International Journal of Research and Review
[Indexed, Peer Reviewed Journal]
Volume 12; Issue: 1; January 2025
Website: www.ijrrjournal.com
Research Paper *E-ISSN: 2349-9788; P-ISSN: 2454-2237*

The Relationship Between Tortuosity and Stenosis of Extracranial Internal Carotid Arteries and Vertebral Arteries Based on Cerebral Digital Subtraction Angiography and Vascular Risk Factors at Pelni Hospital

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DOI: https://doi.org/10.52403/ijrr.20250105

ABSTRACT

Background and purpose: Vascular dysfunction is the main key to cardiovascular, cerebrovascular, neurodegenerative diseases, and the aging process causes disruption of blood vessel function. Vascular Tortuosity (VT) and stenosis are types of blood vessel deformities resulting from vascular dysfunction. Both conditions can be diagnosed through cerebral Digital Subtraction Angiography (DSA) examination. This study aims to analyze the relationship between tortuosity and stenosis of extracranial internal carotid arteries and vertebral arteries on vascular risk factors at Pelni Hospital.

Methode: This research was a descriptive observational study with a cross-sectional approach on 608 subjects with a history of stroke who met the inclusion criteria. Conducted from January to September 2024, analyzing demographic data and risk factors, the presence or absence of stenosis and Vascular Tortuosity through cerebral DSA, also correlation these factors.

Result: From the 608 patients, 334 (54.9%) were male and 274 (45.1%) were female. Most of the subjects were aged 41-59 years (31.1%) with the most common risk factor being hypertension (76.6%). Carotid stenosis was significantly associated with age 51-59 years [odds ratio (OR): 2.452, 95% confidence interval (CI): 1.102-2.481, p=0.031)], female gender (OR): 1.665, 95% CI: 1.102-2.481, p=0.015; and hypertension (OR): 1.761, 95% CI: 1.099-2.821, p=0.019. Vertebral stenosis was significantly associated with female gender (OR): 2.160, 95% CI: 1.176-3.968, p=0.013; and diabetes (OR): 2.079, 95% CI: 1.015-4.255, p=0.045. Both stenosis conditions were significantly correlated with tortuosity conditions with OR: 2.320 for carotid, and OR: 12.090 for vertebral. Carotid tortuosity was significantly associated with diabetes (OR): 2.049, 95% CI: 1.051-4.000, p=0.035. Vertebral tortuosity was significantly associated with dyslipidemia (OR): 2.710, 95% CI: 1.099-6.711, p=0.030 and hypertension (OR): 2.079, 95% CI: 1.234-3.496, p=0.006. The combination of carotid stenosis and tortuosity was significantly associated with female gender (OR): 2.367,

95% CI: 1.378-4.066, p=0.002. The combination of stenosis and tortuosity in both arteries did not show a significant correlation with existing risk factors.

Conclusion: Carotid stenosis is correlated with female gender, age, and hypertension. Vertebral stenosis is correlated with female gender and diabetes. Carotid tortuosity is correlated with diabetes. Vertebral tortuosity correlates with dyslipidemia and hypertension. The combination of carotid stenosis and tortuosity correlates with female gender.

Keywords: Vascular Tortuosity, Stenosis, Cerebral Digital Subtraction Angiography

INTRODUCTION

In general, strokes are classified into ischemic and hemorrhagic strokes, with ischemic strokes accounting for almost 85% of the total. Ischemic stroke can be caused by intracranial thrombosis or extracranial embolism. Intracranial thrombosis is caused by atherosclerosis, while extracranial embolism generally originates from extracranial arteries or from the cardiac because of myocardial infarction, mitral stenosis, endocarditis, atrial fibrillation, cardiomyopathy or congestive heart failure.[2,3] Vascular dysfunction is the main key to cardiovascular, cerebrovascular and neurodegenerative diseases, where the aging process causes disruption of blood vessel function. Many conditions participate in the process of vascular dysfunction, such as the aging process, a history of hypertension, diabetes mellitus (DM) or dyslipidemia, all of which will create complex structural and functional changes in the blood vessels.[5,6]

Cerebral atherosclerosis is the main cause of ischemic stroke, it can be divided into extracranial atherosclerosis and intracranial atherosclerosis, anterior and posterior circulation atherosclerosis.[2,7] The internal carotid arteries and vertebral arteries are the main supplying arteries to the brain and have an important role in providing energy intake and maintaining normal neuronal function. Extracranial arteries are susceptible to geometric and morphological changes during normal aging. Due to the long structure of the extracranial arteries in the neck area, age-related morphological variations will manifest as twisting, turns and loops which will be found in older patients which contrasts with the normal anatomical structure. These changes in vascular morphology will limit blood flow, which will cause stroke and other ischemic events such as *Transient Ischemic Attack* (TIA) and vertigo. It is important to assess Vascular Tortuosity (VT) and the degree of stenosis in blood vessels to gain a better understanding of how these conditions can affect blood flow.[7,8]

Cerebral Digital Subtraction Angiography (DSA) with submillimeter and subsecond resolution is considered the gold standard in vascular imaging, for extra- and intracranial cerebral vessels. Through DSA examination we can see the turquoise index, detect occlusion and stenosis, and detect small aneurysms. Vascular turbidity has recently become a common angiographic finding in several clinical examinations and screenings.[9,10,11]

Based on this background, this study aims to look at the overall profile of stroke patients who undergo cerebral DSA examination so that they can find out what risk factors are involved and what the condition of the blood vessels in these patients is so that they can provide optimal secondary prevention and a good quality of life.

MATERIALS & METHODS

This research was a descriptive observational study with a cross-sectional approach on 608 subjects with a history of stroke who met the inclusion criteria (patients with a history of Stroke Non-Hemorrhagic undergoing cerebral DSA). Conducted from January to September 2024, analyzing demographic data and risk factors (hypertension, dyslipidemia, DM) the presence or absence of stenosis and VT through cerebral DSA, also correlation

these factors.

STATISTICAL ANALYSIS

Data collection was carried out manually by collecting medical record data from non-hemorrhagic stroke patients who underwent cerebral DSA examination. The data that has been collected is checked for completeness and correctness, then coding, editing, cleaning, tabulation is carried out and entered the computer using the IBM SPSS Statistics for Windows version 22 program.

Results are presented in tabular form. To determine patient demographic data (age and gender), risk factors (hypertension, dyslipidemia, DM) in non-hemorrhagic stroke patients. Then a correlation analysis was carried out between these risk factors and the presence of stenosis and VT, a correlation test was carried out with a confidence level of 95%. Variables that are thought to be independent variables, namely age, gender, hypertension, dyslipidemia, and DM, will be subjected to bivariate tests using the $\chi 2$ (Chi-square) test. Results are said to be significant if $P<0.05$.

This research has received approval from the Medical and Health Research Ethics Committee, Faculty of Medicine, Al-Azhar Islamic University, Mataram (no. 190/EC-04/FK-06/UNIZAR/XI/2024). All costs related to the research will be borne by the researcher. Patient identities in medical record data are kept confidential in this study.

RESULT

This study was conducted at the Cathlab Unit of Pelni Hospital Jakarta, from January to September 2024. From this study, 608 research subjects were obtained who met the inclusion and exclusion criteria.

Table 1. Characteristics of subjects (n = 608)

	Male n = 334 (54,9%)	**Female n = 274 (45,1%)**	**Total**
Age Category (year, n [%])			
30-40	48 (14,4%)	19 (6,9%)	67 (11,0%)
41-50	104 (31,1%)	72 (26,3%)	176 (28,9%)
51-59	77 (23,1%)	97 (35,4%)	174 (28,6%)
60-69	71 (21,3%)	51 (18,6%)	122 (20,1%)
>69	34 (10,2%)	35 (12,8%)	69 (11,4%)
Diabetes mellitus (n, %)			
Yes	99 (29,6%)	79 (28,8%)	178 (29,3%)
No	235 (70,4%)	195 (71,2%)	430 (70,7%)
Dyslipidemia (n, %)			
Yes	42 (12,6%)	31 (11,3%)	74 (12,0%)
No	292 (87,4%)	243 (88,7%)	534 (78,9%)
Hypertension (n, %)			
Yes	275 (82,3%)	191 (69,7%)	466 (76,6%)
No	59 (17,7%)	83 (45,1%)	133 (23,4%)

From all subjects, it was found that 54.9% were male, and 45.1% were female. Most of the subjects were aged 41-59 years, with the most common risk factor being hypertension (around 76.6% of subjects) (Table 1).

Table 2 Characteristics of patients with tortuosity and stenosis

	Carotid tortuosity and stenosis	**Vertebralis tortuosity and stenosis**	**None / only one**
Gender (n, %)			
Male	34 (39,5%)	25 (48,1%)	275 (58,5%)
Female	52 (60,5%)	27 (51,9%)	195 (41,5%)
Age Category (year, n[%])			

30-40	5 (5,8%)	4 (7,7%)	58 (12,3%)
41-50	17 (19,8%)	11 (21,2%)	148 (31,5%)
51-59	29 (33,7%)	20 (38,5%)	125 (26,6%)
60-69	18 (20,9%)	11 (21,2%)	93 (19,8%)
>69	17 (19,8%)	6 (11,5%)	46 (9,8%)
Diabetes mellitus (n, %)			
Yes	27 (31,4%)	8 (15,4%)	143 (30,4%)
No	59 (68,6%)	44 (84,6%)	327 (69,6%)
Dyslipidemia (n, %)			
Yes	9 (10,5%)	3 (5,8%)	61 (13,0%)
No	77 (89,5%)	49 (94,2%)	409 (87,0%)
Hypertension (n, %)			
Yes	65 (75,6%)	34 (65,4%)	367 (78,1%)
No	21 (24,4%)	18 (34,6%)	103 (21,9%)

From 86 subjects with a combination of tortuous and carotid stenosis, most were female (60.5%), with the largest age range at 51-59 years (33.7%), and the highest risk factor was hypertension at 65 (75 .6%) subjects. Of the 52 subjects with a combination of tortuous and vertebral stenosis, most were women (51.9%) with the largest age range being 51-59 years (38.5%), and the largest risk factor was hypertension (65.4%) (Table 2).

Table 3. Analysis of factors influencing the incidence of stenosis

	Carotid stenosis		**Vertebral stenosis**	
	OR (IK95%)	Nilai p	OR (IK95%)	P value
Gender (n, %)				
Male	Reference	0,015	Reference	0,013
Female	1,665 (1,102-2,481)		2,160 (1,176-3,968)	
Age Category (year, n[%])				
30-40	Reference		Reference	
41-50	0,494 (0,253-0,964)	0,039	0,821 (0,240-2,814)	0,754
51-59	2,452 (1,087-5,530)	0,031	0,984 (0,337-2,874)	0,977
60-69	1,321 (0,754-2,313)	0,330	0,815 (0,345-1,924)	0,641
>69	0,990 (0,568-1,728)	0,973	0,762 (0,323-1,798)	0,535
Diabetes mellitus (n, %)				
Yes	0,911 (0,599-1,385)	0,663	2,079 (1,015-4,255)	0,045
No	Reference		Reference	
Dyslipidemia (n, %)				
Yes	0,689 (0,393-1,206)	0,192	0,655 (0,240-1,791)	0,410
No	Reference			
Hypertension (n, %)				
Yes	1,761 (1,099-2,821)	0,019	1,258 (0,628-2,517)	0,518
No	Reference		Reference	
Tortuosity (n, %)				
Yes	2,320 (1,469-3,664)	<0,001	12,090 (6,721-21,749)	<0,001
No	Reference		Reference	

It is found that there is a significant relationship between female gender and the incidence of carotid stenosis with an OR of 1.665 and a 95% CI between 1.102-2.481. In the age range, it was found to be most significant in the 51–59-year age range with the largest OR, namely 2.452. The risk factor most associated with the incidence of carotid stenosis is hypertension with an OR of 1.761, which means that hypertensive patients have a 1.76 times higher chance of experiencing carotid stenosis than patients without hypertension, where this result is statistically significant. Carotid stenosis

patients also have a significant correlation with the incidence of tortuosity with an OR of 2.32, which means that patients with tortuosity will have a 2.32 times higher chance of experiencing carotid stenosis (Table 3).

Similar results were also obtained in the condition of vertebral stenosis, a significant relationship was found with female patients with an OR of 2.160 and a CI of 95%. The most significant risk factor is diabetes with an OR of 2.079, which means that diabetes patients have a chance of experiencing vertebral stenosis 2 times higher than patients without diabetes. Vertebral stenosis patients also have a significant correlation with the incidence of tortuosity with an OR of 12.090, which means that patients with tortuosity will have a 12 times higher chance of experiencing vertebral stenosis (Table 3).

Table 4 Analysis of factors influencing the incidence of tortuosity

	Carotid Tortuosity		**Vertebralis Tortuosity**	
	OR (IK95%)	Nilai p	OR (IK95%)	P value
Gender (n, %)				
Male	Reference		Reference	
Female	0,682 (0,386-1,202)	0,185	1,202 (0,752-1,919)	0,443
Age Category (year, n[%])				
30-40	Reference		Reference	
41-50	1,449 (0,568-3,696)	0,437	1,129 (0,462-2,756)	0,790
51-59	0,609 (0,203-1,823)	0,375	0,697 (0,279-1,746)	0,441
60-69	0,828 (0,373-1,836)	0,642	1,244 (0,647-2,391)	0,513
>69	1,261 (0,589-2,701)	0,550	1,204 (0,622-2,328)	0,581
Diabetes mellitus (n, %)				
Yes	2,049 (1,051-4,000)	0,035	0,604 (0,356-1,025)	0,062
No	Reference		Reference	
Dyslipidemia (n, %)				
Yes	0,726 (0,306-1,721)	0,467	2,710 (1,099-6,711)	0,030
No	Reference		Reference	
Hypertension (n, %)				
Yes	0,713 (0,369-1,380)	0,316	2,079 (1,234-3,496)	0,006
No	Reference		Reference	

There was no significant relationship between gender and the incidence of tortoise in both the carotid and vertebral arteries. The risk factor most associated with the incidence of carotid tortuosity is diabetes mellitus with an OR of 2.049, which means that patients with diabetes mellitus have a chance of experiencing carotid tortuosity 2 times higher than patients without diabetes, where this result is statistically significant. Meanwhile, in vertebral tortuosity, the most associated risk factors were dyslipidemia and hypertension with an OR of 2.710 and 2.079 respectively, which means that patients with risk factors for dyslipidemia and hypertension had a 2 times higher chance of experiencing vertebral artery tortuosity compared to patients without the risk factors (Table 4).

Table 5. Factors that influence the incidence of stenosis and tortuosity

	Carotid Stenosis and Tortuosity		**Vertebralis Stenosis and Tortuosity**	
	OR (IK95%)	Nilai p	OR (IK95%)	P value
Gender (n, %)				
Male	Reference	0,002	Reference	0,383
Female	2,367 (1,378-4,066)		0,688 (0,298-1,590)	
Age Category (year, n [%])				
30-40	Reference		Reference	

41-50	2,013 (0,858-4,722)	0,108	1,955 (0,541-7,067)	0,315
51-59	0,418 (0,131-1,337)	0,141	1,072 (0,314-3,660)	0,575
60-69	0,459 (0,208-1,011)	0,053	Reference	0,307
>69	1,013 (0,493-2,081)	0,972	0,289 (0,062-2,454)	0,912
Diabetes mellitus (n, %)				
Yes	1,467 (0,832-2,579)	0,183	0,483 (0,175-1,332)	0,164
No	Reference		Reference	
Dyslipidemia (n, %)				
Yes	0,789 (0,341-1,823)	0,579	0,392 (0,115-2,111)	0,340
No	Reference		Reference	
Hypertension (n, %)				
Yes	1,068 (0,571-1,998)	0,836	0,516 (0,205-1,298)	0,160
No	Reference		Reference	

We found a significant relationship between the combination of carotid artery stenosis and tortuosity and female gender, with an OR of 2.370 and a 95% CI with a range of 1.379-4.065, which means that female patients have a 2.3 times higher chance of experiencing stenosis accompanied by tortuosity and statistically significant. Meanwhile, in the age group and risk factors, it was found that nothing had a significant relationship to the carotid or vertebral arteries (Table 5).

DISCUSSION

This study discusses the relationship between stenosis and tortuosity of the carotid and vertebral arteries with gender, age, and risk factors such as diabetes, dyslipidemia, and hypertension in patients who have a history of stroke.

Of the 608 subjects included in this study, the number of subjects was almost the same, both men and women. In female subjects, the largest age range was 51-59 years who had a history of stroke. In the analysis of factors influencing the incidence of carotid and vertebral stenosis, it was found that women had a 1.6 times higher chance of carotid stenosis than men, and 2.1 times higher odds of vertebral artery stenosis. In subjects with a combination of stenosis and carotid tortuosity, a significant relationship was also found in female subjects of 2.37 times compared to male subjects.

These results are consistent with the theory that age-related increases in tortuosity correlate with lower blood flow and velocity in extracranial arteries, suggesting changes in tortuosity in the elderly may limit efficient blood supply and affect neuronal function, especially when neural activity increases with energy demand.[8] In a large retrospective study reported Martins et al found internal carotid artery abnormalities, including tortuosity (80% carotid kinking, 16% coiling, and 1% looping) in 2678 patients (13.5%) of a total of 19,804 patients examined.[10,11,17] The results of research conducted by Kamesnky et al., showed that the geometry of the normal carotid artery changes during aging with increasing bulb diameter, tortuosity of the CCA (Common Carotid Artery) and ICA (Internal Carotid Artery), as well as the carotid bifurcation angle.[19,20,28] As the meta-analysis results reported by Song P et al., age can also cause changes in structure and function, such as decreased stiffness and elasticity. A meta-analysis conducted using 59 studies conducted in 21 countries showed a significant increase of 85% in carotid artery thickening and plaque formation in subjects aged 50–59 years from 2000 to 2020.[11,19]

The results of this study also support the theory that gender is another important factor influencing vascular conditions. It is said that women are more susceptible to tortuosity of blood vessels, stiffer large arteries, and higher pulse pressure. After menopause, women's blood vessels become more susceptible to stiffness and tortuousness in large arteries, due to

decreased steroid secretion in women associated with a decreased elastin/collagen ratio. As a result, arterial wall growth can alter blood flow.[5,6] Several studies have shown an association between arterial tortuosity and female sex. The underlying pathophysiological mechanisms include mechanical factors, such as smaller arterial diameters in women than in men, causing decreased wall resistance in the premenopausal years, while in older years the opposite effect occurs. Hormonal factors have effects on inflammation, atherosclerosis, and changes in arterial shape. Estrogen reduces collagen deposition and increases elastin deposition. Conversely, progesterone reduces elastin deposition as observed through 17-β-estradiol. Thus, high cyclic progesterone levels in premenopausal women may attenuate the beneficial effects of 17-β-estradiol on the elastin/collagen ratio of the blood vessel wall. After menopause, low 17-β-estradiol levels increase blood vessel stiffness and decrease arterial elasticity, leading to stiffer arteries and higher pulse pressure in older women than in age-matched men.[15,16] In the large study of Martins et al., mentioned above, the prevalence of internal carotid artery anomalies was higher in women than in men (17% versus 10% P<0.01).[17]

Here was also found that the risk factor most associated with the incidence of carotid stenosis was hypertension with an OR of 1.761, which means that hypertensive patients had a 1.76 times higher chance of experiencing carotid stenosis than patients without hypertension, where this result was statistically significant. In vertebral tortuosity, it was found that the most correlated risk factors were dyslipidemia and hypertension with an OR of 2.710 and 2.079 respectively, which means that patients with risk factors for dyslipidemia and hypertension had a 2 times higher chance of experiencing vertebral artery tortuosity compared to patients without these risk factors. In this study, it was also found that in conditions of vertebral stenosis, diabetes mellitus was the most significant risk factor with an OR of 2.079, which means that diabetic patients had a chance of experiencing vertebral stenosis that was 2 times higher than patients without diabetes. Diabetes is also the risk factor most associated with the incidence of carotid tortuosity with an OR of 2.049, which means that patients with diabetes mellitus have a chance of experiencing carotid tortuosity that is 2 times higher than patients without diabetes, where this result is statistically significant.

The results of this study are in line with a multi-center, prospective study conducted by Kim JS, et al. in 2012, in 10,000 atherosclerotic strokes, it was found that hypertension was the largest risk factor (72.5%), followed by diabetes mellitus (35.6%). There are differences in the prevalence of risk factors between anterior and posterior circulation strokes. Multiple logistic regression analysis showed hypertension (OR, 1.826; 95% CI, 1.274–2.618; P=0.001) and diabetes mellitus (OR, 1.490; 95% CI, 1.105–2.010; P=0.009) were more frequent factors in posterior circulation disease.[5,14] Research conducted by Pancera et al, also showed a relationship between arterial hypertension and Carotid artery kinking was assessed by Echo-Doppler in 2 cross-sectional studies, involving 3300 (P<0.001) and 590 patients (P<0.02).[20,21]

In research conducted by Kim JS, et al. found that in multiple logistic regression analysis it was found that hyperlipidemia was associated with extracranial arterial stenosis compared to intracranial stenosis (OR 1.502; 95% CI, 1.117–2.018; P=0.007), this finding was also consistent with previous single-center studies conducted in Korea.[5,22] Hyperlipidemia was also found to be more associated with extracranial stenosis in anterior circulation stroke (OR 1.582; 95% CI, 1.28-2.217; p = 0.008).[5]

These results are in line with the theory that the initial phase begins with injury that lasts for a long period of time to the endothelial layer, usually due to risk factors such as hypertension, hyperlipidemia, diabetes and smoking. This exposure causes monocyte adhesion and an increase in leukocytes due to increased endothelial permeability. Macrophages will be activated, and a "fibrous cap" is formed which contains smooth muscle, elastin and collagen tissue. The thicker this tissue is, the more difficult it is for the atheroma to be separated and will cause thrombosis.[10,11,12,13]

The weakness of this study is that it does not directly explain the causes of stenosis and tortuosity of the carotid and vertebral arteries, so further research is needed that examines the direct causes of stenosis and tortuosity of the carotid and vertebral arteries. It is hoped that the results obtained from this research can be a reference for people with related risk factors, such as hypertension, diabetes mellitus, hyperlipidemia, and especially women who have experienced menopause (with or without a history of stroke) who can carry out regular health checks, especially examination to assess the condition of extracranial blood vessels (carotid and vertebral arteries).

CONCLUSION

Carotid stenosis is correlated with female gender, age, and hypertension. Vertebral stenosis is correlated with female gender and diabetes. Carotid tortuosity is correlated with diabetes. Vertebral tortuosity correlates with dyslipidemia and hypertension. The combination of carotid stenosis and tortuosity correlates with female gender.

Declaration by Authors

Ethical Approval: Approved
Acknowledgement: None
Source of Funding: None
Conflict of Interest: The authors declare no conflict of interest.

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How to cite this article: Fritz Sumantri Usman, Bagus Ngurah Mahasena Putera Awatara, Rivan Hododjojo, Dhayu Mart Hindrasyah, Merlin Prisilia Kastilong, Leny Kurnia. The relationship between tortuosity and stenosis of extracranial internal carotid arteries and vertebral arteries based on cerebral digital subtraction angiography and vascular risk factors at Pelni Hospital. *International Journal of Research and Review*. 2025; 12(1): 22-30. DOI: *https://doi.org/10.52403/ijrr.20250105*

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