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Original Article

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Mediating Effect of the NLR on the Relationship Between HbA_1c and Left Atrial Stiffness in Overweight Patients With Hypertension

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BACKGROUND: We aimed to investigate the association between hemoglobin A1c (HbA1c) and left atrial (LA) stiffness in patients with hypertension and to explore the mediating effect of the neutrophil/lymphocyte ratio (NLR) on this association.

METHODS: Essential hypertensive patients (n = 292) aged 18–83 years were enrolled and divided into two groups based on the LA stiffness index (LASI): Group I (LASI ≤ 0.32, n = 146) and Group II (LASI > 0.32, n = 146). The LASI was defined as the ratio of early diastolic transmitral flow velocity/lateral mitral annulus myocardial velocity (E/e') to LA reservoir strain. Multivariate linear regression analysis was performed to determine the independent predictors of the LASI.

RESULTS: Age, BMI, SBP, HbA1c, CRP, and NLR were significantly greater in Group II than in Group I ($P < 0.05$). Additionally, Group II had a greater LA volume index (LAVI), left ventricular mass index (LVMI), and early diastolic transmitral flow velocity/lateral mitral annulus myocardial velocity (E/e') and lower LA reservoir, conduit, and booster pump strains than Group I ($P < 0.001$). Univariate and multivariate linear regression models revealed that age, SBP, HbA1c, and the NLR were independently associated with the LASI. Further mediation analysis was performed to determine the mediating effect of the NLR on the association between HbA1c and the LASI and revealed that the NLR had a mediating role only in overweight hypertensive patients, and the proportion of the mediating effect was 21.9%.

CONCLUSIONS: The NLR was independently correlated with the LASI and played a mediating role in the relationship between HbA1c and the LASI in overweight hypertensive patients.

Keywords: blood pressure; diabetes; hypertension; overweight; left atrial stiffness; neutrophil/lymphocyte ratio.

Hypertension, identified as the most prevalent cardiovascular disorder, affects 1.28 billion adults aged 30–79 years worldwide.[1] Hypertension exhibits a robust correlation with several metabolic disorders, including overweight, abnormal lipid levels, and type 2 diabetes mellitus (T2DM), and metabolic diseases have notably risen as primary global health concerns. Hypertension is a widely recognized and established factor that increases the risk of heart disease, peripheral artery disease, stroke, and kidney disease.[2] The hypertension-related damage to the heart includes alterations in the left ventricular (LV) and left atrial (LA) structure and function.[3] Dysfunction of the left atrium not only causes hemodynamic impairment, resulting in pulmonary hypertension but is also a significant factor that increases the risk of cardiovascular mortality and events.[4] Therefore, it is valuable to dedicate additional time to the study of LA function. The LA stiffness index (LASI) is a noninvasive measurement that evaluates the function and stiffness of the left atrium by calculating the ratio of E/e' to LA reservoir strain.[5] The LASI has been proposed as a valuable measure of LA performance.

Chronic low-grade systemic inflammation is often linked to metabolic disorders such as hypertension, obesity, and type 2 diabetes, which can impact LA function. Furthermore, a prior investigation indicated that inflammatory pathways play a crucial role in the impairment of the left atrium.[6] The neutrophil/lymphocyte ratio (NLR), a biomarker for inflammation, has been found to be independently associated with the occurrence of LA remodeling in hypertension patients.[7] Nevertheless, there is currently a lack of studies examining the involvement of the NLR in metabolic disorders that result in LA dysfunction. Hence, the present study aimed to examine the correlation between HbA1c and LA stiffness in individuals with hypertension and to explore the role of the NLR in mediating this correlation.

METHODS

Study population

A total of 292 patients who were diagnosed with essential hypertension (aged 18–83 years) at the Hypertension and Heart Failure Ward of the Cardiac Department of the First Affiliated Hospital of Dalian Medical University between October 2018 and September 2019 were included in this cross-sectional study. The patients

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were classified into two groups based on their median LASI: Group I (LASI ≤ 0.32, n = 146) and Group II (LASI > 0.32, n = 146). The participants did not have secondary hypertension, acute coronary syndrome, acute left heart failure, atrial fibrillation, moderate or severe valvular disease, chronic renal failure [estimated glomerular filtration rate (eGFR) less than 45 ml/min/1.73 m^2], stroke/transient ischemic attack, or obstructive sleep apnea. The study was conducted following the principles outlined in the Declaration of Helsinki and received approval from the Ethics Committee of the First Affiliated Hospital of Dalian Medical University. All patients signed written informed consent forms before enrollment.

Complete blood count assay

An automated hematology analyzer (Sysmex XE-5100, Japan) and Hitachi Company 7600-020 (Japan) were utilized to measure complete blood count (CBC) and biochemical parameters. Venous blood samples were collected into tubes containing dipotassium ethylenediaminetetraacetic acid (EDTA) for the complete blood count (CBC) test and tubes containing sodium fluoride and dipotassium EDTA for the biochemical tests, following a minimum fasting period of 8 h. The hospital laboratories conducted all tests in accordance with the quality standards set by the Technical Specifications (TS) European (EN) International Organization for Standardization (ISO) 15189. The NLR was determined by dividing the neutrophil count by the lymphocyte count. To calculate the platelet/lymphocyte ratio (PLR), the platelet count was divided by the lymphocyte count.

Echocardiographic measurements

In accordance with the American Society of Echocardiography's recommendation, all patients underwent echocardiographic measurements using a Vivid E9 ultrasound system (GE Vingmed Ultrasound, Horten, Norway) that was equipped with an M5S phased array transducer (2.5–5.0 MHz). We acquired visual representations and information, which were digitally saved for offline analysis.

The measurement of the maximum LA volume (LAV) was conducted using apical four-chamber and apical two-chamber views according to the improved Simpson's law in two planes prior to the opening of the mitral valve. The LAVI was calculated using body surface area (BSA). Measurements were taken on the LV long-axis view for the LV chamber size (LVD), the thickness of the interventricular septum (IVST) in the left ventricle, and the LV posterior wall thickness (LVPWT). To calculate the LV mass (LVM), the formula suggested by the American Society of Echocardiography was utilized: $\mathrm{LVM} = 0.8 \times 1.04\left[(\mathrm{LVD} + \mathrm{IVST} + \mathrm{LVPWT})^3 - \mathrm{LVD}^3\right] + 0.6$. The LVM index (LVMI) (g/m^2) was determined by dividing the LVM by the BSA. To assess the LVEF, the modified biplane Simpson's method was used. Additionally, the PW-Doppler technique was utilized to measure the transmitral flow velocity during the diastolic period. Measurements were taken for early diastolic flow velocity (E) and late diastolic flow velocity (A), and the E/A ratio was calculated. The myocardial velocity of the lateral mitral annulus (e′) was assessed using the tissue Doppler technique in the apical four-chamber view, and the ratio of E to e′ (E/e′) was computed.[8]

LA strain and strain rate

Two-dimensional speckle tracking echocardiography (2DSTE) was used to determine the LA strain and strain rate. Standard 2D gray images were obtained from the apical four-chamber and two-chamber views.

The data were acquired at a rate exceeding 40 frames/second while the participants held their breath. Offline analysis of three continuous heart rhythm cycles in digital form. The deformation of LA mechanics in the apical four- and two-chamber views was analyzed using 2DSTE. The click method was employed to monitor the LA endocardial surface from the septal to lateral mitral annulus after the completion of cardiac contraction. The offline 2DSTE data were analyzed by EchoPAC (EchoPAC version 202, GEVingmedB super). The region of interest was manually modified to match the total width of the left atrium.

The software automatically generated longitudinal curves of strain and strain rate for both the global and regional walls of the left atrium. LA strains were measured by collecting myocardial segments from apical two-chamber and four-chamber views. Zero strain was set at the end of the LV diastole, which is the starting point of the QRS wave (QRS wave is an electrocardiogram term, which is a group of Q waves,R waves, and S waves, representing ventricular depolarization). The LA strains exhibited certain curves, with the initial peak occurring at the end of LV systole, indicating the reserve strain of the LA (LAS-S) and its association with the reserve function. Following LAS-S, there was a plateau (LAS-E) during the initial diastolic phase and a lesser positive summit (LAS-A) in the late diastolic phase, denoting the functions of the conduit and booster pump, respectively. The difference between LAS-S and LAS-A was defined as the LA conduit strain in early diastole (LAS-E). The LASI was calculated as the ratio of E/e′ (where E represents the peak early transmittal flow velocity and e′ represents the lateral mitral annular velocity) to the LA reservoir strain.[9,10]

Covariates and statistical analysis

The variables used in this examination were selected by considering the possible factors that could influence the LASI. The data were analyzed and presented statistically using SPSS 21.0 software (SPSS, Chicago, Illinois, USA) and R v.4.1.0 software (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables are expressed as the mean ± standard deviation or the median, while categorical variables are expressed as percentages. To evaluate the normality of the data distribution, either the Shapiro–Wilk test or the Kolmogorov–Smirnov test was employed. Independent samples t-tests were used to compare the variances of two separate groups with normally distributed continuous variables, while the Mann–Whitney U test was employed for comparing non-normally distributed variables. To identify the factors that independently predict the LASI, both univariate and multivariate linear regression models were utilized. To ascertain whether the NLR mediated the correlation between HbA1c and the LASI in individuals who were overweight or not, mediation analyses were conducted. A difference was considered significant if the associated P value was less than 0.05. The intraclass correlation coefficients for the interobserver variabilities of the LA reservoir, conduit, and booster pump strains were 0.927, 0.833, and 0.867, respectively. Additionally, the intraclass correlation coefficients for intraobserver variabilities were 0.950, 0.907, and 0.932, respectively.

RESULTS

Patient characteristics

Table 1 presents the participant demographics, including risk factors, drug usage, and echocardiographic parameters. Our findings revealed that individuals in Group II exhibited a tendency toward advanced age and a greater body mass index (BMI) than did those in Group I (P < 0.001), and the hypertension duration between the two groups was statistically significant

Table 1. Baseline characteristics of Group I (LASI < 0.305; *n* = 146) and Group II (LASI > 0.305; *n* = 146) patients

Variable	Group I (LASI < 0.305 *n* = 146)	Group II (LASI > 0.305 *n* = 146)	*P* values
Age, y	48.56 ± 10.88	54.95 ± 12.40	0.000
HT duration, y	7.85 ± 7.48	9.30 ± 9.16	0.004
Sex, F/M	79/67	85/61	0.481
BMI, kg/m^2	26.52 ± 3.43	28.07 ± 3.98	0.000
Smoking, *n*	106/40	101/45	0.521
SBP, mm Hg	139.19 ± 17.42	151.04 ± 20.66	0.000
DBP, mm Hg	88.32 ± 12.43	90.16 ± 15.81	0.279
UA, umol/l	353.47 ± 91.46	367.46 ± 92.96	0.196
Cre, IU/l	64.79 ± 18.69	70.59 ± 30.41	0.051
HbA1c, %	5.95 (5.5, 6.0)	6.34 (5.7, 6.6)	0.000
TC, mmol/l	4.73 ± 0.96	4.81 ± 1.11	0.512
TG, mmol/l	1.77 ± 1.56	1.99 ± 1.60	0.304
Inflammatory factor			
CRP	0.85 (0.46, 1.72)	1.5 (0.65, 2.75)	0.001
NLR	1.67 ± 0.58	1.96 ± 1.06	0.004
PLR	96.47 (78.95, 126.20)	96.95 (68.07, 129.73)	0.498
Medication, *n* (%)			
CCB	55 (37.6%)	57 (39%)	0.811
ACEIs/ARBs/ARNIs	97 (66.4%)	77 (52.7%)	0.017
β-blockers	115 (78.7%)	104 (71.2%)	0.138
Diuretics	135 (92.4%)	126 (86.3%)	0.088

Abbreviations: BMI, body mass index; Cre, creatinine; CRP: C-reactive protein; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; LASI, left atrial stiffness index; NLR, neutrophil/lymphocyte ratio; PLR: platelet/lymphocyte ratio; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; UA, uric acid.

Table 2. Conventional echocardiographic parameters

Variable	Group I (LASI ≤ 0.305)	Group II (LASI > 0.305)	*P* values
LVEF, %	60 (59, 62)	60 (58, 60)	0.000
LAVI, ml/m^2	25.30 ± 6.38	30.73 ± 8.34	0.000
LVMI, g/m^2	89.04 ± 37.49	92.82 ± 52.07	0.004
E/A ratio	1.62 (0.77, 1.16)	2.70 (0.75, 1.72)	0.829
E/e′ ratio	8.13 (5.9, 8.3)	13.32 (9.5, 16)	0.000
LAS-S, %	27.98 (26.20, 34.34)	18.84 (15.88, 26.02)	0.000
LAS-E, %	13.02 (11.24, 16.50)	7.71 (3.83, 11.72)	0.000
LAS-A, %	13.96 (12.62, 17.63)	10.50 (8.76, 14.71)	0.000

Abbreviations: A, peak late transmittal flow velocity; E, peak early transmittal flow velocity; e′, lateral mitral annular velocity; LAS-A, left atrial longitudinal strain during late diastole; LAS-E, left atrial longitudinal strain during early diastole; LAS-S, peak left atrial longitudinal strain; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index.

(*P* = 0.004). Furthermore, compared to Group I, Group II exhibited greater systolic blood pressure (SBP), and HbA1c (*P* < 0.001), while the remaining risk factors were not significantly different. Compared with Group I, Group II exhibited greater NLRs (*P* = 0.004) and CRP levels (*P* = 0.001), while there was no significant difference in the PLR between the two groups (*P* = 0.498). Antihypertensive medications were administered to all enrolled patients with hypertension. The findings indicated that the use of ACEIs/ARBs/ARNIs significantly differed between the two groups (*P* = 0.017), whereas there were no significant differences in the use of the remaining medications. Table 2 shows the traditional echocardiographic evaluation and LA strain parameters. LAVI (*P* < 0.001) and LVMI (*P* = 0.004) were greater in Group II than in Group I. Furthermore, Group II exhibited a greater E/e′ ratio than Group I (*P* < 0.001), while there was no significant difference in the E/A ratio (*P* = 0.829). Compared with Group I, Group II exhibited significantly lower LA strains, including LAS-S, LAS-E, and LAS-A (*P* < 0.001).

Univariate/multivariate linear regression analysis

Table 3 displays the outcomes of both the univariate and multivariate linear regression models. The LASI was correlated with age, BMI, SBP, HbA1c, and the NLR according to the univariate linear regression. Furthermore, Figure 1 illustrates that age (*B* = 0.005, 95% CI = 0.003–0.007, *P* < 0.001), SBP (*B* = 0.004, 95% CI = 0.002–0.005, *P* < 0.001), HbA1c (*B* = 0.025, 95% CI = 0.001–0.050, *P* = 0.041), and the NLR (*B* = 0.047, 95% CI = 0.020–0.074, *P* = 0.001) were independent factors that impacted the LASI.

Mediation effect analysis

To further investigate the influence of the NLR on the correlation between HbA1c and the LASI, we conducted a mediation analysis to assess the degree to which the NLR acted as a mediator in the relationship between HbA1c and the LASI among patients with either normal weight or overweight. We divided the statistical analysis into three parts to separately test (i) the effect of the NLR on HbA1c, (ii) the effect of HbA1c on the LASI, and (iii) the total effect of HbA1c and the NLR on the LASI. After adjusting for potential confounding variables such as age, sex, and SBP, the relationship between HbA1c and the LASI in overweight patients with hypertension was partially mediated by the NLR. The direct effect was 0.023 (95% CI 0.0037–0.04; *P* = 0.04), the indirect effect was 0.0069 (95% CI 0.0004–0.02; *P* = 0.04), and the proportion of the mediation effect of the NLR was 21.9%. Nevertheless, the association between HbA1c and the LASI in hypertensive individuals

Table 3. Univariable and multivariate analyses of the determinants of the LASI

Variable	Univariate			Multivariate		
	B	95% CI	*P*	*B*	95% CI	*P*
Age, y	0.004	0.002–0.006	0.000	0.005	0.003–0.007	0.000
History, y	0.001	–0.003 to 0.003	0.817			
BMI, kg/m^2	0.008	0.002–0.015	0.014	0.004	–0.002 to 0.011	0.192
SBP, mm Hg	0.004	0.002–0.005	0.000	0.004	0.002–0.005	0.000
HbA1c, %	0.053	0.027–0.079	0.000	0.025	0.001–0.050	0.041
CRP	0.004	0.000–0.009	0.061			
NLR	0.062	0.034–0.091	0.000	0.047	0.020–0.074	0.001

Abbreviations: BMI, body mass index; CRP: C-reactive protein; HbA1c, hemoglobin A1c; NLR, neutrophil/lymphocyte ratio; SBP, systolic blood pressure.

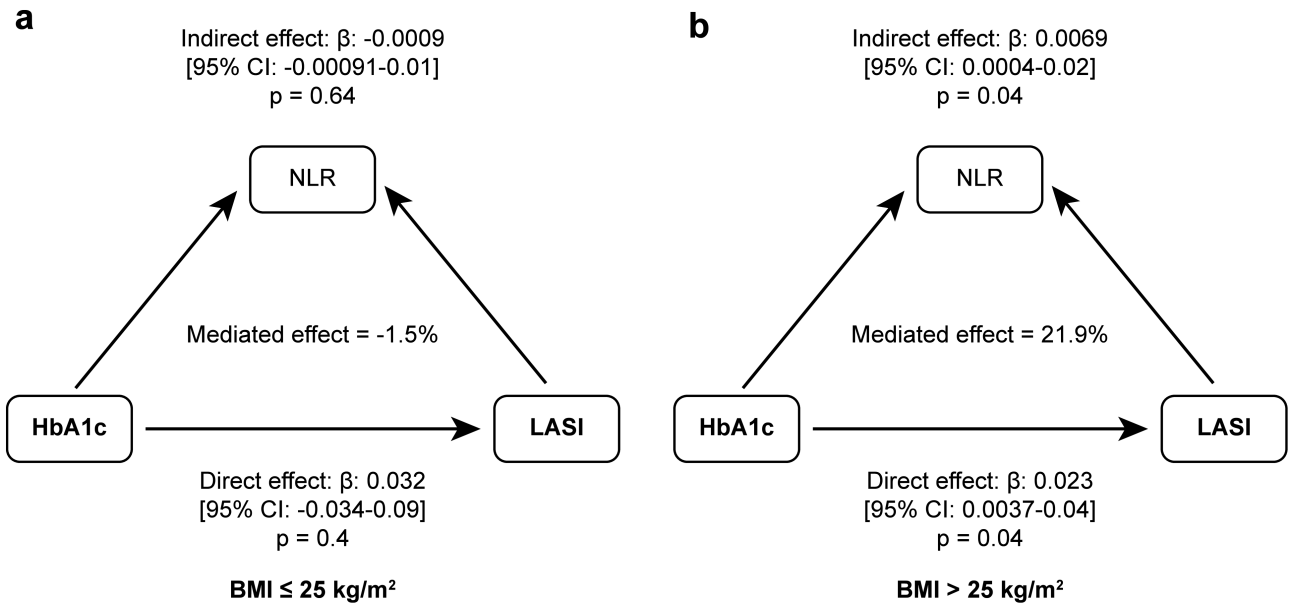

Figure 1. Stratified analysis for the association of risk factors with the LASI via multivariate linear regression analysis. LASI, left atrial stiffness index.

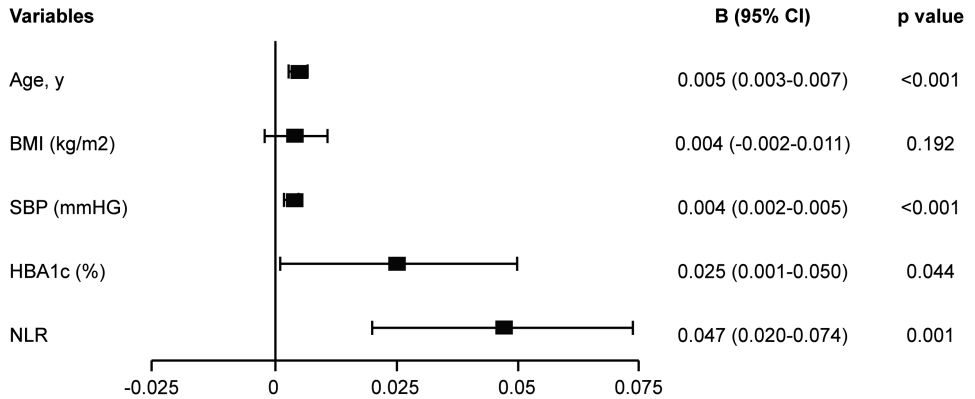

Figure 2. The mediating effect of the NLR on the relationship between HbA1c and the LASI. (**a**) Hypertensive normal weight patients. (**b**) Hypertensive overweight patients. HbA1c, hemoglobin A1c; LASI, left atrial stiffness index; NLR, neutrophil/lymphocyte ratio.

with a healthy weight was not influenced by the NLR, as depicted in Figure 2.

DISCUSSION

The present study revealed a significant association between HbA1c, inflammatory markers, and LA stiffness in individuals with hypertension. Moreover, based on our current knowledge, this is the first study to reveal that the NLR, an inflammatory biomarker, plays a mediating role in the relationship between HbA1c, and the LASI in hypertensive overweight patients.

Diabetes is a common comorbidity in patients with hypertension, affecting 20%–60% of hypertensive patients.[11] Conversely, hypertension is highly prevalent in patients with T2DM, affecting 50%–80% of those patients.[12] Additionally, the presence of diabetes worsens cardiac remodeling induced by hypertension.

Our previous study[13] revealed that the impairment of LA conduit function induced by hypertension was exacerbated by the coexistence of diabetes. In this study, 81.16% of patients with high blood pressure had type 2 diabetes, and the LASI showed an independent correlation with HbA1c levels. HbA1c serves as a stable biomarker indicating impaired glucose metabolism, reflecting the average blood glucose concentration over the past 2–3 months. It not only plays a pivotal role in diagnosing diabetes and assessing the efficacy of diabetes treatment but it is also associated with adverse cardiovascular outcomes in diabetic individuals. HbA1c levels reflect various physiological processes, including functional deficits of pancreatic β cells, insulin resistance, the initiation of proinflammatory pathways, oxidative stress, endothelial damage, and the activation of the renin–angiotensin–aldosterone system.[14] Recent studies have expanded our understanding, revealing associations between HbA1c, and hypertension risks,[15] subclinical atherosclerosis incidence and extent[16] and increased cardiovascular disease risk and mortality,[17] even in nondiabetic individuals. In our current study, which included hypertensive patients with and without diabetes, we discovered that elevated HbA1c levels were independently correlated with LA dysfunction. These findings reinforce the clinical significance of routinely measuring HbA1c levels for assessing cardiovascular risks in nondiabetic patients.

Furthermore, cardiac remodeling can be influenced by various metabolic factors, including but not limited to obesity and dyslipidemia. According to a study conducted by Steele *et al.*,[18] individuals with obesity and T2DM exhibited notably impaired LA function and LV diastolic dysfunction. Obesity can also lead to subclinical cardiac dysfunction.[19] Moreover, obesity is a significant trait associated with the phenotype of HFpEF[20] and cardiac remodeling caused by obesity plays a role in adverse cardiovascular consequences.[21] Previous studies[22,23] have shown that obesity, whether accompanied by diabetes or not, can lead to impaired LA functions. As evaluated by the 2DSTE-based strain, the underlying mechanisms involve an increase in epicardial adipose tissue, chronic volume overload, heightened sympathetic activities, and inflammation.

According to a study conducted by Deal *et al.*,[24] obesity resulted in LA myopathy in obese individuals who did not have any obvious cardiovascular conditions. This LA myopathy includes LA enlargement and LA reservoir dysfunction. Furthermore, that study revealed that weight loss completely reversed the subclinical LA myopathic phenotype. In the present study, BMI was greater in Group II (higher LASI group) than in Group I and univariate regression analysis revealed a significant association between an increased BMI and an increased LASI, indicating a correlation between obesity/overweight and decreased LA function. However, after a further multivariate regression analysis, we did not find a significant independent correlation between increased BMI and LASI after adjusting for clinical confounders. This suggests that the correlation between an increased BMI and LASI may be influenced by other factors.

Systemic inflammation plays an important role in the development of hypertension and diabetes.[19] Furthermore, chronic low-grade inflammation also contributes partially to cardiac dysfunction. In a study carried out by Cauwenberghs *et al.*,[25] metabolic and inflammatory indicators were connected with subclinical impairment of the heart, such as LV diastolic dysfunction, LA enlargement, and LA reservoir dysfunction. Furthermore, systemic inflammation has been reported to induce atrial electrical and structural remodeling,[26,27] which is also considered as a strong indicator of atrial fibrillation.[28,29] Metabolic syndromes, such as obesity and diabetes, often involve an increase in epicardial adipose tissue and abnormal inflammation-associated atrial substrate, leading to a greater risk of "stiff LA syndrome" and atrial fibrillation recurrence. In this study, the group with a higher LASI exhibited a significant increase in inflammatory biomarkers, namely, CRP and NLR, which were found to be associated with the LASI. Nevertheless, only the NLR exhibited an independent correlation with the LASI following adjustment for confounding variables. The NLR is an easily obtainable and cost-effective biomarker for detecting subclinical cardiac and noncardiac inflammation. Earlier studies have indicated that the NLR is associated with insulin resistance and glucose intolerance in diabetes patients[30,31] and serves as a predictive indicator of initial organ damage caused by diabetes.[32] Additionally, the NLR has been linked not only to coronary heart disease,[33] atrial fibrillation,[34] and cardiac remodeling[35] but also to heart failure prognosis in a series of studies.[36,37]

Strikingly, in this study, the NLR played a role in mediating the relationship between HbA1c and the LASI solely in overweight individuals with hypertension. Obesity-related adipocyte hypertrophy and hyperplasia reportedly lead to the accumulation and expansion of adipose tissue, which becomes dysfunctional and inflamed, promoting low-grade systemic inflammation.[38] Weight gain leading to an increase in BMI is linked to the concentration of inflammatory markers.[39] A study by Efremov *et al.*[40] revealed that a metabolically healthy but obese phenotype was correlated with cardiac remodeling, such as an increase in LA volume and LVMI, as well as an increase in inflammatory biomarkers. Hence, persistent mild inflammation originating from visceral adipose tissue contributes to the acceleration of cardiac remodeling, including LA function and stiffness, even in metabolically healthy obese individuals.

Limitations

First, the cross-sectional design of the present study limits the ability to establish strong causal inferences based on the results. Second, this study population included a small number of hospitalized hypertensive patients and only a cross-sectional design was used in this study. Thus, a large-scale prospective cohort study is needed to further confirm our findings. Third, it should be noted that medical treatments for hypertension and T2DM may have an effect on LA function, which could confound the results. Finally, the LASI is a useful noninvasive measurement of LA function; however, it is not the gold standard. Other modalities for assessing LA function and stiffness, such as 3D echocardiography, cardiac MRI, and invasive methods, were not used in the current study.

CONCLUSIONS

The NLR, a traditional inflammatory marker, showed an independent correlation with the LASI and acted as a mediator in the association between HbA1c and the LASI in hypertensive overweight patients.

Acknowledgments

We thank all the study participants.

Conflict of Interest

The authors declare that they have no conflicts of interest regarding the submitted work.

Ethical Approval

The study was performed according to the guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of the Department of the First Affiliated Hospital of Dalian Medical University (Approval Number: PJ-KS-KY-2019-97).

Informed Consent

Written informed consent was obtained from all participants.

Author Contributions

RZ and YP contributed equally to this study. The study was conceptualized and designed by YNJ and YL. ZR and YP were responsible for the writing of the manuscript. QBS and TTF collected the cardiac ultrasonography data. YKR analyzed and interpreted the data. XZ collected the clinical data. All the authors have read and approved the final manuscript.

Data availability

The data are available from the corresponding author upon reasonable request.

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