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Independent association of serum uric acid levels with arterial stiffness in the absence of established cardiovascular disorders

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Abstract

Background: The impact of serum uric acid (SUA) on atherosclerosis has been suspected to be epiphenomenal owing to its close relationship with metabolic abnormalities. The aim of the present study was to evaluate the association between SUA levels and arterial stiffness in the absence of established cardiovascular (CV) disorders.

Methods: The relationship between SUA levels and brachial-ankle pulse wave velocity (baPWV) was examined in 353 asymptomatic adults (57 ± 8 years, 11.9% men) without established CV disorders defined as systolic blood pressure (BP) ≥140 mmHg or diastolic BP ≥ 90 mmHg; total cholesterol ≥240 mg/dL; low-density lipoprotein cholesterol ≥160 mg/dL; high-density lipoprotein cholesterol <40 mg/dL; fasting glucose ≥126 mg/dL; body mass index ≥25.0 kg/m^2; current smoking; and history of medication for hypertension, diabetes, and dyslipidemia. Subjects were stratified into four groups based on the quartiles of their SUA levels.

Results: Mean baPWV was significantly different in all groups: group I, 1320 ± 195 cm/s; group II, 1336 ± 195 cm/s; group III, 1404 ± 199 cm/s; and group IV, 1483 ± 248 cm/s ($P < .001$). SUA levels were significantly correlated with baPWV ($r = .364$) ($P < .001$). Multivariate linear regression analysis showed that SUA (β: 32.93; 95% confidence interval [CI]: 18.99-54.87), together with age (β: 11.44; 95% CI: 9.36-13.53) and systolic BP (β: 8.98; 95% CI: 6.80-11.16), was significantly associated with baPWV ($P < .001$).

Conclusions: High SUA levels have an independent association with increased arterial stiffness even in subjects without established CV disorders.

1 | INTRODUCTION

Increased serum uric acid (SUA) levels are strongly linked to metabolic abnormalities, including hypertension, obesity, and hyperlipidemia.[1-3] Epidemiologic studies have suggested that SUA is an important risk factor for cardiovascular (CV) disease.[4-9] The impact of SUA on atherosclerosis has been suspected to be epiphenomenal owing to its close relationship with diverse metabolic abnormalities.[10] Previous studies have investigated the association between SUA levels and subclinical atherosclerosis in coronary or carotid arteries, but the results have been conflicting.[11-15] Specifically, there is a paucity of data on the impact of SUA on subclinical atherosclerosis in the absence of established CV disorders. This is an important issue because atherosclerotic adverse CV events commonly occur in individuals with a low CV risk burden.[16-18]

Arterial stiffness is an important risk factor for many major CV diseases and is an indicator of functional changes related to atherosclerosis.[19] Currently, the brachial-ankle pulse wave velocity (baPWV) is widely used as a simple and reliable tool for measuring arterial stiffness owing to its high reproducibility in clinical practice.[20,21] Additionally, baPWV is strongly correlated with aortic and carotid-femoral pulse wave velocities.[21,22] In the present study, we hypothesized that high

SUA levels is correlated with an increase in arterial stiffness even in the absence of established CV disorders. Therefore, this study evaluated the association between SUA levels and baPWV in asymptomatic adults without established CV disorders in the Korean population.

What's known

- Previous epidemiologic studies strongly suggested that serum uric acid (SUA) is an important risk factor for cardiovascular (CV) disease.
- However, the impact of SUA on atherosclerosis has been suspected to be epiphenomenal owing to its close relationship with diverse metabolic abnormalities.

What's new

- We evaluated the association between SUA levels and arterial stiffness reflected in brachial-ankle pulse wave velocity (baPWV) in asymptomatic adults without established CV disorders.
- In the present study, SUA levels, together with age and systolic blood pressure, were independently associated with baPWV, even in the absence of established CV disorders.

2 | METHODS

2.1 | Study design and subjects

This study analyzed baseline data collected for a prospective cohort registry. Between April 2010 and November 2012, a total of 2,560 asymptomatic subjects without a clinical history of CV disease, cerebrovascular disease, neurological abnormalities, cerebral hemorrhage, or malignancy had participated in baseline health examinations for a community-based cohort study. Of these, 2207 subjects with established CV disorders including (a) systolic blood pressure (BP) ≥140 mmHg, diastolic BP ≥ 90 mmHg, or previous diagnosis or medication history of hypertension (n = 1273); (b) fasting glucose ≥126 mg/dL or previous diagnosis or medication history of diabetes (n = 125); 3) total cholesterol ≥240 mg/dL, low-density lipoprotein (LDL) cholesterol ≥160 mg/dL, high-density lipoprotein (HDL) cholesterol <40 mg/dL, or previous diagnosis or medication history of dyslipidemia (n = 517); and 4) body mass index (BMI) ≥25.0 kg/m^2 (n = 199) and those currently smoking (n = 93) were consecutively excluded. Finally, 353 subjects (57 ± 8 years, 11.9% men) were selected to participate in the present study (Figure 1). Participants were stratified into four groups based on the quartiles of their SUA levels. The study protocol was approved by the local ethics committee of the institution, and informed consent for the procedure was obtained from each participant. Neither the patients nor the public were involved in the design, conduct, reporting, or dissemination of our research.

Height and weight were measured with the subjects wearing light clothing and no shoes. BMI was calculated as weight (kg)/height (m^2). Blood samples were obtained after 8 hours of fasting and analyzed. Total cholesterol, triglyceride, HDL cholesterol, LDL cholesterol, and creatinine levels were measured by enzymatic colorimetry using Toshiba 200FR Neo (Toshiba Medical System Co., Ltd, Tokyo, Japan). Glucose levels were measured by enzymatic colorimetry using a Toshiba 200 FR auto-analyzer. After achieving blood samples, baPWV was measured as per the standard protocol in clinical practice.[23] Regular medication was permitted for all participants, but smoking, alcohol consumption, and caffeine consumption were strictly prohibited on the day of examination. Brachial BP was measured twice using an automatic cuff oscillometric device (WatchBP office; Microlife, Widnau, Switzerland), after the patient was made to rest in the supine position for at least 5 minutes in a quiet room with ambient temperature between 22°C and 24°C, with a 3-minutes interval between measurements. baPWV was measured using an automated waveform analyzer (Colin VP-2000, Colin Medical Instruments Corp., Komaki, Japan). Pneumatic cuffs were wrapped around both upper arms and both ankles, and connected to a plethysmographic sensor to determine the volume pulse waveform. After simultaneous measurement of waveforms in all four limbs, the time interval between the brachial and ankle waveforms (ΔTba) was determined. The distance between the brachium and the ankle (La − Lb) was estimated automatically based on the subject's height. After these data were collected, baPWV was calculated using the equation: baPWV = (La − Lb)/ΔTba (cm/s). The higher value of the baPWV measured on either side of each patient was used for analysis. All procedures were in accordance with the ethical standards of the institutional research committee and the Helsinki declaration.

2.2 | Statistical analysis

Continuous variables are expressed as mean ± SD and categorical variables are presented as number (%). Continuous variables were compared using the one-way analysis of variance test and categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Correlational analysis between SUA levels and baPWV was performed using Pearson's correlation test. Multivariate regression analysis was performed to identify the independent impact of clinical variables on baPWV. Variables with $P < .05$ on univariate analysis were defined as confounding factors and were entered into the multivariate regression analysis. SPSS version 18 (SPSS Inc, Chicago, IL, USA) was used for all statistical analyses. All statistical tests were two-tailed, and $P < .05$ was considered significant.

3 | RESULTS

Table 1 shows the clinical characteristics of the study participants. The mean levels of uric acid were 3.1 ± 0.4, 3.8 ± 0.1, 4.3 ± 0.1, and 5.4 ± 0.9 in groups I (lowest), II, III, and IV (highest), respectively.

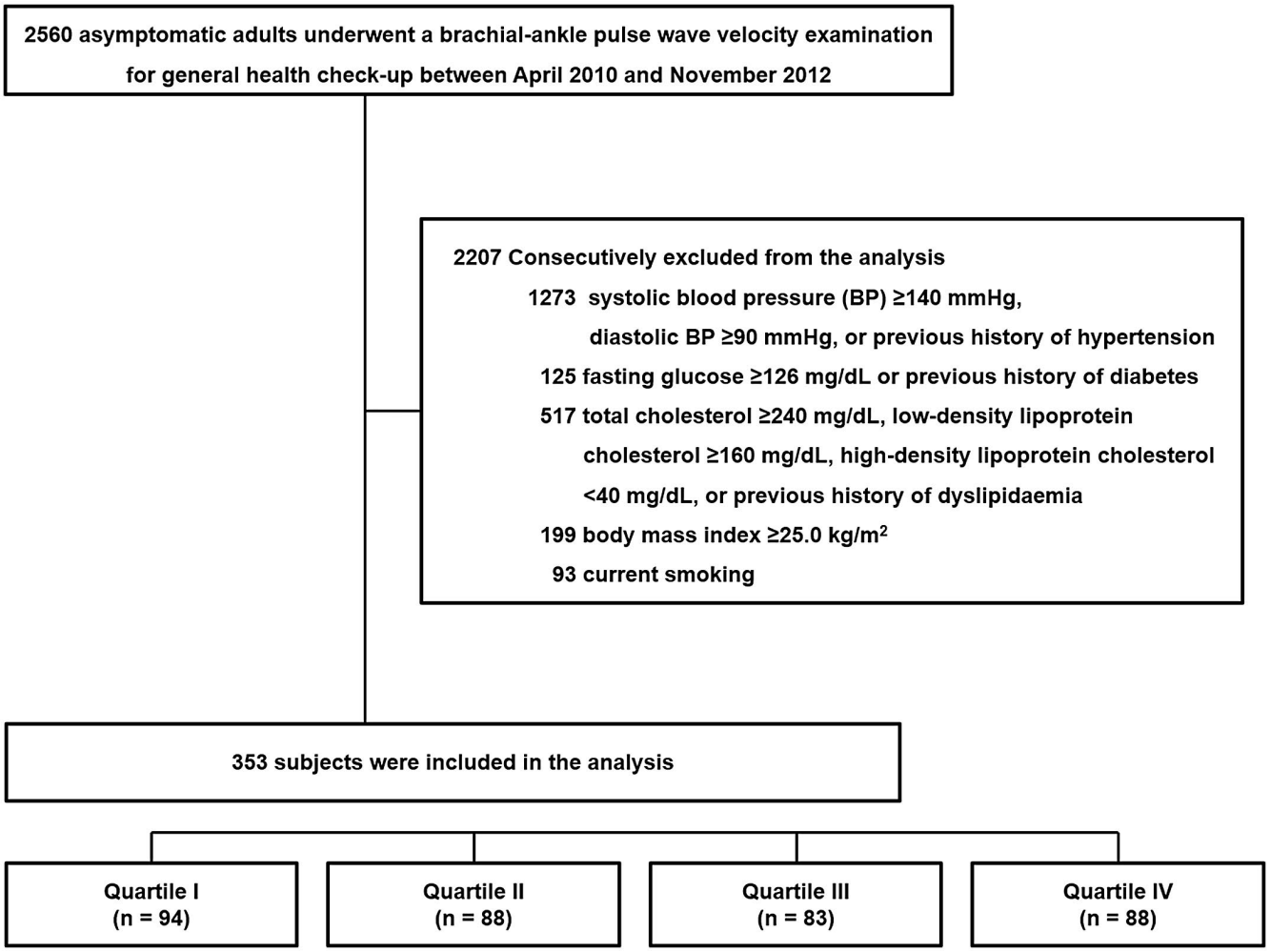

FIGURE 1 Overview of the study population

There were significant differences between the groups in age, sex, systolic and diastolic BP, BMI, and the levels of triglyceride, HDL cholesterol, and fasting glucose.

Figure 2 shows that mean baPWV (group I: 1320 ± 195; group II: 1336 ± 195; group III: 1404 ± 199; group IV: 1483 ± 248 cm/s) was significantly different among all groups ($P < .001$). SUA levels were significantly correlated with baPWV ($r = .364$; $P < .001$) (Figure 3).

Univariate linear regression analysis showed that age, male sex, systolic BP, diastolic BP, and triglyceride, fasting glucose, and SUA levels were significantly associated with baPWV. In multivariate linear regression analysis, age, systolic BP, and SUA levels were independently associated with baPWV (Table 2).

4 | DISCUSSION

To the best of our knowledge, this is the first study to investigate the relationship between SUA levels and baPWV in asymptomatic adults without established CV disorders. We identified that SUA levels, together with age and systolic BP, were significantly associated with baPWV after adjustment for confounding factors. This result strongly suggests that SUA is an independent risk factor for subclinical atherosclerosis even in the absence of established CV disorders.

Studies have reported that SUA levels are frequently elevated in subjects at risk for CV disease.[4-9] However, the role of uric acid in atherosclerosis remains uncertain. Several studies have suggested that uric acid has an anti-oxidative function.[24,25] Thus, an increase in SUA levels might reflect a compensatory mechanism against the oxidative stress that occurs in cases of CV disease.[26] However, this hypothesis does not fully explain why high SUA levels are related to worse clinical outcomes in patients with CV disease. In contrast, other studies have suggested that uric acid is closely associated with endothelial dysfunction,[27-30] vascular smooth cell proliferation,[31-33] and inflammation.[34]

Recent large cohort studies have reported the association between SUA levels and adverse CV outcomes. A Progetto Ipertensione Umbria Monitoraggio Ambulatoriale study found that increased SUA levels were strong risk factors for subsequent CV disease and all-cause mortality in 1,720 untreated patients with essential hypertension, for up to 12 years of follow-up.[35] A Rotterdam study also revealed that SUA levels were powerful markers for the development of myocardial infarction and stroke in 4385 participants free from stroke or coronary

TABLE 1 Baseline characteristics

	Quartiles of uric acid				
	I (lowest) (n = 94)	II (n = 88)	III (n = 83)	IV (highest) (n = 88)	*P*
Age, y	56.3 ± 8.1	56.3 ± 7.4	57.2 ± 7.7	60.0 ± 7.7	.003
Male, n (%)	0 (0.0)	7 (8.0)	9 (10.8)	26 (29.5)	<.001
Systolic BP, mmHg	111.7 ± 10.5	111.1 ± 10.5	113.4 ± 10.6	117.9 ± 11.3	<.001
Diastolic BP, mmHg	66.5 ± 8.6	66.1 ± 8.7	68.8 ± 8.1	71.8 ± 8.3	<.001
BMI, kg/m^2	21.8 ± 1.8	22.5 ± 1.7	22.4 ± 1.4	22.9 ± 1.4	<.001
Total cholesterol, mg/dL	190.9 ± 23.9	196.0 ± 21.0	194.1 ± 25.9	197.2 ± 24.5	.307
Triglyceride, mg/dL	86.7 ± 30.2	89.6 ± 47.9	104.7 ± 46.5	110.9 ± 46.9	<.001
HDL cholesterol, mg/dL	62.4 ± 13.7	62.3 ± 13.6	61.2 ± 14.5	57.1 ± 11.2	.027
LDL cholesterol, mg/dL	113.8 ± 23.1	116.1 ± 18.8	114.4 ± 24.9	120.7 ± 23.2	.165
Fasting glucose, mg/dL	90.2 ± 8.1	91.6 ± 7.4	93.7 ± 9.0	92.1 ± 8.3	.023
Uric acid, mg/dL	3.1 ± 0.4	3.8 ± 0.1	4.3 ± 0.1	5.4 ± 0.9	<0.001

Note: Values are given as mean ± standard deviation or number (%).

Abbreviations: BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

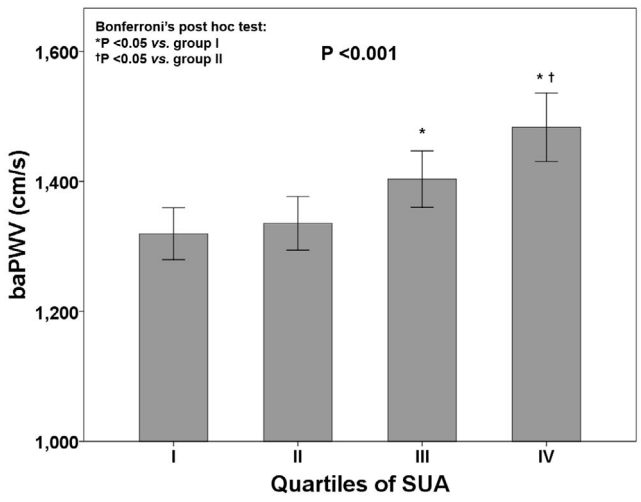

FIGURE 2 Comparison of baPWV according to the quartiles of SUA levels

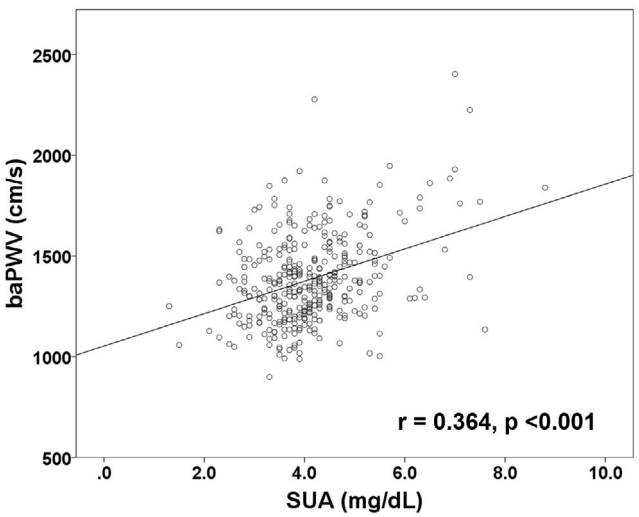

FIGURE 3 Correlation between SUA levels and baPWV

heart disease, during an average 8.4-year follow-up.[36] It is not clear whether uric acid has a pathogenic effect on atherosclerosis formation or if it is only a marker reflecting the protective process against atherosclerosis, however, it is certain that increased SUA levels are closely related to poor prognosis.

Due to the close relationship between SUA levels and metabolic abnormalities, the effect of SUA on atherosclerosis has been suspected to be epiphenomenal. A Genetic Epidemiology Network of Arteriopathy (GENOA) study, consisting of 1107 non-Hispanic white subjects who belonged to sibships with more than two individuals

TABLE 2 Association between clinical variables and baPWV

	Univariate			Multivariate		
	β	95% CI	*P*	*β*	95% CI	*P*
Age, per 1-y increase	15.83	13.42-18.25	<.001	11.44	9.36-13.53	<.001
Male	133.65	63.947-203.36	<.001	−10.83	−63.71 to 42.04	.687
Systolic BP, per 1 mmHg increase	11.93	10.26-13.60	<.001	8.98	6.80-11.16	<.001
Diastolic BP, per 1 mmHg increase	10.52	8.12-12.92	<.001	−0.41	−3.10 to 2.29	.768
BMI, per 1 kg/m^2 increase	2.14	−12.18-16.47	.769			
Total cholesterol, per 1 mg/dL increase	0.46	−0.50-1.43	.345			
Triglyceride, per 1 mg/dL increase	0.72	0.21-1.24	.006	0.06	−0.30-0.42	.731
HDL cholesterol, per 1 mg/dL increase	−0.51	−2.23-1.21	.560			
LDL cholesterol, per 1 mg/dL increase	0.17	−0.84-1.19	.738			
Fasting glucose, per 1 mg/dL increase	4.84	2.11-7.56	.001	1.06	−0.83-2.96	.271
SUA, per 1 mg/dL increase	80.36	58.81-101.91	<.001	32.93	18.99-54.87	<.001

Abbreviations: baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; BP, blood pressure; CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein;SUA, serum uric acid.

with hypertension diagnosed before 60 years of age, reported that SUA was related to several indices for the risk of coronary artery disease and coronary artery calcification (CAC), but not independently of conventional risk factors.[11] Santos et al[12] also reported that high SUA levels were associated with CAC in subjects with metabolic syndrome, but not in subjects without metabolic syndrome, in a study with 371 asymptomatic Brazilian men (mean age of 48 ± 7 years) with an average 10-year Framingham risk score of 10.8 ± 7.8%. In contrast, Chen et al found that SUA levels were positively associated with elevated carotid intima-media thickness, independent of the established risk determinants of CV disease, in 10 281 community-based participants of 40 years of age or older.[15] A recent observational cohort study with 6431 asymptomatic Korean adults who underwent coronary computed tomography angiography for general health examination found that high SUA levels were independently associated with non-calcified coronary plaque, suggesting an increased CV risk.[37]

Most previous studies have investigated the association between SUA levels and arterial stiffness in patients with diverse metabolic abnormalities or with established CV disease. However, the results of these studies are inconsistent. Ishizaka et al[38] found that SUA levels were independently related to increased baPWV in cross-sectional cohort data of 982 Japanese people. In this study, approximately 30% of the participants were taking anti-hypertensive, anti-diabetic, and anti-hyperlipidemic drugs. Lim et al[39] reported, in a study with 1276 Korean subjects, that elevated SUA levels were associated with abdominal obesity among individual components of metabolic syndrome (MetS), but were not associated with baPWV, in both male and female subjects. Similarly, 30.1% of the participants in this study had systolic/diastolic BP ≥ 140/90 mmHg and 24.8% of the participants had MetS. Moreover, 24.6% of the participants in this study were current smokers. These conflicting results may have been influenced by the medication being taken or by established CV disorders. It should be noted that, in the present study, SUA levels were significantly associated with arterial stiffness after adjusting for confounding clinical factors in subjects without established CV disease including previous medication history. This result suggests that SUA has a significant impact on the functional changes related to atherosclerosis, regardless of the presence of other metabolic abnormalities. Furthermore, the present study indicates that SUA levels can be useful subclinical atherosclerotic markers even in the absence of traditional CV risk factors such as hypertension, diabetes, dyslipidemia, obesity, and smoking.

The exact mechanisms SUA involvement in arterial stiffness are uncertain. One possible mechanism is related to the inflammatory properties of SUA that cause arteriosclerosis. Nod-like receptor family protein 3 inflammasome is activated by urate crystal engulfed macrophages.[40] Through this pathway, urate-stimulated human

macrophages secrete interleukin-1β and cause inflammation and collagen production, which lead to the development of arteriosclerosis. Another mechanism is the expression of urate transporters in human blood vessels, which move urate via glucose transporter 9 and voltage-driven urate efflux transporter 1, causing inflammation in the vasculature.[41] Further investigation in clinical practice is necessary to fully identify the mechanism.

This study has some limitations. First, all subjects participated voluntarily in the general health examination; therefore, a selection bias might exist. Second, we only included the Korean population. Third, though the impact of SUA on arterial stiffness may differ across different age groups, it was difficult to perform a sub-analysis of different age groups because none of the cohort study participants were very young. Fourth, we could not evaluate the impact of sex on the association between SUA levels and arterial stiffness because most participants were female. In addition, despite the possible effect of estrogen status on arterial stiffness,[42,43] menstrual (early or late follicular) phase or menopausal status at the time of measuring arterial stiffness were not considered because of the limited data in this cohort registry. Fifth, although we excluded subjects with established CV disorders to minimize the effects of metabolic abnormalities on arterial stiffness measurement, there is the possibility of confounding factors that were unaccounted having influenced the results. Finally, we did not have participant information regarding environmental risk factors, including diet, physical activity, and exercise. Despite these limitations, we identified independent impact of SUA levels on arterial stiffness in the absence of established CV disorders.

5 | CONCLUSION

High SUA levels were independently related to increased arterial stiffness in asymptomatic adults without established CV disorders. Further prospective and randomized investigations with large sample sizes are necessary to identify the association between SUA levels and other subclinical atherosclerosis parameters in this population.

DISCLOSURES

The authors have no commercial, proprietary, or financial interest in any products or companies described in this article.

AUTHOR CONTRIBUTIONS

HHK, RH, DH, and HJC contributed to the conception and design of the study. HHK and KBW contributed to the analysis and the interpretation of data. HHK drafted the manuscript. HJC critically revised the manuscript. All authors gave the final approval and agreed to be held accountable for all aspects of the study, ensuring its integrity and accuracy.

DATA PREVIOUSLY PRESENTED

None.

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