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The Partial Mediating Role of Arterial Stiffness in the Association Between Systemic Inflammation and Declining Renal Function in Type 2 Diabetes Mellitus: A Cross-Sectional Study

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Background: Type 2 diabetes mellitus (T2DM) is associated with chronic low-grade inflammation and increased arterial stiffness, both of which have been independently linked to declining renal function in diabetic nephropathy. This study aims to investigate whether arterial stiffness mediates the relationship between systemic inflammation and renal function in patients with T2DM, potentially revealing a novel pathophysiological pathway.

Methods: In this cross-sectional study of 307 T2DM patients, neutrophil-to-lymphocyte ratio (NLR) was calculated as an inflammatory marker, ambulatory arterial stiffness index (AASI) was derived from 24-hour ambulatory blood pressure monitoring, and estimated glomerular filtration rate (eGFR) was determined. Multiple linear regression models were used to examine the relationships between NLR, AASI, and eGFR. Mediation analysis with bootstrap resampling (5000 replications) was performed to assess whether AASI mediated the association between NLR and eGFR.

Results: Patients with lower eGFR had significantly higher NLR and AASI than those with higher eGFR. After adjusting for confounders, both NLR ($\beta = -8.27$, 95% CI: −12.32 to −4.22, $P < 0.001$) and AASI ($\beta = -22.55$, 95% CI: −43.67 to −1.43, $P = 0.037$) were independently associated with reduced eGFR. Mediation analysis revealed that AASI accounted for 8.17% of the total effect in the fully adjusted model (mediation effect: −0.717, 95% CI: −1.570 to −0.067, $P = 0.024$), demonstrating a partial mediation of the relationship between NLR and eGFR.

Conclusion: AASI partially mediates the association between NLR and eGFR in T2DM patients, providing new insights into the pathophysiological links between inflammation, vascular dysfunction, and kidney damage. Therapeutic strategies targeting inflammation and arterial stiffness might offer synergistic benefits for preserving renal function.

Keywords: type 2 diabetes mellitus, neutrophil-to-lymphocyte ratio, ambulatory arterial stiffness index, estimated glomerular filtration rate, mediation analysis

Introduction

Type 2 diabetes mellitus (T2DM) represents a global health epidemic affecting over 400 million individuals worldwide, with diabetic kidney disease (DKD) standing as one of its most devastating complications.[1] As the leading cause of end-stage renal disease (ESRD), DKD progression is characterized by declining estimated glomerular filtration rate (eGFR) and the presence of albuminuria.[2] Despite significant advances in understanding DKD pathophysiology, the mechanisms driving kidney dysfunction in T2DM remain incompletely elucidated. Compelling evidence increasingly suggests that chronic low-grade inflammation and vascular dysfunction, particularly arterial stiffness, play pivotal roles in DKD progression.[3,4]

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The neutrophil-to-lymphocyte ratio (NLR) has emerged as a powerful marker of systemic inflammation, reflecting the delicate balance between pro-inflammatory and anti-inflammatory processes.[5] NLR demonstrates remarkable stability in chronic metabolic conditions and exhibits superior sensitivity and specificity for detecting early diabetic microvascular damage compared to conventional inflammatory markers.[6] While NLR has limitations as a nonspecific marker potentially influenced by acute stressors and comorbidities, its clinical utility in diabetes remains well-established. This enhanced diagnostic performance stems from NLR's ability to simultaneously capture neutrophil-mediated inflammatory activation and impaired lymphocyte-dependent immunoregulation—both critical in diabetic vascular pathology.[7] Elevated NLR has been consistently associated with poor outcomes across various chronic diseases, including T2DM and its complications.[8,9] In T2DM patients, increased NLR correlates strongly with DKD progression, microvascular complications, and cardiovascular events.[10,11] The underlying mechanisms likely involve neutrophil-mediated oxidative stress, endothelial dysfunction, and lymphocyte-mediated immune dysregulation-all contributing to renal injury and eGFR decline.[12–14] However, the precise pathways through which NLR influences kidney function remain inadequately characterized, and potential mediators in this relationship warrant comprehensive investigation.

Arterial stiffness, a hallmark of vascular aging and diabetes-related vascular damage, has been implicated in DKD pathogenesis. The ambulatory arterial stiffness index (AASI), derived from 24-hour ambulatory blood pressure monitoring (ABPM), represents a clinically accessible measure of arterial stiffness with predictive value for cardiovascular and renal outcomes in T2DM patients.[15,16] While AASI offers advantages in its derivation from routine ABPM data without specialized equipment, it has limitations compared to pulse wave velocity (PWV), the gold standard for arterial stiffness assessment.[17] AASI calculations can be influenced by blood pressure variability patterns and nocturnal dipping status, potentially affecting measurement precision.[18] Nevertheless, elevated AASI reflects increased arterial rigidity, which impairs the vasculature's ability to accommodate pulsatile blood flow, leading to disrupted renal hemodynamics and subsequent kidney damage.[19]

Emerging evidence suggests that AASI may serve as a critical link between systemic inflammation and renal dysfunction, as inflammatory pathways—including pro-inflammatory cytokine activation and oxidative stress—directly contribute to vascular remodeling and increased arterial stiffness in T2DM.[20,21] Several studies have provided indirect evidence supporting this potential mediating pathway. Peyster et al[4] demonstrated that inflammatory markers (IL-6, CRP) were independently associated with arterial stiffness in chronic kidney disease patients, suggesting inflammation-induced vascular changes. Similarly, Georgianos et al[22] identified arterial stiffness as an independent risk factor for kidney injury progression, proposing mechanisms including altered renal microcirculation and glomerular hemodynamics. In the context of diabetes, Amorim et al[23] highlighted the cross-linking between inflammation, vascular dysfunction, and kidney disease, but did not specifically test the mediating relationships among these factors.

Despite substantial evidence implicating both NLR and AASI in DKD progression, their interrelationship remains poorly understood. The potential mediating role of arterial stiffness in the association between systemic inflammation and renal function decline in T2DM represents a knowledge gap that warrants investigation. Understanding this pathway could inform therapeutic strategies targeting both inflammation and vascular dysfunction to preserve renal function. This study evaluates whether AASI mediates the relationship between NLR and eGFR in patients with T2DM, hypothesizing that systemic inflammation promotes arterial stiffening, which subsequently contributes to renal dysfunction.

Methods

Study Population and Design

We consecutively enrolled patients with type 2 diabetes who visited the Department of Endocrinology at Cangzhou Central Hospital (Hebei, China) from January 2021 to December 2023. Type 2 diabetes diagnosis was established according to the American Diabetes Association criteria. Exclusion criteria comprised: (1) type 1 diabetes; (2) acute diabetic complications; (3) severe hepatic dysfunction (alanine aminotransferase or aspartate aminotransferase >3 times the upper limit of normal); (4) advanced renal impairment (eGFR <30 mL/min/1.73 m²); (5) malignancy; (6) autoimmune disease; (7) acute or chronic infection; (8) pregnancy or lactation; and (9) incomplete critical medical data. This study

received approval from the ethics committee of Cangzhou Central Hospital and strictly adhered to the Declaration of Helsinki principles. The requirement for informed consent was waived due to the study's cross-sectional nature.

Data Collection and Definitions

Demographic information, medical history, and specific clinical parameters were systematically extracted from patients' electronic health records. The collection encompassed historical health events, including hypertension, diabetes mellitus duration, smoking status, and alcohol consumption. These self-reported historical details were subsequently corroborated through medical records.

Fasting venous blood samples were collected to measure plasma levels of fasting blood glucose (FBG), glycated hemoglobin (HbA1c), blood urea nitrogen (BUN), serum creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and complete blood count, including neutrophil and lymphocyte counts. The neutrophil-to-lymphocyte ratio (NLR) was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count.[24] All laboratory parameters were measured using standardized laboratory methods.

The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[25] The albumin-to-creatinine ratio (ACR) was measured using an immune turbidimetry assay (Hitachi 7070E; Hitachi High-Technologies, Tokyo, Japan) from a single urine specimen collected on the same day as the blood sample. Based on urinary ACR values, patients were categorized as having either normal albuminuria (ACR < 30 mg/g) or microalbuminuria (ACR 30–300 mg/g). Patients with macroalbuminuria (ACR > 300 mg/g) were excluded from this study.

Patients with macroalbuminuria (ACR > 300 mg/g) were excluded to focus on earlier stages of diabetic kidney disease where the relationships between inflammation, arterial stiffness, and renal function may be less confounded by advanced pathological processes. In established nephropathy, multiple concurrent pathways and complex treatment regimens could potentially obscure the specific associations under investigation. This approach, while enhancing internal validity, does limit our findings' applicability primarily to patients with early to moderate stages of diabetic kidney disease.

24-Hour ABPM and AASI Calculation

All patients underwent 24-hour ambulatory blood pressure monitoring (ABPM) using an oscillometric device (Spacelabs 90217, Spacelabs Healthcare, USA). Blood pressure readings were obtained at 15-minute intervals during the day (06:00–22:00) and 30-minute intervals during the night (22:00–06:00). ABPM recordings with at least 70% successful readings were considered valid for analysis. For AASI calculation, systolic and diastolic blood pressure readings from each identical time point were paired. Individual readings were excluded if they met any of the following criteria: systolic blood pressure <70 or >250 mmHg, diastolic blood pressure <40 or >150 mmHg, pulse pressure <20 mmHg, or readings flagged as technical errors by the device.[26] The ambulatory arterial stiffness index (AASI) was calculated as one minus the regression slope of diastolic blood pressure on systolic blood pressure from individual 24-hour ABPM recordings.[27] Mean arterial pressure (MAP) was calculated as diastolic blood pressure plus one-third of pulse pressure.

Statistical Analysis

Continuous variables were characterized by the mean ± standard deviation (SD) or the median with interquartile range (IQR) based on data distribution normality. Group differences were analyzed using *t*-tests, or Mann–Whitney *U*-tests as appropriate. Categorical variables were summarized as frequencies and percentages, with between-group comparisons performed using the chi-square (χ^2) test or Fisher's exact test.

Based on eGFR levels, participants were stratified into three groups: Low eGFR, Middle eGFR, and High eGFR, using tertile cutoff values. One-way analysis of variance (ANOVA) or the Kruskal–Wallis test was employed to compare continuous variables across the three groups. In contrast, the chi-square test was used for categorical variables. Correlations among variables, including NLR, AASI, and clinical parameters, were evaluated using Spearman correlation coefficients. Additionally, a heatmap was generated to represent each correlation coefficient visually.

Restricted cubic spline analyses were performed to visualize potential nonlinear relationships between NLR, AASI, and eGFR. Multiple linear regression models assessed the relationship between NLR, AASI, and eGFR. Effect estimates (β) with 95% confidence intervals (CI) were calculated. We implemented multiple adjusted models to evaluate the robustness and reliability of the findings thoroughly. Additionally, several subgroup analyses were conducted to explore whether the relationship between NLR, AASI, and eGFR remained consistent across various demographic and clinical subgroups. Interaction terms were introduced into the regression models to test for heterogeneity.

To assess the impact of NLR (exposure) on eGFR (outcome) via AASI (mediator), we employed mediation analysis for continuous variables. This method involved fitting two distinct regression models: one for the mediator and another for the outcome. The significance of the mediating effect was assessed by examining bootstrap samples with 5000 replications.

In multiple linear regression analysis, subgroup analysis, and mediation analysis, we employed multiple adjusted models with various independently adjusted covariates to thoroughly evaluate the robustness and reliability of the findings. Covariates were selected based on either a >10% change in the regression coefficient of the primary predictor after inclusion in the basic model (or removal from the full model) or if the covariate's regression coefficient demonstrated a p-value <0.05 to the outcome. During this process, we evaluated several additional potential confounding factors including other medications (calcium channel blockers, beta-blockers, statins), detailed lifestyle parameters beyond smoking and alcohol consumption, additional comorbidities, and other inflammatory markers. These variables were ultimately excluded as they either did not significantly alter the primary predictor coefficients, showed no significant association with eGFR, or had limited availability across our study population. In all adjusted models, model I was adjusted for age, sex, and BMI; Model II was adjusted for age, sex, BMI, diabetes duration, HbA1c, hypertension, total cholesterol, LDL cholesterol, microalbuminuria, RAAS antagonists, and SGLT2 inhibitors.

All analyses were performed using the statistical software package R (http://www.R-project.org, The R Foundation) and EmpowerStats (http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA). P values less than 0.05 (two-sided) were considered statistically significant.

Results

Baseline Characteristics

307 patients with type 2 diabetes were stratified into three groups based on eGFR levels (low, middle, and high). As shown in Table 1, patients with low eGFR were significantly older and had longer diabetes duration compared to those with middle and high eGFR ($P < 0.001$ for both). Interestingly, despite longer diabetes duration, the low eGFR group exhibited lower HbA1c levels (7.91 ± 1.79%) compared to the middle (8.43 ± 1.78%) and high (8.58 ± 1.88%) eGFR groups ($P = 0.009$), a finding that contrasts with the typical association between poor glycemic control and DKD progression. The low eGFR group also demonstrated higher 24-hour SBP ($P < 0.001$) and higher prevalence of hypertension ($P < 0.001$). Notably, both inflammatory and arterial stiffness markers were elevated in the low eGFR group, with significantly higher NLR ($P = 0.003$) and AASI ($P < 0.001$) compared to the middle and high eGFR groups. RAAS antagonist use was also more prevalent in the low eGFR group ($P = 0.017$). Furthermore, the correlation matrix heatmap (Figure 1) demonstrates significant negative correlations between NLR and eGFR ($r = -0.21$, $P < 0.001$), as well as between AASI and eGFR ($r = -0.28$, $P < 0.001$).

Association of NLR and AASI with eGFR

Restricted cubic spline analyses examined potential nonlinear relationships between NLR, AASI, and eGFR (Figure 2). NLR demonstrated a significant linear inverse relationship with eGFR (P for overall < 0.001, P for nonlinearity = 0.995) (Figure 2A). The high P-value for nonlinearity (>0.05) indicates the absence of a significant non-linear relationship, supporting the appropriateness of using linear models in subsequent analyses. As NLR increased, eGFR decreased in a dose-dependent manner. Similarly, AASI exhibited a significant inverse relationship with eGFR (P for overall < 0.001, P for nonlinearity = 0.663) (Figure 2B), again with no evidence of significant nonlinearity. The relationship between NLR, AASI, and eGFR was assessed using multiple linear regression analysis (Table 2). In the unadjusted model, NLR

Table 1 Baseline Characteristics of Participants Stratified by eGFR Levels

Characteristic	Low eGFR T1 (N=102)	Middle eGFR T2 (N=102)	High eGFR T3 (N=103)	*P*-value
Age (years)	63.33 ± 11.07	57.31 ± 11.86	49.72 ± 13.11	<0.001
BMI (kg/m²)	26.15 ± 3.66	26.44 ± 3.77	26.77 ± 3.67	0.573
Sex				0.924
Male	47 (46.08%)	47 (46.08%)	45 (43.69%)	
Female	55 (53.92%)	55 (53.92%)	58 (56.31%)	
Smoking				0.104
No	67 (65.69%)	79 (77.45%)	79 (76.70%)	
Yes	35 (34.31%)	23 (22.55%)	24 (23.30%)	
Alcohol Drinking				0.353
No	70 (68.63%)	67 (65.69%)	77 (74.76%)	
Yes	32 (31.37%)	35 (34.31%)	26 (25.24%)	
Diabetes Duration (years)	10.00 (4.00–16.75)	8.00 (1.00–15.00)	4.00 (0.75–10.00)	<0.001
HbA1c (%)	7.91 ± 1.79	8.43 ± 1.78	8.58 ± 1.88	0.009
ALT (U/L)	20.40 (16.47–29.00)	23.70 (16.75–32.86)	25.30 (18.50–35.49)	0.024
AST (U/L)	19.40 (15.80–23.20)	21.40 (17.15–27.45)	20.40 (16.05–26.02)	0.101
BUN (mmol/L)	6.67 ± 2.52	5.09 ± 1.14	4.67 ± 1.22	<0.001
Creatinine (μmol/L)	79.48 ± 23.11	56.90 ± 8.23	46.84 ± 7.71	<0.001
eGFR (mL/min/1.73 m^2)	84.76 ± 18.33	121.78 ± 7.13	157.27 ± 19.21	<0.001
TC (mmol/L)	4.71 ± 1.12	4.95 ± 1.19	5.22 ± 1.38	0.035
TG (mmol/L)	1.61 (1.18–2.17)	1.85 (1.21–3.02)	1.51 (1.04–2.71)	0.290
HDL (mmol/L)	1.14 ± 0.25	1.17 ± 0.30	1.16 ± 0.26	0.869
LDL (mmol/L)	2.81 ± 0.93	2.92 ± 0.98	3.24 ± 1.13	0.018
Neutrophils (×10^9/L)	3.71 ± 1.58	3.64 ± 1.33	3.77 ± 1.40	0.875
Lymphocytes (×10^9/L)	1.84 ± 0.83	2.20 ± 0.94	2.24 ± 0.72	<0.001
NLR	2.17 ± 0.97	1.82 ± 0.71	1.76 ± 0.69	0.003
24-Hour SBP (mmHg)	134.75 ± 13.97	130.22 ± 11.74	127.76 ± 11.70	<0.001
24-Hour DBP (mmHg)	73.74 ± 8.86	75.29 ± 9.17	75.63 ± 8.58	0.311
24-Hour HR (bpm)	71.99 ± 9.32	73.58 ± 9.07	76.01 ± 9.71	0.009
24-Hour MAP (mmHg)	94.11 ± 9.15	93.59 ± 8.96	93.01 ± 8.73	0.682
AASI	0.52 ± 0.15	0.43 ± 0.16	0.41 ± 0.17	<0.001
Hypertension				<0.001
No	17 (16.67%)	22 (21.57%)	40 (38.83%)	
Yes	85 (83.33%)	80 (78.43%)	63 (61.17%)	
Microalbuminuria				0.101
No	59 (57.84%)	73 (71.57%)	70 (67.96%)	
Yes	43 (42.16%)	29 (28.43%)	33 (32.04%)	
RAAS antag				0.017
No	43 (42.16%)	53 (51.96%)	64 (62.14%)	
Yes	59 (57.84%)	49 (48.04%)	39 (37.86%)	
SGLT2i				0.055
No	62 (60.78%)	75 (73.53%)	77 (74.76%)	
Yes	40 (39.22%)	27 (26.47%)	26 (25.24%)	

was inversely associated with eGFR (β = −8.02, 95% CI: −12.45 to −3.59, P < 0.001). This association remained significant after adjustment for age, sex, and BMI (Model I: β = −7.97, 95% CI: −12.03 to −3.91, P < 0.001) and after further adjustment for diabetes duration, HbA1c, hypertension, total cholesterol, LDL cholesterol, microalbuminuria, RAAS antagonists, and SGLT2i (Model II: β = −8.27, 95% CI: −12.32 to −4.22, P < 0.001). Similarly, AASI showed a significant inverse association with eGFR in both the unadjusted model (β = −50.63, 95% CI: −72.53 to −28.72, P <

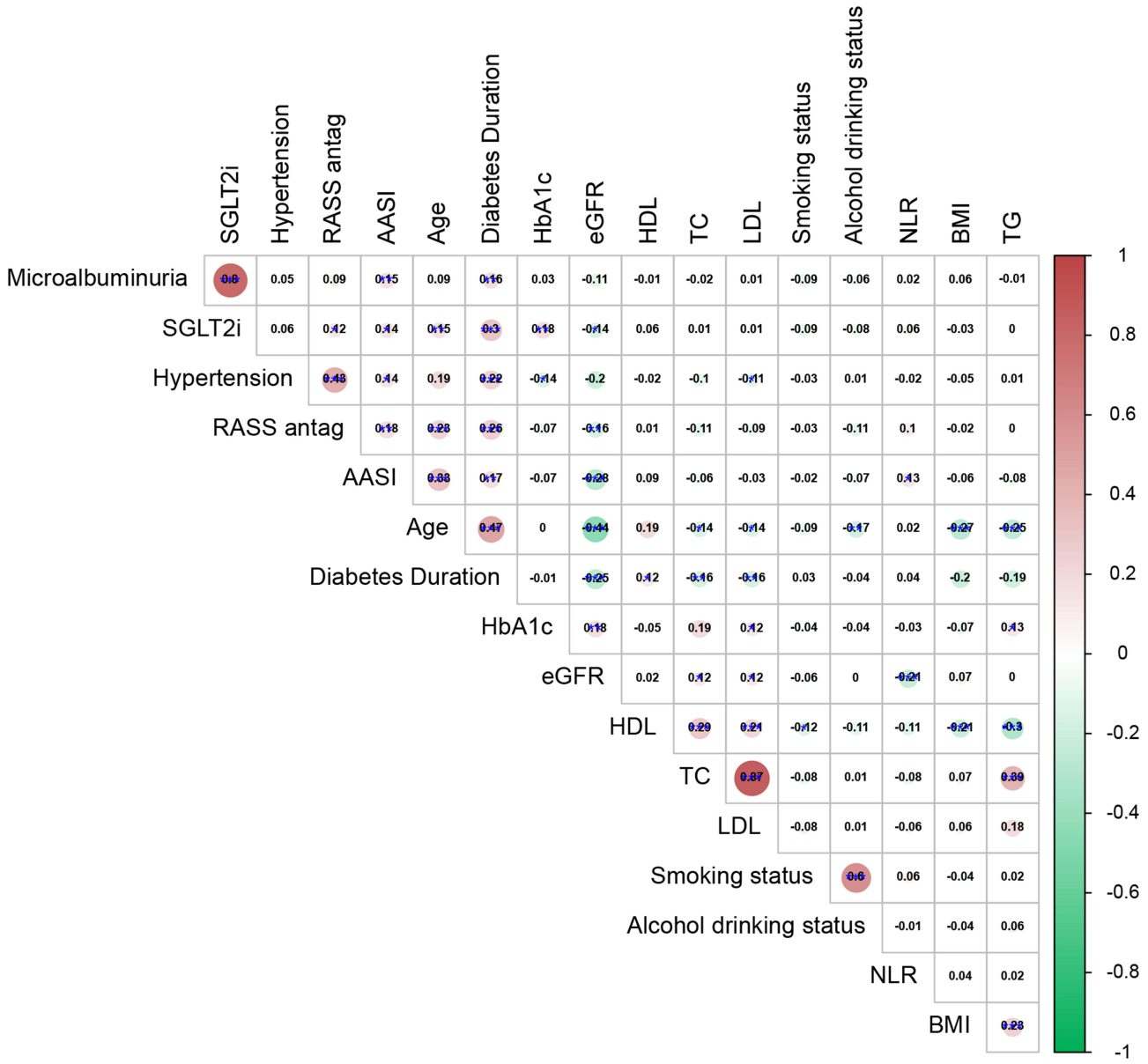

Figure 1 Correlation heatmap of clinical and laboratory parameters in patients with type 2 diabetes. The color intensity indicates the strength and direction of correlations between variables, with red indicating positive correlations and green indicating negative correlations. The numerical values represent Spearman correlation coefficients.
Abbreviations: SGLT2i, sodium-glucose cotransporter-2 inhibitor; RASS antag, renin-angiotensin-aldosterone system antagonists; AASI, ambulatory arterial stiffness index; HbA1c, glycated hemoglobin; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; TC, total cholesterol; LDL, low-density lipoprotein; NLR, neutrophil-to-lymphocyte ratio; BMI, body mass index; TG, triglycerides.

0.001) and the adjusted models (Model I: β = −25.78, 95% CI: −46.81 to −4.76, P = 0.017; Model II: β = −22.55, 95% CI: −43.67 to −1.43, P = 0.037).

Subgroup Analyses

To identify potential effect modifiers, we conducted subgroup analyses stratified by demographic and clinical characteristics (Table 3). A significant interaction was observed between alcohol drinking status and the association between NLR and eGFR (P for interaction = 0.026). The negative association between NLR and eGFR was significant in non-drinkers (β = −12.87, 95% CI: −18.06 to −7.68, P < 0.001) but not in alcohol drinkers (β = −2.35, 95% CI: −10.35 to 5.66, P = 0.565). The association between AASI and eGFR varied by SGLT2i use (P for interaction = 0.035). The negative association between AASI and eGFR was more potent in patients using SGLT2 inhibitors (β = −82.20, 95% CI: −124.01

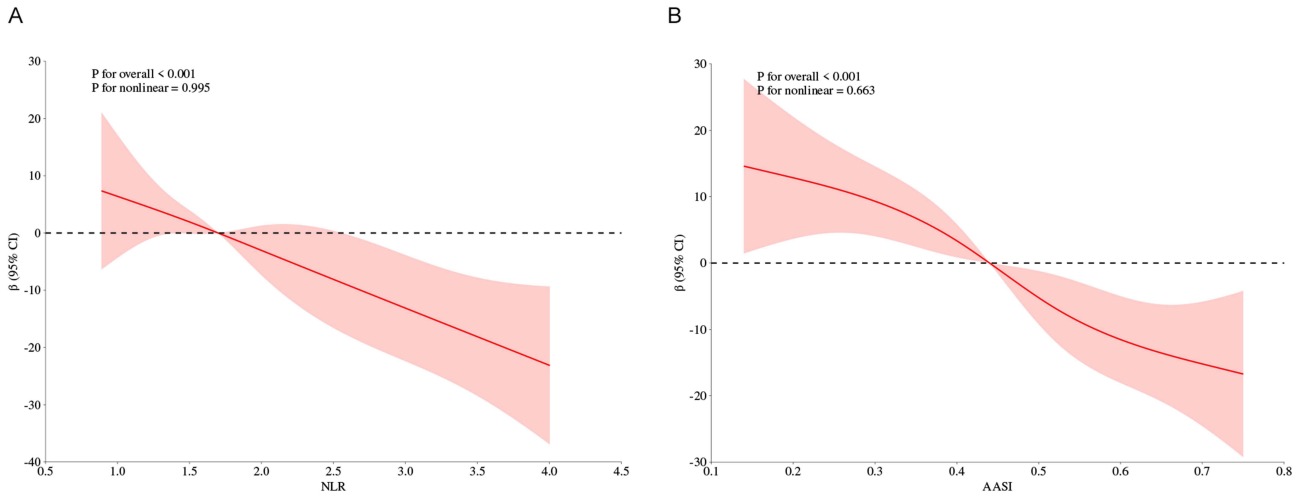

Figure 2 Restricted cubic spline analyses of the association between inflammatory and arterial stiffness markers with renal function. (**A**) Association between neutrophil-to-lymphocyte ratio (NLR) and estimated glomerular filtration rate (eGFR). (**B**) Association between ambulatory arterial stiffness index (AASI) and eGFR. The solid red lines represent the regression coefficients (β), and the pink shaded areas represent the 95% confidence intervals. P for overall indicates the significance of the entire relationship, while P for nonlinear indicates the significance of nonlinear components of the relationship.

to −40.38, P < 0.001) compared to those not using SGLT2 inhibitors (β = −30.65, 95% CI: −56.84 to −4.47, P = 0.022). These findings suggest potentially important biological interactions whereby alcohol consumption may attenuate inflammation-related renal effects, while SGLT2i treatment appears to modify the relationship between vascular stiffness and kidney function. These unexpected interactions, particularly the enhanced AASI-eGFR relationship in SGLT2i users, highlight mechanistic complexities that warrant further investigation.

Mediation Analysis

The mediation analysis demonstrated that AASI partially mediated the relationship between NLR and eGFR across different adjustment models (Figure 3). In the unadjusted model (Figure 3A), the direct effect of NLR on eGFR was −8.100 [95% CI: (−11.644, −4.428), P < 0.001], while the mediation effect through AASI was −1.746 [95% CI: (−2.956, −0.706), P < 0.001], accounting for 17.73% of the total effect. In Model I (Figure 3B) adjusted for age, sex, and BMI, the direct effect was −7.600 [95% CI: (−11.321, −3.664), P < 0.001], with a mediation effect of −0.897 [95% CI: (−12.207, −4.618), P < 0.004], accounting for 10.56% of the total effect. In the fully adjusted Model II (Figure 3C), which additionally controlled for diabetes duration, HbA1c, hypertension, total cholesterol, LDL cholesterol, microalbuminuria, RAAS antagonists, and SGLT2 inhibitors, the direct effect remained significant at −8.052 [95% CI: (−11.793, −3.991),

Table 2 Relationship Between NLR, AASI, and eGFR Levels

Variables	NLR		AASI	
	β (95% CI)	*P*	β (95% CI)	*P*
Unadjusted	−8.02 (−12.45, −3.59)	<0.001	−50.63 (−72.53, −28.72)	<0.001
Adjust Model I	−7.97 (−12.03, −3.91)	<0.001	−25.78 (−46.81, −4.76)	0.017
Adjust Model II	−8.27 (−12.32, −4.22)	<0.001	−22.55 (−43.67, −1.43)	0.037

Notes: Model I was adjusted for age, sex, and BMI. Model II was adjusted for variables in Model I plus diabetes duration, HbA1c, hypertension, total cholesterol, LDL cholesterol, microalbuminuria, RAAS antagonists, and SGLT2 inhibitors. Effect (β) coefficients with 95% confidence intervals (CI) represent the change in eGFR (mL/min/1.73 m²) per unit increase in NLR or AASI.

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; AASI, ambulatory arterial stiffness index; eGFR, estimated glomerular filtration rate; BMI, body mass index; HbA1c, glycated hemoglobin; TC, total cholesterol; LDL, low-density lipoprotein; RAAS, renin-angiotensin-aldosterone system; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

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Table 3 Subgroup Analysis of the Relationship Between NLR, AASI, and eGFR by Demographic and Clinical Factors

Characteristic	NLR			AASI		
	β (95% CI)	P	P for interaction	β (95% CI)	P	P for interaction
Sex			0.107			0.072
Male	−13.66 (−20.24, −7.08)	<0.001		−67.09 (−100.37, −33.81)	<0.001	
Female	−6.42 (−12.39, −0.46)	0.035		−27.30 (−57.19, 2.58)	0.074	
Age (years)			0.454			0.449
<60	−8.38 (−13.74, −3.02)	0.002		−40.61 (−70.78, −10.43)	0.008	
≥60	−11.51 (−17.96, −5.05)	<0.001		−24.37 (−55.71, 6.97)	0.128	
BMI (kg/m²)			0.946			0.698
<25	−10.31 (−18.34, −2.28)	0.012		−42.07 (−79.08–5.05)	0.026	
≥25, <30	−9.84 (−15.83, −3.86)	0.001		−52.27 (−83.23, −21.32)	0.001	
≥30	−8.12 (−19.09, 2.85)	0.148		−23.82 (−87.82, 40.19)	0.466	
Alcohol Drinking			0.026			0.375
No	−12.87 (−18.06, −7.68)	<0.001		−51.96 (−79.53, −24.39)	<0.001	
Yes	−2.35 (−10.35, 5.66)	0.565		−31.80 (−69.15, 5.54)	0.096	
Smoking			0.343			0.867
No	−11.15 (−16.67, −5.63)	<0.001		−45.56 (−72.35, −18.78)	<0.001	
Yes	−6.84 (−14.11, 0.43)	0.066		−41.60 (−82.00, −1.20)	0.044	
Diabetes duration (years)			0.969			0.206
Low	−9.51 (−17.82, −1.21)	0.025		−57.37 (−97.80, −16.94)	0.005	
Middle	−8.85 (−17.99, 0.29)	0.058		−12.10 (−55.60, 31.41)	0.586	
High	−10.20 (−16.52, −3.88)	0.002		−55.46 (−88.75, −22.18)	0.001	
HbA1c (%)			0.656			0.781
<8	−10.81 (−17.50, −4.13)	0.002		−42.07 (−73.14, −11.01)	0.008	
≥8	−8.83 (−14.71, −2.94)	0.003		−48.12 (−79.74, −16.49)	0.003	
Hypertension			0.689			0.521
No	−11.23 (−20.12, −2.34)	0.014		−58.33 (−105.67, −10.98)	0.016	
Yes	−9.21 (−14.23, −4.19)	<0.001		−41.40 (−66.60, −16.19)	0.001	
Microalbuminuria			0.622			0.058
No	−8.76 (−14.57, −2.95)	0.003		−30.79 (−57.75, −3.83)	0.025	
Yes	−11.02 (−17.98, −4.06)	0.002		−75.63 (−114.98, −36.29)	<0.001	
RASS antag			0.961			0.870
No	−9.58 (−16.10, −3.06)	0.004		−43.30 (−74.31, −12.28)	0.006	
Yes	−9.79 (−15.71, −3.87)	0.001		−46.91 (−79.10, −14.73)	0.004	
SGLT2i			0.607			0.035
No	−8.86 (−14.32, −3.40)	0.002		−30.65 (−56.84, −4.47)	0.022	
Yes	−11.30 (−18.96, −3.64)	0.004		−82.20 (−124.01, −40.38)	<0.001	

Notes: All models were adjusted for age, sex, BMI, hypertension, diabetes duration, HbA1c, TC, LDL, microalbuminuria, RAAS antagonists, and SGLT2 inhibitors, except for the stratification variable. Diabetes duration was categorized into tertiles. Effect (β) coefficients with 95% confidence intervals (CI) represent the change in eGFR (mL/min/1.73 m²) per unit increase in NLR or AASI. P for interaction was calculated by including the product term of the stratification variable and NLR or AASI in the regression models.

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; AASI, ambulatory arterial stiffness index; eGFR, estimated glomerular filtration rate; BMI, body mass index; HbA1c, glycated hemoglobin; TC, total cholesterol; LDL, low-density lipoprotein; RAAS, renin-angiotensin-aldosterone system; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

P < 0.001], with a mediation effect of −0.717 [95% CI: (−1.570, −0.067), P = 0.024], accounting for 8.17% of the total effect.

Discussion

In this cross-sectional study of patients with type 2 diabetes, we demonstrated that both systemic inflammation (measured by NLR) and arterial stiffness (measured by AASI) were independently associated with reduced renal function (eGFR). Furthermore, our mediation analysis revealed that AASI partially mediated the relationship between NLR and eGFR, with the proportion of the total effect mediated by AASI ranging from 8.17% in the fully adjusted model to 17.73% in the

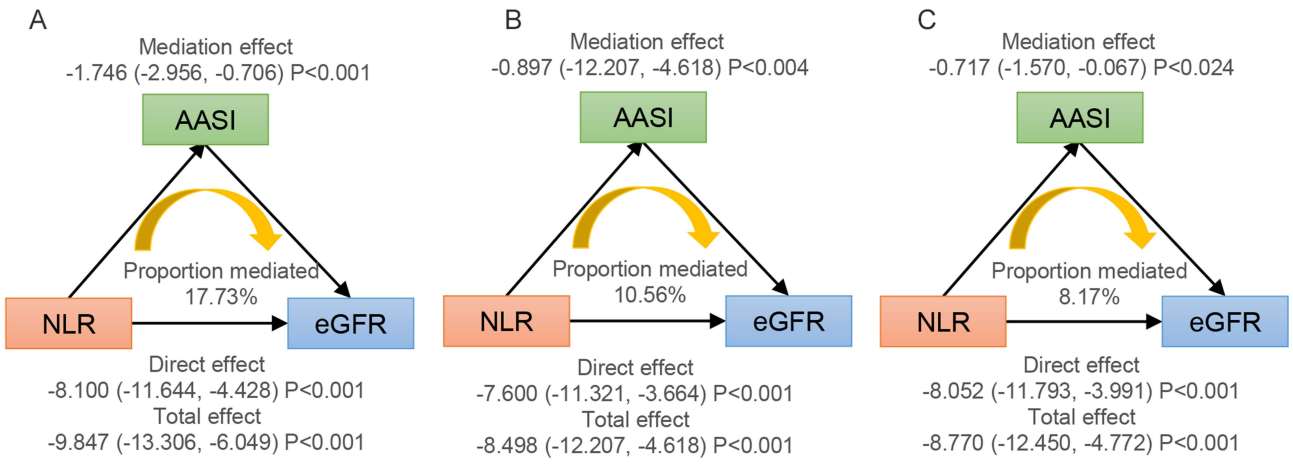

Figure 3 Mediation analysis of the relationship between NLR, AASI, and eGFR in patients with type 2 diabetes. (**A**) Unadjusted model. (**B**) Model adjusted for age, sex, and BMI. (**C**) Model adjusted for age, sex, BMI, diabetes duration, HbA1c, hypertension, TC, LDL, microalbuminuria, RAAS antagonists, and SGLT2 inhibitors. Direct effects, mediation effects, and total effects are presented with their corresponding 95% confidence intervals and P values. The proportion mediated represents the percentage of the total effect of NLR on eGFR that is mediated through AASI.
Abbreviations: NLR, neutrophil-to-lymphocyte ratio; AASI, ambulatory arterial stiffness index; eGFR, estimated glomerular filtration rate.

unadjusted model. These findings provide novel insights into the pathophysiological mechanisms underlying diabetic kidney disease (DKD) and highlight the complex interplay between inflammation, vascular dysfunction, and renal impairment in patients with type 2 diabetes.

Our study's inverse association between NLR and eGFR aligns with previous investigations demonstrating the predictive value of elevated NLR for kidney function decline in various populations, including those with diabetes.[11,28] For instance, Gao et al[29] demonstrated that Higher NLR levels are associated with an increased prevalence of chronic kidney disease (CKD) in diabetic patients. Similarly, Li et al[30] found NLR is positively correlated with urinary albumin-to-creatinine ratio and negatively correlated with estimated glomerular filtration rate, suggesting its potential as a predictor of diabetic kidney disease. NLR, as an accessible and cost-effective marker of systemic inflammation, reflects the balance between neutrophil-mediated inflammatory responses and lymphocyte-dependent immune regulation.[31] In the diabetic milieu, persistent low-grade inflammation contributes to endothelial dysfunction, oxidative stress, and fibrotic changes within the kidney, accelerating the decline in renal function.[32]

The underlying mechanisms through which systemic inflammation impacts renal function involve multiple pathways. Neutrophils, when activated, release reactive oxygen species, proteolytic enzymes, and pro-inflammatory cytokines that can directly damage renal parenchyma.[33] Additionally, neutrophil extracellular traps (NETs) formation in the diabetic kidney may further exacerbate tissue injury and promote fibrosis.[34] Conversely, lymphocytes, particularly regulatory T cells, mitigate inflammatory responses and promote tissue repair.[35] Therefore, an elevated NLR represents increased pro-inflammatory processes and decreased immunoregulatory capacity, creating an environment conducive to progressive kidney damage.

Arterial stiffness, as reflected by AASI, independently predicted reduced eGFR in our cohort, consistent with previous studies linking vascular dysfunction to renal impairment. The ambulatory arterial stiffness index (AASI) has been identified as an independent risk factor for renal failure in non-proteinuric patients with type 2 diabetes.[16] In Chinese patients with chronic kidney disease, AASI correlated with reduced estimated GFR, elevated serum cystatin C, and increased left ventricular mass index.[36] Due to their unique hemodynamic characteristics with high perfusion rates and low vascular resistance, the kidneys are particularly vulnerable to alterations in arterial elasticity.[37] Increased arterial stiffness results in enhanced transmission of pressure pulsatility to the glomerular microcirculation, leading to baro-trauma, endothelial damage, and progressive nephron loss.[22]

A significant contribution of our study is the novel finding that AASI partially mediates the relationship between NLR and eGFR in patients with type 2 diabetes. This mediation effect suggests that systemic inflammation contributes to renal dysfunction partly by exacerbating arterial stiffness. Several potential mechanisms could explain this relationship in the

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diabetic milieu. Chronic inflammation promotes vascular remodeling through enhanced collagen deposition, elastin degradation, and calcification of the arterial wall, all of which increase arterial stiffness and subsequently impair renal microcirculation.[38] The inflammatory cytokines prevalent in diabetic nephropathy, including TNF-α, IL-6, and IL-1β, stimulate vascular smooth muscle cell proliferation and extracellular matrix production while reducing elastin synthesis, accelerating arterial stiffening.[39] Additionally, inflammation impairs endothelial function by reducing nitric oxide bioavailability and increasing oxidative stress, a process significantly amplified in the presence of hyperglycemia and insulin resistance.[40] Furthermore, inflammation-induced alterations in vascular tone through effects on the sympathetic nervous system and renin-angiotensin-aldosterone system may exacerbate arterial stiffness, promoting sodium retention, vasoconstriction, and glomerular hypertension that further compromise renal function in diabetic patients.[41]

The complex interplay between inflammation, arterial stiffness, and renal function in diabetes likely involves additional bidirectional and feed-forward mechanisms. For instance, renal impairment can amplify systemic inflammation through reduced clearance of pro-inflammatory cytokines and uremic toxins, which may further worsen arterial stiffness.[42] Furthermore, shared pathogenic factors in diabetes, such as hyperglycemia, advanced glycation end products, and oxidative stress, simultaneously promote inflammation, vascular dysfunction, and renal injury through interconnected molecular pathways.[23] The relatively small proportion of the total effect mediated by AASI (8.17–17.73%) indicates that other pathways likely play substantial roles in the inflammation-renal function relationship. From a clinical perspective, this partial mediation suggests that therapeutic strategies targeting arterial stiffness alone, while potentially beneficial, would address only a fraction of inflammation-mediated renal damage in T2DM patients. A more comprehensive approach addressing multiple pathophysiological mechanisms—including direct effects of inflammatory mediators on tubular epithelial cells, podocytes, and mesangial cells; alterations in intraglomerular hemodynamics; and metabolic disruptions—would likely provide more substantial renoprotection.[43] This interpretation aligns with the emerging clinical paradigm of combination therapy in DKD, where agents with complementary mechanisms of action (such as RAAS inhibitors, SGLT2 inhibitors, and anti-inflammatory medications) show synergistic benefits for preserving renal function.[44] Additionally, chronic inflammation may influence renal function through metabolic pathways, including insulin resistance and dyslipidemia,[45] which were not fully captured in our mediation analysis.

Our subgroup analyses revealed interesting interactions that deserve mechanistic consideration. The attenuated NLR-eGFR relationship in alcohol drinkers might reflect alcohol's complex immunomodulatory effects, potentially reducing pro-inflammatory cytokine production and modifying immune cell function.[46] Meanwhile, the stronger AASI-eGFR association in SGLT2i users could be explained by SGLT2 inhibitors' unique renal hemodynamic effects, including afferent arteriolar vasoconstriction and altered glomerular pressure dynamics.[47] These hemodynamic adaptations might enhance kidney sensitivity to arterial stiffness. Additionally, SGLT2i-induced modulation of the renin-angiotensin-aldosterone system could strengthen the pathophysiological connection between vascular dysfunction and renal impairment.[48] Alternatively, our SGLT2i users might represent a subpopulation with more advanced vascular pathology. These preliminary mechanistic hypotheses require validation in larger, prospective studies.

Beyond the subgroup interactions observed, another intriguing finding from our baseline data warrants attention. Patients in the low eGFR group exhibited significantly lower HbA1c levels (7.91 ± 1.79%) compared to middle (8.43 ± 1.78%) and high eGFR groups (8.58 ± 1.88%). This counterintuitive observation likely reflects more intensive diabetes management in patients with early renal function decline, as clinicians typically escalate monitoring and treatment when initial signs of diabetic kidney disease emerge.[49] The higher prevalence of RAAS antagonists in the low eGFR group may further contribute to this finding. This observation underscores the complex interplay between clinical management and pathophysiological processes in diabetic patients with varying degrees of renal function.

Several limitations of our study warrant consideration. First, the cross-sectional design precludes definitive conclusions about causality or the temporal sequence of NLR, AASI, and eGFR changes. The relationships observed might be bidirectional, as declining renal function could exacerbate inflammation and vascular stiffness. Longitudinal studies are needed to clarify whether interventions targeting inflammation or arterial stiffness can preserve renal function in patients with diabetes. Second, while NLR is a widely used marker of systemic inflammation, it does not capture the full spectrum of inflammatory processes relevant to diabetic kidney disease. Future studies incorporating comprehensive inflammatory panels (including IL-6, TNF-α, CRP) and tissue-specific markers would provide deeper insights into the

inflammatory mechanisms underlying renal dysfunction. Third, AASI as a measure of arterial stiffness has inherent limitations, influenced by nocturnal blood pressure dipping patterns and heart rate variability. Fourth, our study population consisted exclusively of Chinese patients with type 2 diabetes and excluded those with advanced renal impairment (eGFR <30 mL/min/1.73 m²), potentially limiting the generalizability of our findings to other ethnic groups or patients with more severe kidney disease. Finally, residual confounding cannot be excluded despite adjusting for multiple confounders. Unmeasured factors such as medication adherence, dietary habits, physical activity levels, and other antihypertensive medications might influence the observed relationships between inflammation, arterial stiffness, and renal function.

Several priority directions for future research emerge from our findings and limitations. Longitudinal studies with repeated measurements of inflammatory markers, arterial stiffness, and renal function are essential to establish causality and temporal relationships in this pathway. Interventional trials targeting specific inflammatory mediators (such as IL-1β or TNF-α) while monitoring arterial stiffness and renal outcomes would provide valuable mechanistic insights. Additionally, studies employing gold-standard arterial stiffness measures (eg, pulse wave velocity) alongside comprehensive inflammatory panels in diverse diabetic populations, including those with advanced renal impairment, would enhance the generalizability and clinical applicability of our findings.

Conclusion

In conclusion, our findings demonstrate that arterial stiffness, as measured by AASI, partially mediates the association between systemic inflammation (NLR) and renal function (eGFR) in patients with type 2 diabetes. This novel insight into the pathophysiological pathways linking inflammation, vascular dysfunction, and kidney damage in diabetes provides a foundation for developing integrated therapeutic strategies. Future interventional studies should explore whether combined approaches targeting both inflammation and arterial stiffness offer synergistic benefits for preserving renal function in patients with diabetes, potentially slowing the progression to diabetic kidney disease and its associated complications.

Data Sharing Statement

All data relevant to the study are included in the article. Some or all of the datasets generated and/or analyzed in the current study are not publicly available, but are available on reasonable request by the relevant authors.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of Cangzhou Central Hospital. The Ethics Committee specifically exempted the requirement for informed consent due to the cross-sectional and retrospective nature of the study, as the research involved no more than minimal risk to subjects and utilized existing clinical data. This exemption is in accordance with Article 39 of the "Measures for the Ethical Review of Biomedical Research Involving Humans" issued by the National Health Commission of the People's Republic of China (Order No. 11), which states that informed consent may be waived for "retrospective studies that do not affect the rights and interests of the subjects". This waiver is also consistent with international guidelines, including: The Council for International Organizations of Medical Sciences (CIOMS) Guidelines, specifically Guideline 10 on modifications and waivers of informed consent. The World Health Organization (WHO) Standards and Operational Guidance for Ethics Review of Health-Related Research with Human Participants. All patient data were de-identified before analysis and handled in compliance with the principles of the Declaration of Helsinki. Patient privacy and confidentiality were strictly maintained throughout the study process.

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Disclosure

The authors declare no competing interests in this work.

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