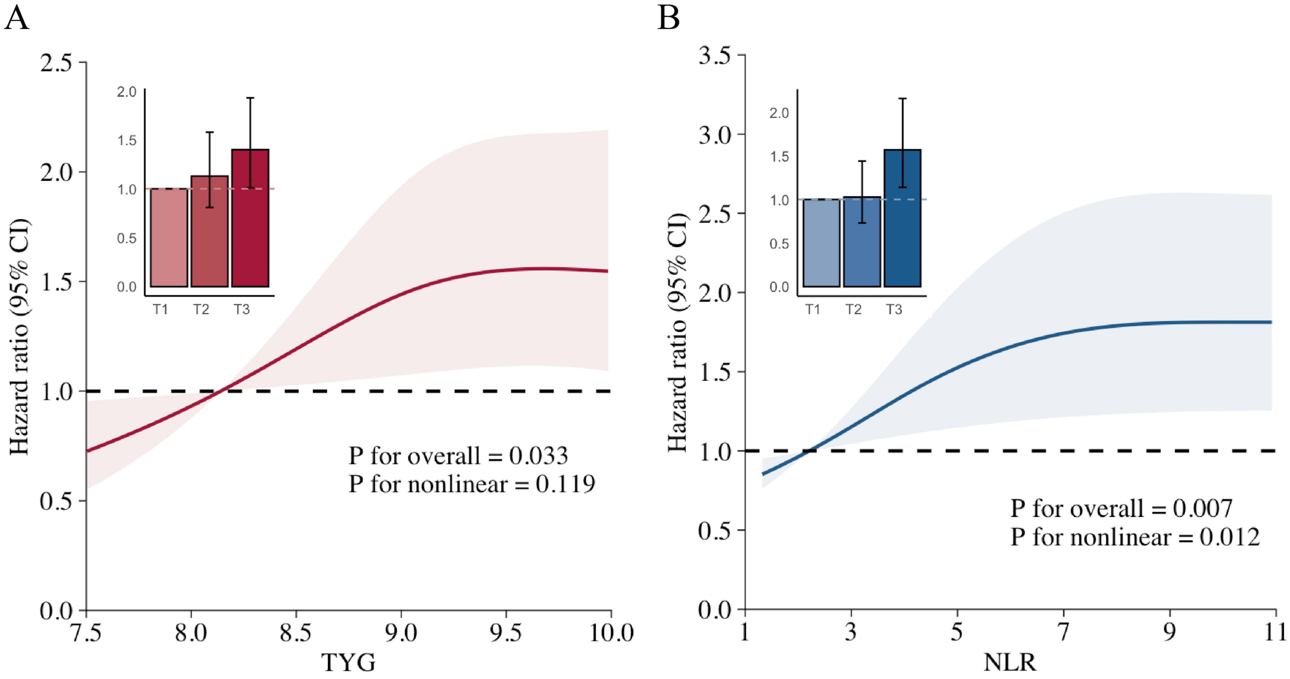

Figure 3 Dose - response relationship of TyG index and NLR with 3-year all-cause mortality. (**A**) The smooth curve fitting diagram of TyG index. (**B**) The smooth curve fitting diagram of NLR.
Abbreviations: TyG index, triglyceride-glucose index; NLR, neutrophil - lymphocyte ratio.

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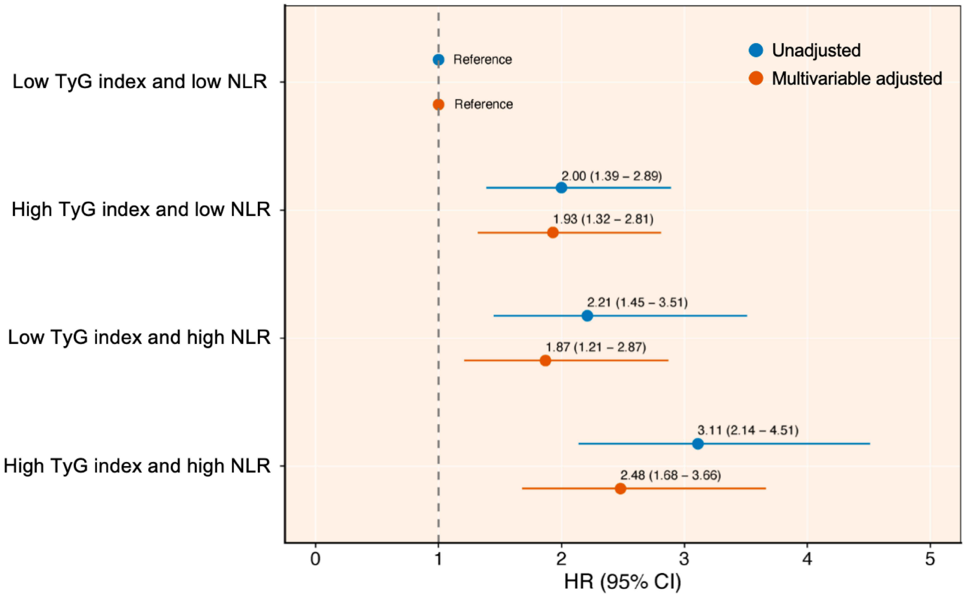

Figure 4 Forest plot of all-cause mortality in combination with TyG index and NLR. Multivariable adjusted for Model II in the Cox regression analysis.
Abbreviations: TyG index, triglyceride-glucose index; NLR, neutrophil - lymphocyte ratio; HR, hazard ratio; CI, confidence interval.

NLR, the ideal threshold was set at 4.941, yielding a sensitivity of 48.9% and a specificity of 68.6%. TyG index≥8.981 was classified as high TyG index, otherwise was low TyG index, and NLR was also divided. Reclassification revealed a marked difference in all-cause mortality across the four groups (Supplementary Figure 4). Even after considering multiple factors, individuals with elevated TyG index (HR=1.93, 95% CI:1.32–2.81, p<0.001) or NLR alone (HR=1.87,95% CI:1.21–2.87, p=0.005) had a higher risk of death compared to those with lower levels of both. Moreover, those who had elevated levels of both the TyG index and NLR faced a significantly increased risk of mortality (HR=2.48, 95% CI:1.68–3.66, p<0.001) as shown in Figure 4.

When the TyG index and NLR were reclassified into categorical variables based on their optimal thresholds to develop the predictive model, compared with TyG single index, the accuracy of the model can be significantly improved, which is specifically reflected in the increase of c-index (0.606 vs 0.561, p<0.001, Table 3). Compared with NLR alone, the c-index, NRI and IDI of the model were significantly higher (c-index: 0.606 vs 0.574, p<0.001; NRI: 0.190 [0.104–0.266], p<0.001; IDI: 0.020 [0.006–0.036], p<0.001), indicating improved accuracy and reclassification capability. Additionally, the TyG index and NLR, when integrated with GRACE scores or the baseline model, outperformed the original model or the original model paired with a single index (Table 4). Furthermore, both the calibration curves and DCA curves demonstrated that incorporating the TyG index and NLR into the GRACE model or the baseline model enhanced the predictive accuracy (Figure 5).

Table 3 Predictive Performance of Combined TyG Index and NLR

Group	c-index	*p* value	NRI	*p* value	IDI	*p* value
TyG index+NLR vs TyG index	0.606 (0.573, 0.639) vs 0.561 (0.530, 0.592)	<0.001	0.177 (−0.063, 0.250)	0.090	0.022 (−0.005, 0.052)	0.159
TyG index+NLR vs NLR	0.606 (0.573, 0.639) vs 0.574 (0.543, 0.605)	<0.001	0.190 (0.104, 0.266)	<0.001	0.020 (0.006, 0.036)	<0.001

Abbreviations: TyG index, triglyceride-glucose index; NLR, neutrophil-lymphocyte ratio; NRI, net reclassification improvement; IDI, integrated discrimination improvement.

Table 4 The Incremental Effects of Incorporating the TyG Index and NLR to GRACE Score and a Baseline Risk Model on Prognostic Prediction

Model	c-index	*p* value	NRI	*p* value	IDI	*p* value
GRACE	0.626 (0.591, 0.661), as reference		reference		reference	
GRACE+TyG index	0.644 (0.609, 0.679)	<0.001	0.190 (0.105, 0.288)	<0.001	0.020 (0.003, 0.047)	<0.001
GRACE+NLR	0.642 (0.607, 0.677)	<0.001	0.177 (0.085, 0.254)	<0.001	0.014 (0.001, 0.036)	0.020
GRACE+TyG index+NLR	0.660 (0.625, 0.695)	<0.001	0.177 (0.079, 0.264)	<0.001	0.027 (0.009, 0.054)	<0.001
Baseline model	0.701 (0.668, 0.734), as reference		reference		reference	
Baseline model +TyG index	0.707 (0.676, 0.738)	<0.001	0.190 ()0.081, 0.266)	0.010	0.017 (0.003, 0.034)	<0.001
Baseline model +NLR	0.705 (0.672, 0.738)	0.002	0.169 (−0.013, 0.256)	0.080	0.010 (−0.001, 0.031)	0.080
Baseline model+TyG index+NLR	0.713 (0.682, 0.744)	<0.001	0.138 (0.025, 0.225)	<0.001	0.020 (0.005, 0.044)	<0.001

Abbreviations: TyG index, triglyceride-glucose index; NLR, neutrophil-lymphocyte ratio; NRI, net reclassification improvement; IDI, integrated discrimination improvement.

Subgroup Analysis and Sensitivity Analysis

Further subgroup investigations were conducted to examine how the TyG index and NLR relate to all-cause mortality within different population segments, including age, sex, diabetes mellitus, myocardial infarction, insulin treatment, and dialysis modality (Supplementary Figure 5). Across all subgroups, the results remained relatively consistent, with no significant interactions detected. Similar findings were observed for NLR, except within the dialysis modality subgroup, where a significant interaction was identified (p for interaction=0.031). Notably, only 64 patients were undergoing

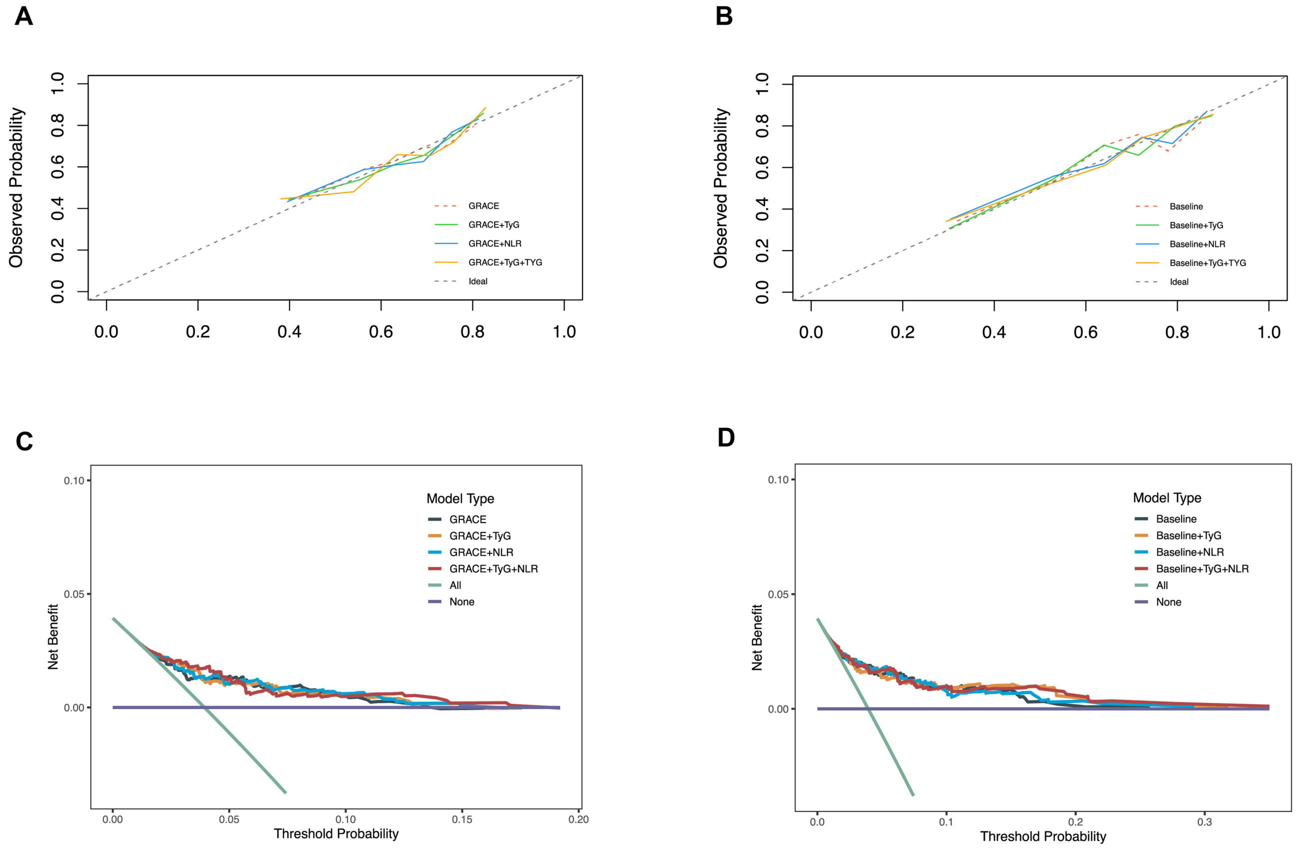

Figure 5 Calibration and Decision Curve Analysis (DCA) for the integration of the TyG index and NLR with the GRACE score or the baseline model. (**A**) Calibration curve of TyG index and NLR with GRACE score. (**B**) Calibration curve of TyG index and NLR with baseline model. (**C**) Decision curve of TyG index and NLR with GRACE score. (**D**) Decision curve of TyG index and NLR with baseline model.

Abbreviations: TyG index, triglyceride-glucose index; NLR, neutrophil - lymphocyte ratio; GRACE score, Global Registry of Acute Coronary Events score.

peritoneal dialysis, and within this cohort, higher NLR levels were tied to greater all-cause mortality risk (HR=1.22, 95% CI:1.07–1.39, p=0.003). However, the findings in the peritoneal dialysis subgroup (n=64 with 22 events) are severely limited by low statistical power and potential model overfitting.

To ensure the conclusions' robustness, a sensitivity analysis was undertaken. At first, 23 patients who died in the hospital were omitted (Supplementary Table 2). Secondly, we excluded 59 patients with hypoglycemia (blood glucose<3.9mmol/L), 2 patients with leukopenia (neutrophil count <1×10^9), and 42 patients with lymphocytopenia (lymphocyte count <0.5×10^9). The analysis ultimately comprised 761 patients (Supplementary Table 3). When assessed in both continuous and categorical formats, the TyG index and NLR were significantly related to 3-year all-cause mortality, after accounting for multiple factors.

Discussion

In this multicenter retrospective cohort study comprising 864 dialysis-dependent patients with CAD, systemic inflammation (NLR: HR=1.02, 95% CI:1.00–1.04, *p*=0.038) and insulin resistance (TyG index, HR=1.22, 95% CI:1.03–1.44, *p*=0.024) emerged as predominant predictors of 3-year all-cause mortality, surpassing traditional lipid profiles (LDLC: HR=0.96, 95% CI:0.83–1.11, *p*=0.624). The joint assessment of the TyG index and NLR outperformed the predictive accuracy of evaluating individual biomarkers. The addition of the TyG index and NLR to the model considerably refined the predictive accuracy of both the GRACE score (c-index: 0.660 vs 0.626, p<0.001) and baseline models (c-index: 0.713 vs 0.701, p<0.001).

Our study provides a unique advance by validating a novel metabolic-inflammatory signature (TyG-NLR) specifically in a high-risk, understudied population: dialysis patients with CAD. This addresses a critical evidence gap, as findings from general ACS cohorts cannot be extrapolated to this unique population. These results challenge traditional cardiovascular risk paradigms in ESRD and are consistent with emerging evidence that underscores the distinct pathophysiology of uremic atherosclerosis.[8,9] Our findings build upon previous research by directly comparing lipid, inflammatory, and metabolic biomarkers, while offering mechanistic and clinical insights into risk stratification for this high-risk population.[7,10,11]

Although lipid-lowering therapies are fundamental in the cardiovascular management of the general population,[12,13] emerging clinical data show a disparity between standard lipid metrics and death rates in ESRD patients. In a randomized controlled trial involving hemodialysis patients, rosuvastatin significantly reduced LDLC levels (mean difference: −43 mg/dL) but did not confer a survival benefit.[14] A meta-analysis assessing the effects of lipid-lowering treatments on clinical outcomes in chronic kidney disease has verified that statins do not have a significant impact on mortality risk for patients on dialysis.[15] Additionally, new findings suggest that ceramide, a specific lipid metabolite, is essential in the advancement of atherosclerosis among those with kidney dysfunction.[8] In alignment with these findings, our research did not find a standalone link between LDLC levels and all-cause mortality over three years (HR=0.96, 95% CI:0.83–1.11, *p*=0.624), indicating that traditional lipid-centric risk stratification may lack clinical significance in this population. Instead, TyG index - a surrogate for adipose tissue insulin resistance - emerged as a robust predictor in ESRD cohorts.[7,16] Notably, our TyG index threshold (>8.141) corresponds with the cut-off values identified in non-dialysis CAD populations (8.840–9.037),[17,18] suggesting a conserved metabolic risk pathway exacerbated by uremia.

Inflammatory biomarkers, including neutrophil, monocyte, and lymphocyte counts, have traditionally served as indicators of systemic inflammatory status. However, their individual variability can result in false negatives or delayed responses, particularly in chronic conditions. Recent advancements underscore the utility of composite indices derived from routine blood counts, such as the NLR, MLR, and PLR, which offer stable and cost-effective prognostic value for assessing the severity and outcomes of CAD.[19–22] In our study comparing the prognostic performance of multiple inflammatory indices, NLR achieved the largest AUC value (0.601). In dialysis patients, NLR is associated with cardiovascular mortality (HR=1.03, 95% CI:1.01–1.05, *p*=0.002),[10] an NLR of 3.5 was identified as the optimal cutoff for predicting death, with patients on dialysis above this threshold having a 1.7-fold increase in mortality.[23] Our study further substantiates this evidence by illustrating the independent prognostic significance of NLR for long-term all-cause mortality in dialysis-dependent CAD patients (adjusted HR=1.02, 95% CI:1.00–1.04, *p*=0.038). Additionally, our identified optimal cutoff (NLR > 4.941) may indicate a higher baseline level of inflammation in dialysis populations with prevalent CAD.[24]

The elevated inflammatory burden reflected by NLR must be understood within the broader pathophysiological context of ESRD, where endothelial dysfunction emerges as the central orchestrator of cardiovascular disease and mortality. The uremic milieu, characterized by the accumulation of toxins, oxidative stress, and fluid overload, directly inflicts damage upon the vascular endothelium.[25] A dysfunctional endothelium, in turn, becomes a prolific source of pro-inflammatory cytokines and adhesion molecules, creating a self-perpetuating cycle of systemic inflammation and immune cell activation that drives atherogenesis and plaque vulnerability.[26] As recently highlighted by Prabhahar et al,[27] this endothelial-centric inflammatory cascade is a hallmark of renal disease and a key therapeutic target.[28]

Inflammation and insulin resistance collectively contribute to cardiovascular risk through a complex bidirectional interaction, largely mediated by endothelial dysfunction. Pro-inflammatory signaling pathways, such as JNK/mTOR activation, impair adipose tissue functionality, leading to increased levels of free fatty acids and inflammatory cytokines while decreasing adiponectin, thereby intensifying insulin resistance.[29] Conversely, insulin resistance amplifies inflammation via oxidative stress caused by high blood sugar levels and the accumulation of advanced glycation end products. This vicious cycle accelerates endothelial injury and plaque instability.[30] Consistent with this paradigm, Cui et al demonstrated that patients with increased TyG index and high-sensitivity C-reactive protein had a 30% greater risk of CAD than those with lower levels of these markers,[31] underscoring the synergistic interplay between insulin resistance and inflammation in CVD pathogenesis.

In dialysis populations, where chronic inflammation and insulin resistance are markedly amplified by uremic toxins and metabolic dysregulation,[32,33] dual-biomarker models integrating these pathways may offer superior risk stratification. Our study addresses this gap by demonstrating that the combined TyG-NLR model outperforms either biomarker alone in predicting all-cause mortality. Furthermore, integrating TyG index and NLR into the GRACE score (0.660 vs 0.626, $p<0.001$) or baseline clinical models (0.713 vs 0.701, $p<0.001$) significantly enhanced predictive performance, with C-index improvements. The TyG-NLR signature offers exceptional clinical practicality. It is derived from routine, low-cost parameters, requiring no specialized assays. This makes it an accessible and immediately implementable tool for risk stratification in global clinical practice, potentially helping to identify high-risk patients for more intensive management.

To explore the mechanistic context of our findings, we hypothesize that the synergy between TyG and NLR reflects a self-reinforcing cycle where uremic milieu-aggravated insulin resistance primes innate immune activation, elevating neutrophil counts and suppressing lymphocytes, which in turn exacerbates metabolic dysfunction through cytokine-mediated impairment of insulin signaling. This entire pathway is both a cause and a consequence of endothelial dysfunction, ultimately culminating in major adverse cardiovascular events. Future studies are warranted to validate this pathophysiological model by: 1) correlating the TyG-NLR signature with direct measures of vascular inflammation and specific inflammatory cytokines in serially collected samples; and 2) investigating in experimental models whether therapeutic modulation of one pathway (eg, using SGLT2 inhibitors to improve metabolism or anti-IL-6 agents to dampen inflammation) elicits concordant changes in the other, ultimately leading to improved outcomes.

Strengths and Limitations

Our study uniquely focuses on the high-risk population of dialysis-dependent patients with CAD, leveraging a nationwide multicenter retrospective cohort spanning 30 Chinese centers to comprehensively evaluate the prognostic relevance of lipid profiles, inflammatory markers, and insulin resistance. By demonstrating the lack of independent association between conventional lipid parameters and 3-year all-cause mortality, we reinforce the paradigm shift away from lipid-centric risk assessment in this population. Crucially, we identified a synergistic prognostic effect of inflammation (NLR) and insulin resistance (TyG index), with their combined model achieving superior discriminative performance. This underscores the clinical utility of integrating routine, cost-effective biomarkers to refine risk stratification in dialysis-complicated CAD.

This study has several limitations that need to be recognized. First, this retrospective study may harbor residual confounding and selection bias. Second, the moderate sample size limits the power for subgroup analyses. Third, the levels of the TyG index and NLR were measured at a single time point upon study enrollment. This retrospective design limits our ability to capture the dynamic changes of these biomarkers over time and to assess their time-dependent association with mortality. Furthermore, our study participants were exclusively recruited from Chinese centers, which may limit the generalizability of our findings to other ethnic populations with differing genetic backgrounds, dietary habits, and healthcare systems. The specific cut-off values of the TyG-NLR signature we identified may require validation in other ethnic cohorts. Finally, while we adjusted for the use of major drug classes (statins, antiplatelet agents, ACEI/ARBs), we lacked data on other anti-inflammatory therapies. Therefore, we cannot fully rule out some unmeasured confounding effects of pharmacotherapy. Further prospective randomized studies are essential to substantiate this conclusion.

Conclusion

In this multicenter cohort of dialysis-dependent CAD patients, systemic inflammation (NLR) and insulin resistance (TyG index) emerged as dominant predictors of 3-year all-cause mortality, while traditional lipid profiles showed no independent prognostic value. The combined TyG-NLR model significantly improved risk stratification beyond GRACE score or baseline model, underscoring the synergistic interplay between metabolic dysregulation and chronic inflammation in this high-risk population.

Our findings advocate for a paradigm shift toward dual-pathway risk assessment. Looking forward, prospective studies are essential to validate these thresholds. Moreover, our results illuminate a compelling therapeutic possibility: the TyG-NLR signature could potentially identify patients for trials with agents that target both metabolism and inflammation (e.g., SGLT2 inhibitors, IL-6 antagonists). Ultimately, interventional research is needed to determine if ameliorating this metabolic-inflammatory axis translates into improved survival.

Data Sharing Statement

The corresponding author Jingang Zheng can supply the relevant data upon reasonable request.

Ethics Approval and Informed Consent

The study adhered to the principles of the Declaration of Helsinki and received approval from the Ethics Committee at China-Japan Friendship Hospital (2020-112-K71). The ethics committee explicitly waived the requirement for informed consent due to the retrospective analysis. All data were handled in a strictly confidential and anonymized manner.

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Disclosure

The authors report no conflicts of interest in this work.

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