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Original Article

Lower serum SFRP5 levels are associated with carotid atherosclerosis in patients with essential hypertension

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Abstract: Objective: To investigate the variation in serum secreted frizzled-related protein 5 (SFRP5) levels among individuals with essential hypertension and its association with carotid atherosclerosis. Methods: 297 subjects were included: 77 with stage 1 hypertension, 73 with stage 2, 67 with stage 3, and 80 normotensive controls. Logistic regression analyses alongside receiver operating characteristic (ROC) curve examinations were used to determine the independent relationship and predictive significance of SFRP5 in relation to carotid atherosclerosis. The primary outcome measure was serum SFRP5 level. Secondary outcome measures included levels of tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), carotid intima-media thickness (CIMT), and incidence of carotid plaque. Results: Serum SFRP5 levels decreased significantly with increasing hypertension severity and were lower in patients with carotid atherosclerosis (P<0.001). A strong inverse relationship was found between SFRP5 levels and carotid atherosclerosis (r = -0.67, P<0.001). Regression analysis revealed SFRP5 was an independent protective factor (adjusted OR = 0.673, 95% CI: 0.585-0.774, P<0.001) after adjusting for age, sex, body mass index (BMI), low-density lipoprotein cholesterol (LDL-C), and hypertension grade. SFRP5's predictive capability for carotid atherosclerosis was indicated by an area under ROC curve of 0.902. Conclusion: Lower serum SFRP5 levels are associated with hypertension severity and heightened risk of carotid atherosclerosis in hypertensive patients. SFRP5 may be a biomarker for risk assessment and may also represent a promising therapeutic target. Additional studies are required to validate these results and unravel the underlying mechanisms.

Keywords: Secreted frizzled-related protein 5, hypertension, carotid atherosclerosis, risk prediction

Introduction

Hypertension, a prevalent cardiovascular condition, continues to pose a significant global health burden due to its rising prevalence and strong association with adverse cardiovascular outcomes [1, 2]. Essential hypertension, the most common form of hypertension, is characterized by persistent elevation of blood pressure (BP) without any identifiable underlying cause [3]. Among the various factors playing a role in the pathogenesis of essential hypertension, such as genetic predisposition, environmental influences, and lifestyle factors, emerging evidence has highlighted the involvement of novel molecules in regulation of blood pressure [4].

Secreted frizzled-related protein 5 (SFRP5), a member of the secreted frizzled-related protein family, has recently come into focus as possibly having a role in the development and progression of essential hypertension [5]. SFRP5 acts as a soluble antagonist of the Wnt signaling pathway, a key molecular pathway involved in atherosclerosis and vascular remodeling [6]. Previous studies have demonstrated altered serum levels of SFRP5 in individuals with essential hypertension, suggesting its potential involvement in the pathophysiology of this condition [7-9].

Additionally, the relationship between SFRP5 and atherosclerosis, a common consequence of hypertension, remains relatively underexplored [10, 11]. Carotid atherosclerosis, a surrogate marker of systemic atherosclerosis, has been extensively studied for its association with hypertension and increased risk of adverse cardiovascular events [12, 13]. If there is a link

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between SFRP5 levels in individuals diagnosed with essential hypertension and the presence/extent of carotid atherosclerosis, it could provide valuable insight into the pathogenesis and progression of both conditions, leading to novel therapeutic targets and preventive strategies [14]. Although the primary objective was to evaluate SFRP5, we measured tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) to explore whether systemic inflammation confounds or mediates the association between SFRP5 and carotid atherosclerosis, given the known interplay between Wnt signaling and inflammatory pathways in vascular remodeling.

Therefore, the present study aimed to discover the variations in serum SFRP5 levels among individuals diagnosed with essential hypertension and their association with carotid atherosclerosis. We hypothesize that altered SFRP5 expression may relate to the development of essential hypertension and may be associated with the presence/extent of carotid atherosclerosis. To address this hypothesis, we measured serum SFRP5 levels in a well-defined cohort of hypertensive individuals and evaluate their carotid atherosclerosis status using high-resolution B-mode ultrasonography. Additionally, we explored confounding effects of traditional cardiovascular risk factors and biological markers of inflammation on the observed associations. This research was the first to assess systematically the graded association between serum SFRP5 levels and hypertension severity, and to quantify its independent predictive value for carotid atherosclerosis through regression and receiver operating characteristic (ROC) analysis using a Chinese hypertensive cohort. SFRP5 may serve as a non-invasive biomarker for early identification of hypertensive patients at high risk for carotid atherosclerosis.

Patients and methods

General information

This study employed a cross-sectional design to investigate the association between serum levels of SFRP5 with hypertension and the occurrence of carotid atherosclerosis in hypertensive patients. This retrospective study included a total of 217 hypertensive patients who were admitted to Zhoukou Central Hospital between December 2021 and December 2025. According to the Chinese Guidelines for Prevention and Treatment of Hypertension (aligned with ESC/ESH guidelines), stage 1 hypertension was defined as a systolic blood pressure (SBP) of 140-159 mmHg and/or a diastolic blood pressure (DBP) of 90-99 mmHg; stage 2 was defined as a SBP of 160-179 mmHg and/or a DBP of 100-109 mmHg; stage 3 as a SBP ≥180 mmHg and/or a DBP ≥110 mmHg [15]. Based on the classification criteria for hypertension, patients were divided into three groups: Stage 1 (77 cases), Stage 2 (73 cases), and Stage 3 (67 cases). Additionally, 80 healthy individuals who underwent a regular health examination in the Department of Physical Examination during the same period were selected as the normotensive group.

This study was approved by the Ethics Committee of Zhoukou Central Hospital. Given the retrospective design, which only used de-identified medical records and did not involve any additional intervention or patient interactions, the need for written informed consent was waived by the Ethics Committee. This study was conducted in accordance with Declaration of Helsinki.

Screening criteria

Inclusion criteria: Meeting diagnostic standards for hypertension as per the Chinese guidelines for preventing and treating hypertension, which are in line with the ESC/ESH guidelines (hypertension is defined as >140/90 mmHg); Age 18 years or older; No prior use of antihypertensive medications or a washout period of at least 2 weeks; Availability of complete clinical data.

Exclusion criteria: Secondary hypertension; Severe cardiovascular diseases such as coronary artery disease, valvular disorders, congenital heart defects, cardiomyopathies, or severe heart failure (NYHA class III-IV, recent myocardial infarction within 6 months); Diabetes mellitus (a fasting glucose level ≥7.0 mmol/L, or current use of antidiabetic therapy); Severe anemia, hyperthyroidism or hypothyroidism, hematological disorders, autoimmune rheumatic diseases; Severe liver or kidney dysfunction (ALT/AST >3× upper limit, eGFR <30 mL/min/1.73 m^2); Malignant tumors; Chronic inflammatory or autoimmune diseases; Sleep apnea syndrome (SAS); Undergoing surgery or experienc-

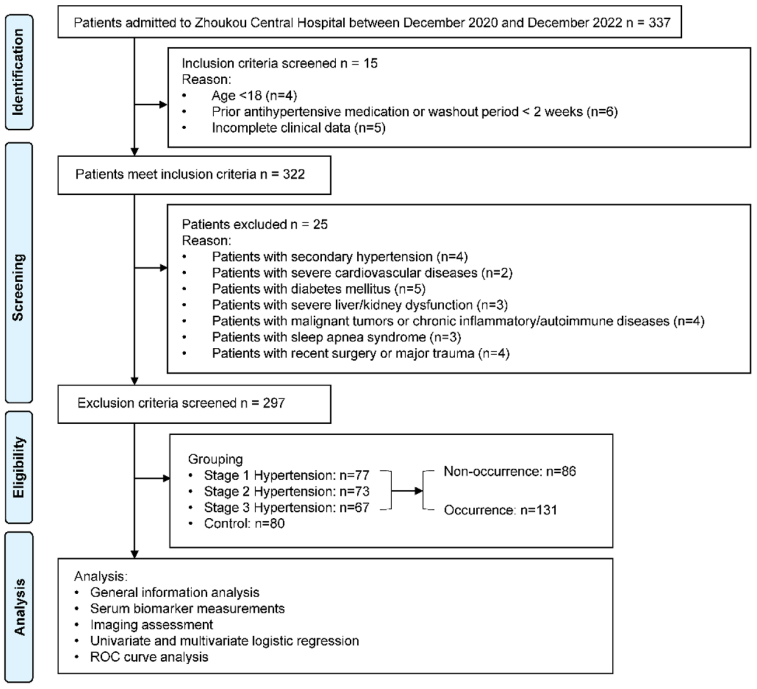

Figure 1. Patient screening process diagram.

ing major trauma within the past three months (**Figure 1**).

Serum biomarker measurements

Blood samples were collected in the morning following admission, after an overnight fasting duration of at least 8 hours, before any antihypertensive treatment was administered. Serum levels of SFRP5 (RC-E105539A, Tianjin Ruichuang Biotechnology Co., LTD., China), TNF-α (E-UNEL-H0175, Elabscience, USA), and IL-6 (ab178013, Abcam, USA) were measured in all participants. The serum samples were collected and processed following standardized ELISA protocols to ensure accuracy and reliability of the measurements.

Carotid intima-media thickness (CIMT)

High-resolution B-mode ultrasonography (iE33) was performed to assess carotid atherosclerosis. Both common carotid arteries and the carotid bifurcations were examined bilaterally. Carotid intima-media thickness (CIMT) was assessed by measuring distance from lumen-intima boundary to media-adventitia boundary.

CIMT values were recorded and categorized as follows: CIMT <0.9 mm was defined as the "Non-occurrence" group (no significant intima-media thickening). CIMT ≥0.9 mm was defined as the "Increased CIMT" group. Additionally, carotid atherosclerotic plaques were identified as focal structures protruding into arterial lumen by at least 0.5 mm or 50% of surrounding CIMT, or as areas with a thickness equal to or greater than 1.5 mm when measured from media-adventitia interface to intima-lumen interface. For the primary analysis of carotid atherosclerosis, patients with either increased CIMT (≥0.9 mm) or the presence of any plaque were classified into the "Occurrence" group.

Statistical analysis

The sample size was determined by the number of eligible patients who met the inclusion criteria during the study period. To assess whether the final sample provided sufficient statistical power, we conducted a *post-hoc* power analysis using G*Power 3.1.9.7. Analysis was based on the primary outcome measure (serum SFRP5 level). Assuming a moderate effect size (Cohen's d = 0.5) for the difference in serum SFRP5 levels between groups, with α = 0.05 and power = 0.80, minimum required sample size per group was 64. Our study included 86 patients without carotid atherosclerosis and 131 patients with carotid atherosclerosis, both exceeding this requirement. Furthermore, the actual observed effect size (d = 0.82) yielded a post-hoc power exceeding 99%. These results confirmed that the retrospective sample size was sufficient to ensure reliable and valid conclusions.

Descriptive statistics were computed for SFRP5, TNF-α, and IL-6 in various groups, encompassing mean values and standard deviations. Statistical comparisons for continuous variables between two groups were carried out through either t-test or Mann-Whitney U test, one-way ANOVA with Tukey's post-hoc correction for multi-group comparisons, or chi-square test for categorical data. To assess the correlation between serum SFRP5 levels as well as

Table 1. Comparison of general characteristics of subjects at different stages of hypertension

Group	n	Gender (M/F)	Age (years)	BMI (kg/m^2)	Duration of hypertension (years)
Stage 1 Hypertension	77	33/44	57.67±5.28	25.11±1.38	3.27±1.41
Stage 2 Hypertension	73	39/34	63.54±5.05	26.14±1.45	7.52±2.16
Stage 3 Hypertension	67	36/31	76.79±5.17	26.21±1.32	12.37±3.54
Control	80	42/38	60.04±5.63	24.08±1.51	N/A
χ^2/F	-	2.254	143.2	33.8	78.4
P	-	0.522	<0.001	<0.001	<0.001

BMI: Body Mass Index; M/F: Male/Female; N/A: not applicable.

the occurrence of carotid atherosclerosis, the Pearson correlation analysis was used. The correlation coefficient (r) was calculated, and its significance was determined using a two-tailed test (P<0.05). Variables with P<0.10 by univariate analysis (age, LDL-C, SFRP5, hypertension grade, smoking) together with clinically relevant variables (gender, BMI) were included in a multivariate model utilizing the Enter method. Categorical variables were encoded in the following manner: gender (male = 1, female = 0); hypertension grade (stage 1 = 1, stage 2 = 2, stage 3 = 3); smoking (yes = 1, no = 0). The entry criterion was P<0.10 and removal criterion P>0.15. No stepwise selection was applied. The Hosmer-Lemeshow test was utilized to evaluate model calibration. Capability of serum SFRP5 levels to predict development of carotid atherosclerosis was analyzed by a receiver operating characteristic (ROC) curve analysis.

Results

Patient general data

This study compared general characteristics and clinical features among patients with different stages of hypertension and normal hypertension. This study involved 297 participants, comprising 77 individuals in the stage 1 hypertension group, 73 in stage 2 hypertension, 67 in stage 3 hypertension, and 80 in the control (normal blood pressure) group (**Table 1**). The gender distribution varied among the groups, with a higher proportion of males in the Stage 2 hypertension group (39 males, 34 females) compared to Stage 1 hypertension (33 males, 44 females) and control (42 males, 38 females) groups, and the variation was not significant (P>0.05). Average age of participants differed across groups, with Stage 3 hypertension group having the highest mean age of 76.79 years (±5.17), followed by Stage 2 hypertension (63.54 years ±5.05), and normotensive (60.04 years ±5.63) groups. The average body mass index (BMI) also varied, with Stage 3 hypertension group having the highest mean BMI of 26.21 kg/m^2 (±1.32), followed by Stage 2 hypertension (26.14 kg/m^2 ±1.45), and normotensive (24.08 kg/m^2 ±1.51) groups. The duration of hypertension increased progressively with hypertension stage: stage 1 (3.27±1.41 years), stage 2 (7.52±2.16 years), and stage 3 (12.37±3.54 years).

Serum levels of SFRP5, TNF-α, and IL-6

To compare the serum levels of SFRP5, TNF-α, and IL-6 in patients with different grades of hypertension as well as with healthy controls, the statistical analysis using one-way ANOVA with Tukey's post-hoc test revealed significant differences in serum SFRP5 and TNF-α among groups (P<0.001). The mean serum levels of SFRP5 were observed to be significantly different among different hypertension groups, with the Stage 3 hypertension group having the lowest mean level of 24.85 ng/mL (±3.56), followed by Stage 2 hypertension (28.45 ng/mL ±4.09), Stage 1 hypertension (34.6 ng/mL ±2.58) and normotensive (42.75 ng/mL ±2.62) groups. Similarly, mean serum levels of TNF-α showed a significant difference among different hypertension groups, with the stage 1 hypertension group having the highest mean level of 7.15 pg/mL (±0.12), followed by stage 3 hypertension (5.82 pg/mL ±0.58), stage 2 hypertension (3.58 pg/mL ±1.34), and normotensive (1.48 pg/mL ±0.32) groups (**Table 2**; **Figure 2**). However, the serum levels of IL-6 did not show significant variation across different hypertension groups (P>0.05).

Table 2. Comparison of serum levels of SFRP5, TNF-α, and IL-6 in patients with different grades of hypertension ($\bar{x} \pm s$)

Group	n	Serum SFRP5 (ng/mL)	TNF-α (pg/mL)	IL-6 (pg/mL)	Carotid Atherosclerosis Occurrence
Stage 1 Hypertension	77	34.60±2.58	7.15±0.12	2.24±0.12	33
Stage 2 Hypertension	73	28.45±4.09	3.58±1.34	2.93±0.61	46
Stage 3 Hypertension	67	24.85±3.56	5.82±0.58	2.43±0.32	52
Control	80	42.75±2.62	1.48±0.32	2.05±0.25	N/A
P	-	<0.001	<0.001	0.329	
$P_{1 \text{ vs. } 2}$	-	<0.001	<0.001	0.564	
$P_{2 \text{ vs. } 3}$	-	<0.001	<0.001	0.939	
$P_{1 \text{ vs. } 3}$	-	<0.001	0.002	0.999	
$P_{1 \text{ vs. Control}}$	-	<0.001	<0.001	0.999	
$P_{2 \text{ vs. Control}}$	-	<0.001	<0.001	0.180	
$P_{3 \text{ vs. Control}}$	-	<0.001	<0.001	0.989	

SFRP5: Secreted Frizzled-Related Protein 5; TNF-α: Tumor Necrosis Factor-alpha; IL-6: Interleukin-6.

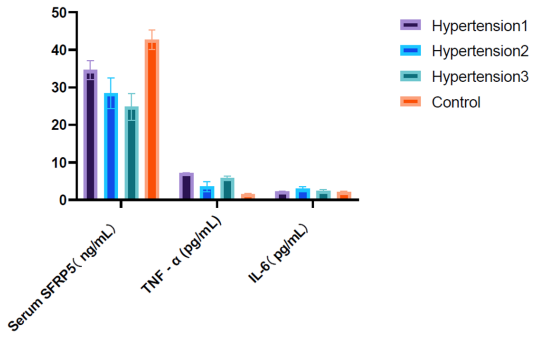

Figure 2. Comparison of serum biomarker levels among patients with different stages of hypertension. Notes: SFRP5: Secreted Frizzled-Related Protein 5; TNF-α: Tumor Necrosis Factor-alpha; IL-6: Interleukin-6.

General clinical characteristics in hypertensive patients with or without coexisting carotid atherosclerosis

217 participants were included, with 86 individuals in the non-occurrence group and 131 individuals in occurrence group (**Table 3**). A notable variation in age was observed between the two groups, with the occurrence group having a higher mean age (67.58±9.49 years) than the non-occurrence group (62.44±8.52 years, P<0.001). Furthermore, the duration of hypertension was notably longer in the occurrence group (10.21±3.18 years) than the non-occurrence group (6.87±2.24 years, P<0.001). No notable variations were found in gender distribution (P = 0.846) or BMI (P = 0.116). Hypertensive stage distribution varied markedly between groups, with a higher proportion of stage 2 and stage 3 hypertension in the occurrence group (P<0.001).

Biochemical indicators in hypertensive patients with or without coexisting carotid atherosclerosis

Among the biochemical indices, only LDL-C levels showed a statistically significant difference, being higher in the occurrence group (3.60±0.38 mmol/L) than the non-occurrence group (3.49±0.39 mmol/L, P = 0.049). No notable variations were observed for fasting blood glucose (FBG, P = 0.327), total cholesterol (TC, P = 0.126), triglycerides (TG, P = 0.866), or high-density lipoprotein cholesterol (HDL-C, P = 0.193). Serum SFRP5 levels were significantly lower in the occurrence group (26.66±4.33 ng/mL) than in the non-occurrence group (33.88±3.34 ng/mL, P<0.001). Conversely, no variations were found for TNF-α (P = 0.087) or IL-6 (P = 0.285) between the two groups (**Table 4**).

Correlation between serum SFRP5 levels and occurrence of carotid atherosclerosis in hypertensive patients

Correlation analysis was performed on all 217 hypertensive patients with carotid atherosclerosis, revealing a substantial inverse relationship between serum SFRP5 levels and carotid atherosclerosis (r = -0.67, P<0.001) (**Table 5**; **Figure 3**).

Univariate logistic regression (**Table 6**) confirmed that higher SFRP5 levels were associated with reduced odds of carotid atherosclero-

Table 3. Comparison of general clinical characteristics in hypertensive patients with or without coexisting carotid atherosclerosis

Variable	Non-occurrence (n = 86)	Occurrence (n = 131)	χ^2/t/U	P
Gender			0.038	0.846
Male	44	64		
Female	42	67		
Age (years)	62.44±8.52	67.58±9.49	3939.5	P<0.001
BMI (kg/m^2)	25.61±1.33	25.92±1.54	1.579	0.116
Smoking (yes)	22 (25.58%)	48 (36.64%)	2.891	0.089
History of dyslipidemia (yes)	31 (36.05%)	59 (45.04%)	1.787	0.181
Duration of hypertension (years)	6.87±2.24	10.21±3.18	8.457	P<0.001
Hypertension			18.409	P<0.001
Stage 1	44	33		
Stage 2	27	46		
Stage 3	15	52		

BMI: Body Mass Index.

Table 4. Comparison of biochemical indicators in hypertensive patients with or without coexisting carotid atherosclerosis

Variable	Non-occurrence (n = 86)	Occurrence (n = 131)	t	P
FBG (mmol/L)	5.29±0.71	5.39±0.73	0.983	0.327
TC (mmol/L)	5.45±0.66	5.59±0.59	1.539	0.126
TG (mmol/L)	2.2±0.23	2.21±0.22	0.169	0.866
LDL-C (mmol/L)	3.49±0.39	3.6±0.38	1.981	0.049
HDL-C (mmol/L)	1.01±0.13	0.99±0.14	1.306	0.193
SFRP5 (ng/mL)	33.88±3.34	26.66±4.33	10164.5	P<0.001
TNF-α (pg/mL)	5.69±1.86	5.44±1.62	6407.5	0.087
IL-6 (pg/mL)	2.52±0.50	2.54±0.49	5148.5	0.285

FBG: Fasting Blood Glucose; TC: Total Cholesterol; TG: Triglycerides; LDL-C: Low-Density Lipoprotein Cholesterol; HDL-C: High-Density Lipoprotein Cholesterol; SFRP5: Secreted Frizzled-Related Protein 5; TNF-α: Tumor Necrosis Factor-alpha; IL-6: Interleukin-6.

sis (OR = 0.626, P<0.001). After adjusting for age, sex, BMI, LDL-C, and hypertension grade in a multivariate logistic regression model, serum SFRP5 continued to serve as an independent protective factor (adjusted OR = 0.673, P< 0.001). Age (adjusted OR = 1.052) and hypertension grade (adjusted OR = 1.811) were also independent risk factors (all P<0.05). The model demonstrated adequate calibration (Hosmer-Lemeshow P = 0.342) with a Nagelkerke R^2 of 0.418.

Predictive significance of serum SFRP5 levels for carotid atherosclerosis development in hypertensive patients

To investigate the predictive value of serum SFRP5 levels for development of carotid atherosclerosis in hypertensive participants, the ROC analysis, based on a total of hypertensive individuals, revealed an AUC of 0.902 for SFRP5 (**Figure 4**). The sensitivity and specificity were 0.763 and 0.884, respectively, with a Youden index of 0.647. These results imply that serum SFRP5 levels had a good predictive value for the occurrence of carotid atherosclerosis in hypertensive patients, with a relatively high AUC and a balance between sensitivity and specificity.

Discussion

Hypertension remains a leading cause of cardiovascular morbidity worldwide, and the search for novel biomarkers that reflect disease severity and predict vascular complications is ongoing [16, 17]. In this cross-sectional study, we analyzed serum levels of SFRP5 in

Table 5. Correlation analysis of the characteristics in hypertensive patients with or without coexisting carotid atherosclerosis

Variable	r	p
Gender (male vs. female)	-0.023	0.741
Age	0.267	P<0.001
BMI (kg/m^2)	0.104	0.127
Duration of hypertension (years)	0.358	<0.001
FBG (mmol/L)	0.067	0.329
TC (mmol/L)	0.107	0.116
TG (mmol/L)	0.012	0.865
LDL-C (mmol/L)	0.134	0.049
HDL-C (mmol/L)	-0.088	0.196
SFRP5 (ng/mL)	-0.666	P<0.001
TNF (pg/mL)	-0.07	0.305
IL-6 (pg/mL)	0.024	0.726
Hypertension (Stage 1/2/3)	0.290	P<0.001

BMI: Body Mass Index; FBG: Fasting Blood Glucose; TC: Total Cholesterol; TG: Triglycerides; LDL-C: Low-Density Lipoprotein Cholesterol; HDL-C: High-Density Lipoprotein Cholesterol; SFRP5: Secreted Frizzled-Related Protein 5; TNF-α: Tumor Necrosis Factor-alpha; IL-6: Interleukin-6.

individuals with essential hypertension and examined their association with carotid atherosclerosis. Our findings offer several insights regarding the effect of SFRP5 in hypertension and its vascular consequences.

We observed a progressive decline in serum SFRP5 levels with increasing hypertension grade. Individuals with stage 3 hypertension had the lowest SFRP5 concentrations, whereas those with stage 1 hypertension showed higher levels, and normotensive controls exhibited the highest values. This graded relationship suggests that SFRP5 expression may be inversely related to the severity of blood pressure elevation. Mechanistically, SFRP5 acts as an endogenous antagonist of the Wnt/β-catenin signaling pathway [18]. Excessive Wnt activation has been implicated in vascular smooth muscle cell proliferation, oxidative stress, and inflammatory responses, all processes that facilitate both the onset and persistence of hypertension. Reduced SFRP5 levels may therefore permit unopposed Wnt signaling, thereby aggravating vascular dysfunction and blood pressure elevation [19, 20]. Previous reports have also noted altered SFRP5 concentrations in hypertensive cohorts, and our data extend those observations by demonstrating a clear stepwise decrease across clinically defined hypertension stages [21, 22].

Among hypertensive patients, those with coexisting carotid atherosclerosis (defined as increased carotid intima-media thickness or presence of plaque) had notably lower serum SFRP5 levels compared with those without such atherosclerotic changes. This association remained robust after adjustment for age, sex, BMI, low-density lipoprotein cholesterol, and hypertension grade, with SFRP5 emerging as an independent protective factor. The inverse relationship between SFRP5 concentration and the presence of carotid atherosclerosis was strong, indicating that lower SFRP5 is linked to a higher likelihood of atherosclerotic lesions in the carotid arteries [23, 24].

The biological rationale for this link is supported by experimental studies. SFRP5 has been shown to suppress Wnt-induced inflammation and oxidative stress, two key drivers of atherogenesis [25]. For example, Zhang and colleagues demonstrated that low serum SFRP5 levels are closely related to coronary heart disease, and that SFRP5 exerts its protective effects against atherosclerosis by suppressing vascular smooth muscle cell proliferation through the Wnt/β-catenin pathway [26]. Similarly, other investigators have reported that SFRP5 attenuates endothelial dysfunction and reduces plaque formation in animal models [27]. Our findings align with these reports and further extend them to the specific context of hypertensive patients with carotid atherosclerosis. Furthermore, carotid atherosclerosis is known to correlate positively with coronary atherosclerosis, as shown by Achim et al. and Nikic et al., reinforcing the clinical relevance of our observations [28, 29].

ROC analysis revealed a high AUC for SFRP5 in discriminating hypertensive patients with versus without carotid atherosclerosis. The sensitivity and specificity were balanced, yielding a favorable Youden index. This suggests that serum SFRP5 measurement may be a valuable method for assessing risk in hypertensive individuals, identifying those who are more likely to have underlying carotid plaque. Nevertheless, the cross-sectional nature of our study means that this predictive performance reflects diagnostic accuracy rather than prospective prediction; and thus longitudinal studies are needed to determine whether baseline SFRP5 levels forecast future atherosclerotic events.

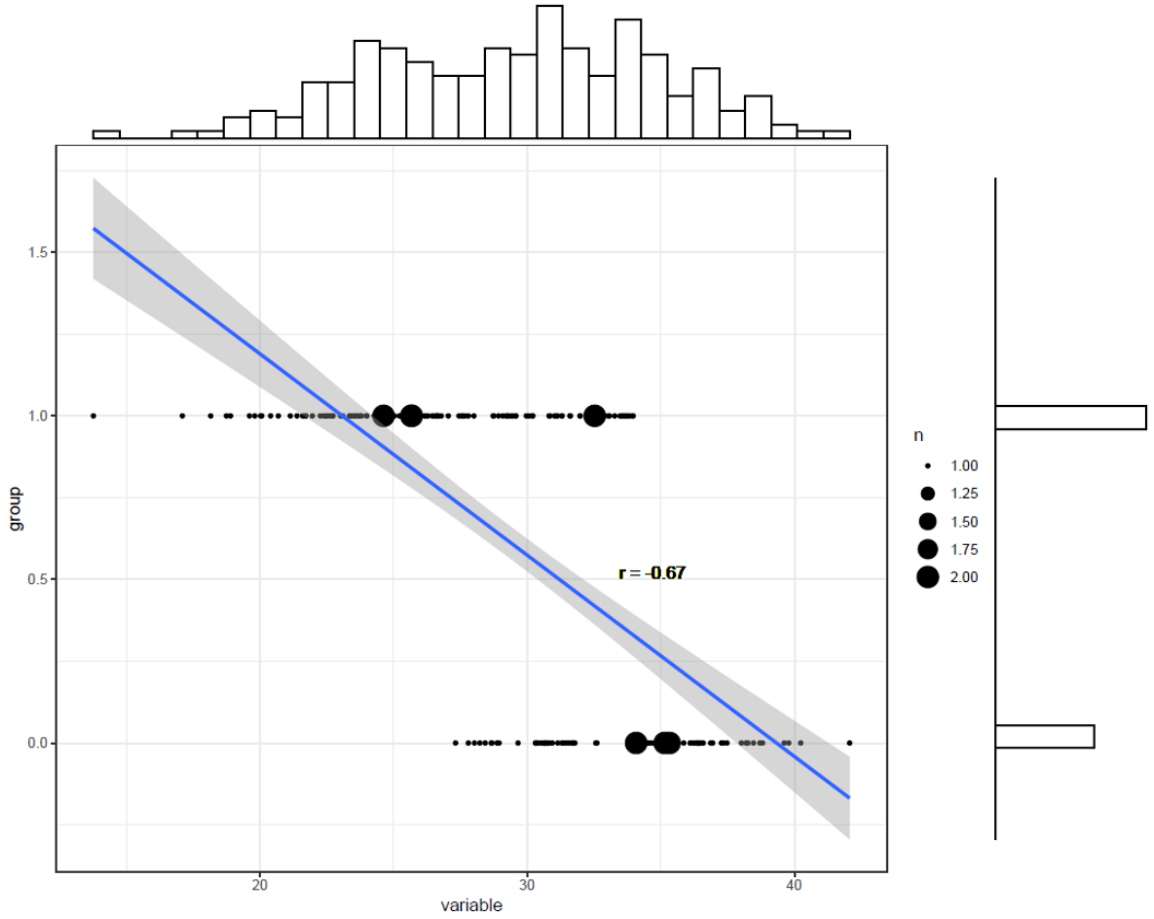

Figure 3. Correlation between serum SFRP5 level and carotid atherosclerosis. Notes: SFRP5: Secreted Frizzled-Related Protein 5.

We also observed a notable variation in serum TNF-α levels among the different hypertension grades, with the highest levels in stage 1 hypertension and lower levels in stage 2 and stage 3 groups. This pattern was unexpected because chronic inflammation is generally considered to worsen with more severe hypertension. One possible explanation is that the inflammatory profile may change dynamically during the course of hypertension, or that long-standing hypertension may lead to exhaustion of certain inflammatory pathways [30]. Importantly, TNF-α did not differ between the groups with and without carotid atherosclerosis in our study, suggesting that in this cohort, systemic TNF-α levels were more closely related to hypertension stage than to the presence of established carotid plaque. IL-6 showed no consistent differences across either hypertension grades or atherosclerosis status, indicating that not all classic inflammatory cytokines follow the same pattern in this setting [31, 32].

Several limitations need to be addressed. The cross-sectional design of the study did not allow for causal interpretations of the relationship between SFRP5 and carotid atherosclerosis; only association can be inferred. Second, the research was a single-center study with a modest sample size, possibly restricting the broader applicability of the results. Third, we did not perform long-term follow-up, so the prospective predictive value of SFRP5 for incident atherosclerotic events remains unknown. Fourth, although the analysis controlled for key confounders, residual confounding due to unmeasured variables (e.g., lifestyle factors, medication adherence) cannot be excluded. Fifth, the exact molecular mechanisms through which SFRP5 influences blood pressure regulation and atherogenesis warrant further investigation in preclinical models.

Future studies ought to concentrate on large-scale, multi-site prospective cohorts to confirm

Table 6. Logistic regression for the characteristics in hypertensive patients with or without coexisting carotid atherosclerosis

Variable	Assignment	Univariate analysis		Multivariate analysis			
		OR (95% CI)	*p* value	β	Wald χ^2	Adjusted OR (95% CI)	*p* value
Gender (male vs. female)	Male = 1, Female = 0	0.912 (0.530-1.570)	0.739	0.098	0.118	1.103 (0.598-2.034)	0.731
Age (years)	Continuous	1.065 (1.034-1.097)	<0.001	0.051	6.312	1.052 (1.011-1.095)	0.012
BMI (kg/m^2)	Continuous	1.157 (0.960-1.394)	0.128	0.075	0.642	1.078 (0.886-1.311)	0.423
Smoking	Yes = 1, No = 0	1.680 (0.928-3.041)	0.089	0.412	2.891	1.510 (0.930-2.452)	0.096
FBG (mmol/L)	Continuous	1.209 (0.827-1.768)	0.327	-	-	-	-
TC (mmol/L)	Continuous	1.428 (0.914-2.231)	0.117	-	-	-	-
TG (mmol/L)	Continuous	1.111 (0.334-3.696)	0.865	-	-	-	-
LDL-C (mmol/L)	Continuous	2.040 (1.001-4.156)	0.051	0.418	2.156	1.519 (0.867-2.661)	0.142
HDL-C (mmol/L)	Continuous	0.261 (0.032-2.153)	0.196	-	-	-	-
Duration of hypertension (years)	Continuous	1.152 (1.082-1.226)	<0.001	-	-	- (not entered due to collinearity)	-
SFRP5 (ng/mL)	Continuous	0.626 (0.558-0.702)	<0.001	-0.396	24.817	0.673 (0.585-0.774)	<0.001
TNF-α (pg/mL)	Continuous	0.919 (0.780-1.082)	0.305	-	-	-	-
IL-6 (pg/mL)	Continuous	1.105 (0.641-1.905)	0.725	-	-	-	-
Hypertension grade (per 1-grade increase)	Stage 1 = 1, Stage 2 = 2, Stage 3 = 3	2.161 (1.468-3.181)	<0.001	0.594	8.158	1.811 (1.210-2.710)	0.004

BMI: Body Mass Index; FBG: Fasting Blood Glucose; TC: Total Cholesterol; TG: Triglycerides; LDL-C: Low-Density Lipoprotein Cholesterol; HDL-C: High-Density Lipoprotein Cholesterol; SFRP5: Secreted Frizzled-Related Protein 5; TNF-α: Tumor Necrosis Factor-alpha; IL-6: Interleukin-6; OR: Odds Ratio; CI: Confidence Interval.

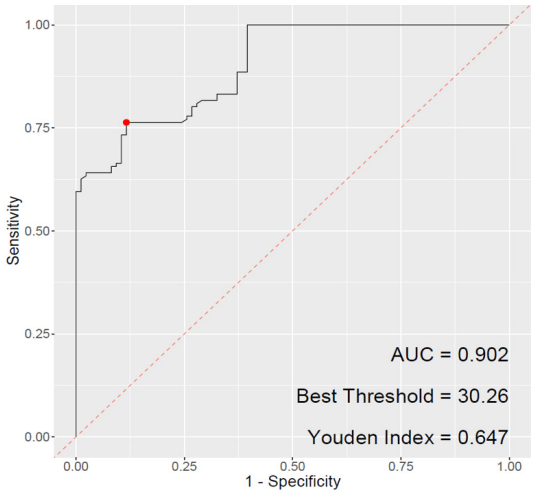

Figure 4. ROC curve of serum SFRP5 levels in predicting carotid atherosclerosis in hypertensive patients. Notes: SFRP5: Secreted Frizzled-Related Protein 5; ROC: Receiver Operating Characteristic; AUC: Area Under the Curve.

the predictive value of SFRP5. Mechanistic studies exploring the interplay between SFRP5, Wnt signaling, and vascular remodeling in hypertensive models would help clarify causality. Additionally, clinical trials evaluating whether interventions that raise SFRP5 levels can reduce carotid atherosclerosis progression would be of interest.

Overall, our findings indicate that lower serum SFRP5 levels are associated with both hypertension severity and carotid atherosclerosis. Lower serum SFRP5 levels are linked to an increased risk of developing carotid atherosclerosis in hypertensive individuals. These results underscore necessity of further investigating role of SFRP5 in pathogenesis of hypertension and atherosclerosis, as well as its use as both a biomarker and a therapeutic target.

Disclosure of conflict of interest

None.

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References

[1] Carey RM, Moran AE and Whelton PK. Treatment of hypertension: a review. JAMA 2022; 328: 1849-1861.

[2] McAtee C. Hypertension. Crit Care Nurs Clin North Am 2022; 34: 373-381.

[3] Rossi GP, Bagordo D, Rossi FB, Pintus G, Rossitto G and Seccia TM. 'Essential' arterial hypertension: time for a paradigm change. J Hypertens 2024; 42: 1298-1304.

[4] Rios FJ, Montezano AC, Camargo LL and Touyz RM. Impact of environmental factors on hypertension and associated cardiovascular disease. Can J Cardiol 2023; 39: 1229-1243.

[5] Song Y, Ma Y, Zhang K, Zhang W, Xiong G, Qi T, Shi J, Qiu H, Zhang J, Han F, Kan C and Sun X. Secreted frizzled-related protein 5: a promising therapeutic target for metabolic diseases via regulation of Wnt signaling. Biochem Biophys Res Commun 2023; 677: 70-76.

[6] Wang X, Wang H, Lu R, Chen S, Gao Y and Yu C. Expression and effects of FUS/Sfrp5/Wnt5 in atherosclerosis development. Ann Clin Lab Sci 2025; 55: 240-246.

[7] Carstensen-Kirberg M, Kannenberg JM, Huth C, Meisinger C, Koenig W, Heier M, Peters A, Rathmann W, Roden M, Herder C and Thorand B. Inverse associations between serum levels of secreted frizzled-related protein-5 (SFRP5) and multiple cardiometabolic risk factors: KORA F4 study. Cardiovasc Diabetol 2017; 16: 109.

[8] Li B, Yao Q, Guo S, Ma S, Dong Y, Xin H, Wang H, Liu L, Chang W and Zhang Y. Type 2 diabetes with hypertensive patients results in changes to features of adipocytokines: Leptin, Irisin, LGR4, and Sfrp5. Clin Exp Hypertens 2019; 41: 645-650.

[9] Yin C, Chu H, Li H and Xiao Y. Plasma Sfrp5 and adiponectin levels in relation to blood pressure among obese children. J Hum Hypertens 2017; 31: 284-291.

[10] Tong S, Du Y, Ji Q, Dong R, Cao J, Wang Z, Li W, Zeng M, Chen H, Zhu X and Zhou Y. Expression of Sfrp5/Wnt5a in human epicardial adipose tissue and their relationship with coronary artery disease. Life Sci 2020; 245: 117338.

[11] Tong S, Ji Q, Du Y, Zhu X, Zhu C and Zhou Y. Sfrp5/Wnt pathway: a protective regulatory system in atherosclerotic cardiovascular disease. J Interferon Cytokine Res 2019; 39: 472-482.

[12] Yu Z, Yang H, Shou B, Cheng Z, Jiang C and Xu J. Association between pulse pressure and carotid plaques in old adults with uncontrolled hypertension: results from a community-based screening in Hangzhou, China. BMC Cardiovasc Disord 2024; 24: 249.

[13] Dženkevičiūtė V, Adomavičius T, Tarutytė G, Rinkūnienė E, Kasiulevičius V and Badarienė J. Carotid plaques and hypertension as risk factors for cardiovascular disease and all-cause mortality in middle-aged adults. J Clin Med 2024; 13: 2804.

[14] Petramala L, Circosta F, Cremonesi L, Menichelli D, Cimò A, Servello A, Anastasi E, Marino L and Letizia C. Neutrophil-lymphocyte ratio and subclinical atherosclerosis in essential hypertensive patients. Front Cardiovasc Med 2025; 12: 1579930.
[15] Bakris G, Ali W and Parati G. ACC/AHA versus ESC/ESH on hypertension guidelines: JACC guideline comparison. J Am Coll Cardiol 2019; 73: 3018-3026.
[16] de Carvalho Ribeiro P, Oliveira LF, Filho DM, Parreira RC, Vieira MS, Marques BL, da Madeira Freitas EM, Silva WN, Santiago HDC, Birbrair A, Ulrich H, da Silva VJD and Resende RR. Biomarkers in hypertension and hypertension-related disorders. Curr Med Chem 2023; 30: 3846-3879.
[17] Lauder L, Mahfoud F, Azizi M, Bhatt DL, Ewen S, Kario K, Parati G, Rossignol P, Schlaich MP, Teo KK, Townsend RR, Tsioufis C, Weber MA, Weber T and Böhm M. Hypertension management in patients with cardiovascular comorbidities. Eur Heart J 2023; 44: 2066-2077.
[18] Yadav SS, Hussain S, Dwivedi P, Khattri S, Sawlani KK and Usman K. Assesement of serum Sfrp5/Wnt-5a level and its utility in the risk stratification of treatment naïve patients with metabolic syndrome. J Immunoassay Immunochem 2023; 44: 1-12.
[19] Koutaki D, Paltoglou G, Manou M, Vourdoumpa A, Ramouzi E, Tzounakou AM, Michos A, Bacopoulou F, Mantzou E, Zoumakis E, Papadopoulou M, Kassari P and Charmandari E. The role of secreted frizzled-related protein 5 (Sfrp5) in overweight and obesity in childhood and adolescence. Nutrients 2024; 16: 3133.
[20] Jia L, Shang S, Yang Y, Zhang J and Lin X. The synergy of serum SFRP5 levels and the TyG index in predicting coronary artery disease and prognosing major adverse cardiovascular events. Lipids Health Dis 2023; 22: 194.
[21] Kelly CJ, Chu M, Untaru R, Assadi-Khansari B, Chen D, Croft AJ, Horowitz JD, Boyle AJ, Sverdlov AL and Ngo DTM. Association of circulating plasma secreted frizzled-related protein 5 (Sfrp5) levels with cardiac function. J Cardiovasc Dev Dis 2023; 10: 274.
[22] Hohlstein P, Brozat JF, Schuler J, Abu Jhaisha S, Pollmanns MR, Bündgens L, Wirtz TH, Yagmur E, Hamesch K, Weiskirchen R, Tacke F, Trautwein C and Koch A. Secreted frizzled related protein 5 (SFRP5) serum levels are decreased in critical illness and sepsis and are associated with short-term mortality. Biomedicines 2023; 11: 313.
[23] Teliewubai J, Bai B, Zhou Y, Lu Y, Yu S, Chi C, Li J, Blacher J, Xu Y and Zhang Y. Association of asymptomatic target organ damage with secreted frizzled related protein 5 in the elderly: the Northern Shanghai Study. Clin Interv Aging 2018; 13: 389-395.
[24] Yu Y, Chen H, Wang R, Xu F, Yin J, Zang T, Zhou C, Liu C, Li C, Shen L and Ge J. sFRP5 ameliorates atherosclerosis by suppressing the JNK/TLR9 pathway in macrophages. Transl Res 2025; 281: 1-13.
[25] Luo J, He Z, Li Q, Lv M, Cai Y, Ke W, Niu X and Zhang Z. Adipokines in atherosclerosis: unraveling complex roles. Front Cardiovasc Med 2023; 10: 1235953.
[26] Zhang M, Li G, Li K, Gao Z, Yin C, Zeng F, Yang H, Dong W, Zhou G, Pan W, Wang Y and Jin J. Prognostic significance of serum secreted frizzled-related protein 5 in patients with acute aortic dissection. Heliyon 2024; 10: e35905.
[27] Wang X, Chen S, Yu C, Lu R, Sun Y, Guan Z and Gao Y. Secreted frizzled-related protein 5 overexpression reverses oxLDL-induced lipid accumulation in human vascular smooth muscle cells. Biosci Biotechnol Biochem 2024; 88: 776-783.
[28] Nikic P, Savic M, Jakovljevic V and Djuric D. Carotid atherosclerosis, coronary atherosclerosis and carotid intima-media thickness in patients with ischemic cerebral disease: is there any link? Exp Clin Cardiol 2006; 11: 102-106.
[29] Achim A, Péter OÁ, Cocoi M, Serban A, Mot S, Dadarlat-Pop A, Nemes A and Ruzsa Z. Correlation between coronary artery disease with other arterial systems: similar, albeit separate, underlying pathophysiologic mechanisms. J Cardiovasc Dev Dis 2023; 10: 210.
[30] Fu L, Li Y, Cheng H, Xiong J, Xiao P, Dong H, Shan X, Li Y and Mi J. Role of inflammatory biomarkers in mediating causal effect of life course body composition on hypertension. Hypertension 2025; 82: e57-e69.
[31] Swamynathan R, Varadarajan V, Nguyen H, Wu CO, Liu K, Bluemke DA, Kachenoura N, Redheuil A, Lima JAC and Ambale-Venkatesh B. Association between biomarkers of inflammation and 10-year changes in aortic stiffness: the multi-ethnic study of atherosclerosis. J Clin Med 2023; 12: 5062.
[32] Özyaşar M and Memioğlu T. Comparative analysis of systemic inflammatory biomarkers on dipper and non-dipper hypertension phenotypes. Medicine (Baltimore) 2025; 104: e42371.