JMedSci

Journal of the Medical Sciences
(Berkala Ilmu Kedokteran)

Volume 55, Number 2, 2023; 127-134
https://doi.org/10.19106/JMedSci005502202304

Correlation between the degree of leukoaraiosis and hyperlipidemia in post-ischemic stroke patients

Dian Angraeni, Lina Choridah*, Evi Artsini

Department of Radiology, Faculty of Medicine, and Public Health, and Nursing, Universitas Gadjah Mada/Dr. Sardjito General Hospital, Yogyakarta, Indonesia

Submitted: 2022-12-07
Accepted : 2023-05-03

ABSTRACT

Leukoaraiosis is a neurological imaging in the periventricular area and the centrum semiovale. This condition occurs due to abnormalities in the small blood vessels in the brain that lead to hypoxia. It is often observed in patients with ischemic stroke and accompanied by risk factors for hyperlipidemia. This study aimed to evaluate the correlation between the degree of leukoaraiosis and hyperlipidemia in post-ischemic stroke patients. A cross-sectional study retrospectively was conducted on post-ischemic stroke patients who underwent brain MRI (magnetic resonance imaging) on T2 and FLAIR (fluid-attenuated inversion recovery) sequence at the Department of Radiology, Dr. Sardjito General Hospital, Yogyakarta, from January 2021 to March 2022. A total of 36 patients were involved in this study. The leukoaraiosis of patient was examined by brain MRI. Degree of the leukoaraiosis was determined based on Fazekas classification. Serum cholesterol, HDL (high-density lipoprotein), LDL (low-density lipoprotein), and triglyceride levels of patients were then examined. The data obtained were then analyzed using Spearman correlation test. A positive correlation was observed between the degree of leukoaraiosis and triglyceride level ($p = 0.042$; $r = 0.292$) and age ($p= 0.004$; $r = 0.464$). However, no correlation was observed between the degree of leukoaraiosis and cholesterol, HDL, and LDL ($p>0.05$). In conclusion, the leukoaraiosis degree is correlated with serum triglyceride levels and age in post-ischemic stroke patients.

ABSTRAK

Leukoaraiosis merupakan gambaran neurologis pada daerah periventrikuler dan sentrum semiovale. Leukoaraiosis terjadi akibat adanya kelainan pembuluh darah kecil di otak akibat hipoksia. Leukoaraiosis banyak dijumpai pada pasien stroke iskemik dan yang disertai faktor risiko hyperlipidemia. Penelitian ini bertujuan mengkaji hubungan antara derajat leukoaraiosis dengan hiperlipidemia pada pasien paska stroke iskemik. Penelitian potong lintang secara retrospektif ini menggunakan data sekunder gambaran MRI (*magnetic resonance imaging*) kepala sekuen T2 dan FLAIR (*fluid-attenuated inversion recovery*) pasien paska stroke iskemik di Departemen Radiologi, RSUP Dr Sardjito Yogyakarta periode Januari 2021 sampai Maret 2022. Total sebanyak 36 pasien terlibat dalam penelitian. Leukoaraiosis pasien diperiksa dengan MRI kepala dan derajat leukoaraiosis ditetapkan berdasarkan klasifikasi Fazekas. Data yang diperoleh selanjutnya dianalisis dengan uji korelasi Spearman. Didapatkan hubungan positif antara derajat leukoaraiosis dengan kadar trigliserida serum ($p=0,042$; $r=0,292$) dan dengan umur ($p=0,004$; $r=0,464$). Namun demikian tidak hubungan antara derajat leukoaraiosis dengan kadar kolesterol, HDL dan LDL serum ($p>0,05$). Simpulan, derajat leuokoaraiosis berhubungan dengan kadar trigliserida serum dan umur pada pasien paska stroke iskemik.

Key words:
leukoaraiosis;
hyperlipidemia;
post-ischemic stroke;
correlationp

*corresponding author: linachoridah@ugm.ac.id

INTRODUCTION

Leukoaraiosis is a neurological abnormality in the white matter area that appears as an area of increased intensity on magnetic resonance imaging, especially in the periventricular and centrum semiovale. This disorder is often found among older people. The term was coined by Hachinski in 1987 and derived from the words leuko (white) and araiosis (smooth). Leukoaraiosis may present as subcortical, multifocal, or diffuse periventricular lesions of varying sizes.[1] Leukoaraiosis may be caused by hypoxic ischemia due to small vessel diseases such as thalamostriate and perforated arteries.[2-4]

Decreased blood flow is one of the causes of nerve cell damage.[5] Several studies have investigated blood-brain barrier damage and endothelial dysfunction.[6] Chutinet *et al.*,[7] reported that age and acute ischemic stroke are the strongest determinants of the severity of leukoaraiosis in hypertension patients. Conde *et al.*,[8] revealed that ischemic stroke patients with a history of hyperlipidemia have an increased intensity in the white matter area, which is milder at stroke time. Ke *et al.*,[9] reported that hypertriglyceridemia is associated with the severity of leukoaraiosis and may play a role in small vessel cerebral disease.

Dyslipidemia can manifest as an increase or decrease in lipid fractions, including increased serum cholesterol, LDL (low density lipoprotein), and triglyceride levels and decreased serum HDL (high density lipoprotein) levels. Pathological changes were observed in the white matter area due to lipid accumulation.[10] Elevated of serum cholesterol, LDL, and HDL levels can lead to the development of atherosclerosis, damage to the vascular endothelium, and changes in vascular endothelial permeability.[11] This study aimed to investigate the association between the degree of leukoaraiosis and hyperlipidemia in post-ischemic stroke patients.

MATERIALS AND METHOD

Design and sample

This study used a cross-sectional design with retrospective sampling using secondary data of brain MRI examination results of post-ischemic stroke patients at the Department of Radiology, and lipid profile of the patients at the Clinical Pathology Installation of Dr. Sardjito General Hospital, Yogyakarta from January 2021 to March 2022. The selected sample was part of the population planned to be directly studied.[12] The target population was post-ischemic stroke patients diagnosed with leukoaraiosis through brain MRI examination and found to have hyperlipidemia. Protocol of this study was approved by the Medical and Health Research Ethics Committee, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr. Sardjito General Hospital, Yogyakarta.

Procedure

Patients who meet the inclusion and exclusion criteria were involved in this study. The inclusion criteria were brain MRI results on T2 and FLAIR sequences with a post-ischemic diagnosis, the presence of leukoaraiosis

images stored on the Picture Archiving and Communication System (PACS) server, and an increase in the levels of cholesterol, LDL, and triglycerides. Patients were excluded when other lesions were found, such as brain infection, hydrocephalus tumor, or bleeding.

The data of brain MRI examination results were displayed on the research computer monitor, and subsequent assessment of leukoaraiosis severity in post-ischemic stroke patients was conducted by a specialist radiologist. During the MRI observation, the examiner was not provided with any information regarding the subjects' identity or clinical data. Degree of the leukoaraiosis was determined based on Fazekas classification. The Fazekas scale classified the white matter area into the periventricular. Each region is graded according to the size and confluency of the lesion. In periventricular white matter (PVWM), 0 is given if no lesion is found; 1 if a "cap" or thin-film image is found; 2 if a "halo" image is found; 3 if irregular periventricular signal extending into the deep white matter is found. In deep white matter (DWM), 0 is given if there is no lesion; 1 if there is a punctate foci; 2 if there is early confluence; 3 if there are large confluent areas.[13]

The lipid profile of the post-ischemic stroke patients was then classified as optimal (LDL <100 mg/dL), above optimal (100-129 mg/dL), borderline high (130-159 mg/dL), high (160-189 mg/dL), and very high (>190 mg/dL), and total cholesterol as desirable (<200 mg/dL), borderline high (200-239 mg/dL), and high (>240 mg/dL). Furthermore, HDL is classified as low (<40 mg/dL) and high (> 60 mg/dL), while triglycerides as normal (< 150 mg/dL), borderline high (150-199 mg/dL), high (200-499 mg/dL), and very high (>500 mg/dL).[14]

Statistical analysis

Data were presented as mean ± standard deviation (SD) or frequency or percentage. Bivariate analysis was applied to evaluate the correlation between leukoaraiosis and hyperlipidemia. A p value < 0.05 was considered to be significant.

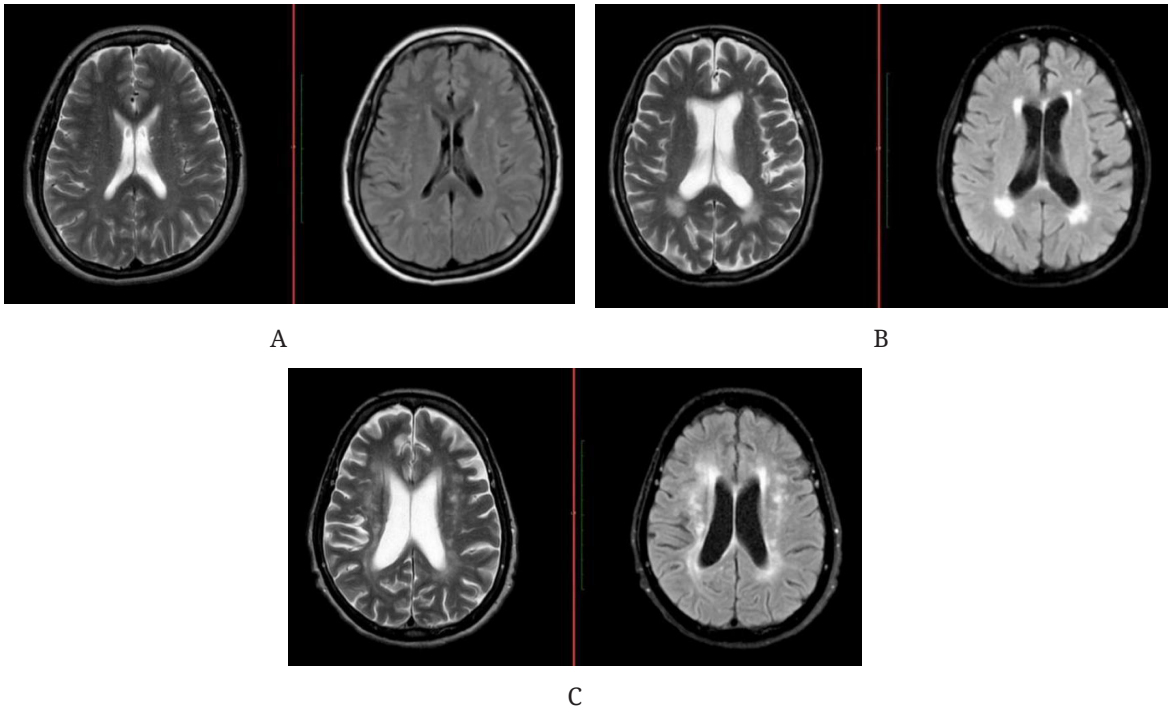
RESULTS

The characteristics of the patients are presented in TABLE 1. A total of 36 post-ischemic stroke patients were involved in this study consisting of 17 (47.2%) male and 19 (52.8%) female with the mean age of 61±11 yo. The mean total cholesterol of all subjects was 199±34 mg/dL, most (58.3%) having cholesterol levels higher than 240 mg/dL (n=21). In terms of HDL levels, the overall mean was 44±14 mg/dL, with most subjects (58.3%) having HDL levels between 40 and 60 mg/dL (n=21), while the mean triglyceride level was 140±67 mg/dL, with almost all subjects (91.7%) having triglyceride levels between 200 and 499 mg/dL. In addition, the mean LDL was 134±31 mg/dL, one-third of which (30.6%) had LDL levels between 100 and 129 mg/dL (n=11). The mean blood pressure was 148±15 mmHg systolic and 85±10 mmHg diastolic, with 58.3% of the subjects classified as hypertension grade 1.

The leukoaraiosis examinations was conducted using 0.4T open MRI. The illustrations of leukoaraiosis lesions obtained from the post-ischemic stroke patients are presented in FIGURE 1.

TABLE 1. Characteristics of patients

Variables	Mean ± SD	n (%)
Age (year)	61 ± 11	
Sex		
• Male		17 (47.2)
• Female		19 (52.8)
Total cholesterol (mg/dL)		
• <200	199 ± 34	15 (41.7)
• 200-239		0 (0.0)
• >240		21 (58.3)
HDL (mg/dL)		
• <40		21 (36.1)
• 40-60	44 ± 14	13 (58.3)
• >60		2 (5.6)
Triglyceride (mg/dL)		
• <150	140 ± 67	3 (8.3)
• 150-199		0 (0.0)
• 200-499		33 (91.7)
• >500		0 (0.0)
LDL (mg/dL)		
• <100		5 (13.9)
• 100-129		11 (30.6)
• 130-159	134 ± 31	10 (27.8)
• 160-189		10 (27.8)
• >190		0 (0.0)
Fazekas scale		
• No lesion		0 (0.0)
• Punctata lesion		18 (50.0)
• Early confluence		15 (41.7)
• Large confluence		3 (8.3)
Hypertension		
• Pre-hypertension		7 (19.4)
• Hypertension grade 1		21 (58.3)
• Hypertension grade 2		8 (22.2)



A B C

FIGURE 1. MRI Images A. Leukoaraiosis Fazekas grade 1, illustrated by the presence of punctata lesions in bilateral centrum semiovale B. Leukoaraiosis Fazekas grade 2, illustrated by the presence of hyperintense periventricular confluent lesions on both sides C. Leukoaraiosis Fazekas grade 3, illustrated by the presence of large confluence lesions in periventricular and centrum semiovale on both sides.

TABLE 2 shows the correlation between the degree of leukoaraiosis and cholesterol, HDL, triglycerides, and LDL of the post-ischemic stroke. A significant and positive correlation was observed only between the serum triglyceride levels and the degree of leukoaraiosis (p=0.042; r= 0.292), indicating the patients with the higher degree of leukoaraiosis had the higher serum triglyceride levels. No correlation was observed between the degree of leukoaraiosis and cholesterol, HDL, and LDL levels (p>0.05).

A significant and positive correlation between degree of leukoaraiosis and age of post-ischemic stroke patients was observed (p= 0.004; r= 0.464) indicating that the older age patients had the higher degree of leukoaraiosis (TABEL 3).

TABLE 2. Correlation between the degree of leukoaraiosis and cholesterol, HDL, triglycerides and LDL

Variables	Degree of leukoaraiosis			r	p
	Punctata lesion	Early confluence	Large confluence		
	n (%)	n (%)	n (%)		
Cholesterol					
• <200	6 (33.3)	8 (53.3)	1 (33.3)		
• 200-239	0 (0.0)	0 (0.0)	0 (0.0)	-0.136	0.214
• >240	12 (66.7)	7 (46.7)	2 (66.7)		
HDL					
• <40	7 (38.9)	5 (33.3)	1 (33.3)		
• 40-60	10 (55.6)	10 (66.7)	1 (33.3)	0.079	0.323
• >60	1 (5.6)	0 (0.0)	1 (33.3)		
Triglyceride					
• <150	3 (16.7)	0 (0.0)	0 (0.0)		
• 150-199	0 (0.0)	0 (0.0)	0 (0.0)	0.292	0.042*
• 200-499	15 (83.3)	15 (100.0)	3 (100.0)		
• >500	0 (0.0)	0 (0.0)	0 (0.0)		
LDL					
• <100	3 (16.7)	2 (13.3)	0 (0.0)		
• 100-129	4 (22.2)	5 (33.3)	2 (66.7)		
• 130-159	7 (38.9)	2 (13.3)	1 (33.3)	-0.015	0.465
• 160-189	4 (22.2)	6 (40.0)	0 (0.0)		
• >190	0 (0.0)	0 (0.0)	0 (0.0)		

TABLE 3. Correlation between the degree of leukoaraiosis and age

Variables	Degree of leukoaraiosis			r	p
	Punctata lesion	Early confluence	Large confluence		
	n (%)	n (%)	n (%)		
Age (year)					
• 36-45	3 (100.0)	0 (0.0)	0 (0.0)		
• 46-55	7 (87.5)	1 (12.5)	0 (0.0)	0.464	0.004*
• 56-65	5 (33.3)	8 (53.3)	2 (13.3)		
• > 65	3 (30.0)	6 (60.0)	1 (10.0)		

DISCUSSION

The mean age of post-ischemic stroke patients in this study was 61±11 yo. This results in accordance with the study conducted by Ke *et al.*,[9] which reported that the mean of patients is 60 yo. Furthermore, Ben-Assayag *et al.*,[2] reported that the mean age of the models was 66.4±13.4 yo. Age is the most substantial non-modifiable risk factor for stroke incidence. About three-quarters of all strokes occur in people aged 65 yo or older.[15] Age is reported as a risk factor for ischemic stroke.[16] It can be linked to an increase in leukoaraiosis

in older people due to the thickening and narrowing of blood vessels. This reduced blood flow to the brain is demonstrated by the development of areas of hyperintensity in the periventricular and centrum semiovale. In addition, increasing age can reduce the elasticity of blood vessels.[17]

Leukoaraiosis is expected in the elderly and is associated with recurrent stroke, cognitive decline, gait disturbances, hemorrhagic transformation, and functional abnormalities after ischemic stroke.[18,19] Most studies have investigated the correlation between active stroke and leukoaraiosis severity using computed tomography visual scales or volumetric measurements. Although faster, computed tomography is not as sensitive as T2 and FLAIR. The Fazekas scale allows rapid assessment of severity on T2 and FLAIR sequences.[10]

This study involved 36 ischemic stroke patients consisting of 17 (47.2%) men and 19 (52.8%) women. This number is lower than the sample size in several previous studies, such as Ben-Assayag *et al.*,[2] which involved 170 acute stroke patients, consisting of 104 males and 66 females.[2] A study in China by Ke *et al.*,[9] reported that among 1,270 involving in the study, 66% are men and 34% are women. Another study reported that the incidence of stroke differs between the sexes.[20]

Hypertension is the most common risk factor for stroke. Hypertension was reported in approximately 64% of patients with stroke. Hypertension, blood pressure variability, and leukoaraiosis are risk factors for early adverse events and poor functional outcomes after ischemic stroke. Previous studies have shown different correlation between leukoaraiosis and blood pressure variability, including in ischemic stroke.[8] In this study, over half of the sample (58.3%) had hypertension grade 1.

Hyperlipidemia is known to have a role in the pathogenesis of ischemic stroke. Hyperlipidemia is independently associated with a reduction in the severity of leukoaraiosis in elderly or ischemic stroke patients.[9] In this study, a strong and positive association between the degree of leukoaraiosis and triglyceride levels (p= 0.042; r= 0.292), indicating that patients with the higher the degree of leukoaraiosis have the higher the triglyceride levels. This result is comparable to that of a study conducted by Park *et al.*,[21] that discovered hypertriglyceridemia is associated with a higher incidence of leukoaraiosis.

The radiological examination is conducted using 0.4T open MRI. It is sensitive and specific for leukoaraiosis assessment lower than 1.5T or 3.0T MRI. Thus, the MRI can not compare the result reflecting the effect of triglycerides on the hyperintensity of white matter area lesions in this study. However, the results of this study are in line with study by Ke *et al.*,[9] which discovered a connection between hypertriglyceridemia (1.7 mmol/L) and the severity of leukoaraiosis (p=0.05). The mechanism of the correlation between triglyceride levels and leukoaraiosis remains largely unknown. However, it is thought to have involved myelin in the brain in white matter areas. Myelin contains 70% lipid which could explain the increased levels of triglycerides and cholesterol in ischemic stroke.[9,22]

In this study, no significant correlation was observed between the degree of leukoaraiosis and serum cholesterol level. Previous study by Wiszniewska *et al.*,[6] in Switzerland also reported no significantly difference in the prevalence of hypercholesterolemia in the leukoaraiosis and non-leukoaraiosis groups. However, this study did not use the Fazekas classification and only divided the research subjects into leukoaraiosis and control.

CONCLUSION

In conclusion, there is a correlation between the degree of leukoaraiosis and the serum triglyceride levels on post-ischemic stroke patients. However, there is no a correlation between the degree of leukoaraiosis and the serum cholesterol, LDL, and HDL levels. In addition, age is one of the risk factors for ischemic stroke.

ACKNOWLEDGEMENTS

Authors would like to thank our colleagues who have supported this study.

REFERENCES

1. Marek M, Horyniecki M, Frączek M, Kluczewska E. Leukoaraiosis new concepts and modern imaging. Pol J Radiol 2018; 83:e76–81. https://doi.org/10.5114/pjr.2018.74344
2. Ben Assayag E, Mijajlovic M, Shenhar S. Leukoaraiosis is a chronic atherosclerotic disease. ScientificWorldJournal 2012; 532141. https://doi.org/10.1100/2012/53214
3. Duan W, Pu Y, Liu H, Jing J, Pan Y, Zou X, Wang Y, *et al.* Association between leukoaraiosis and symptomatic intracranial large artery stenoses and occlusions: the Chinese Intracranial Atherosclerosis (CICAS) Study. Aging Dis 2018; 9(6): 1074-83. https://doi.org/10.14336/AD.2018.0118
4. Huo L, Chen P, Wang Z, Li X, Zhou J, Wang C, *et al.* Impact of leukoaraiosis severity on the association of outcomes of mechanical; thrombectomy for acute ischemic stroke: a systematic review and a meta-analysis. J Neurol 2020; 268:4108-16. https://doi.org/10.1007/s00415-020-10167-0
5. O'Sullivan M. Leukoaraiosis. Pract Neurol 2008; 8:26–38. http://dx.doi.org/10.1136/jnnp.2007.139428
6. Wiszniewska M, Devuyst G, Bogousslavsky J, Ghika J, Melle G. What is significance of leukoaraiosis in patients with acute ischemic stroke. Arch Neurol 2000; 57: 967-73. https://doi.org/10.1001/archneur.57.7.967
7. Chutinet A, Biffi A, Kanakis A, Fitzpatrick K, Furie K, Rost N. Severity of leukoaraiosis in large vessel atherosclerotic disease. Am J Neuroradiol 2012; 33(8):1591–5. https://doi.org/10.3174/ajnr.A3015
8. Conde J, Biffi A, Rahman R, Butler C, Massasa E, Sonni S. Hyperlipidemia and reduced white matter hyperintensity volume in patients with ischemic stroke. Stroke 2010;41(3):437-42. https://doi.org/10.1161/STROKEAHA.109.563502
9. Ke D, Zhou F, Liang H, Xu Y, Lou H. Hypertriglyceridemia is associated with reduced leukoaraiosis severity in patients with a small vessel stroke. Behav Neurol 2018;1361780. https://doi.org/10.1155/2018/1361780
10. Shi J, Hao K, Qi P, Xie X, Yang X, Dong M *et al.* Confirmation of the abnormal lipid metabolism as risk factor for the disease of leukoaraiosis. Saudi J Biol Sci 2017; 24(3):508-13. https://doi.org/10.1016/j.sjbs.2017.01.020
11. Goldstein JL, Brown M S. A century of cholesterol and coronaries: from plaques to genes to statins. Cell 2015; 161(1):161-72. https://doi.org/10/1016/j.cell.2015.01.036
12. Sastroasmoro S, Ismael S. Dasar-dasar metodologi penelitian klinis. 4th ed. Jakarta: Sagung Seto, 2011.
13. Kim W, MacFall J, Payne M. Classification of white matter lesions on magnetic resonance imaging in elderly persons. Biol Psychiatry 2008; 64(4):273-80. https://doi.org/10.1016/j.biopsych.2008.03.024

14. Nelson RH. Hiperlipidemia as a risk factor for cardiovascular disease. Prim Care 2013; 40(1):195-211. https://doi.org/10.1016/j.pop.2012.11.003
15. Reeves MJ, Bushnell CD, Howard G, *et al.* Sex differences in stroke: epidemiology, clinical presentation, medical care, and outcomes. Lancet Neurol 2008; 7(10): 915–26. https://doi.org/10.1016/S1474-4422(08)70193-5
16. Kelly-Hayes M. Influence of age and health behaviors on stroke risk: lessons from longitudinal studies. J Am Geriatr Soc 2010;58 (Suppl 2):S325-8. https://doi.org/10.1111/j.1532-5415.2010.02915.x
17. Boehme AK, Esenwa C, Elkin MS. Stroke risk factors, genetics, and prevention. Circ Res 2017; 120(3):472–95. https://doi.org/10.1161/CIRCRESAHA.116.308398
18. Christidi F, Tsiptsios D, Sousanidou A, Karamanidis S, Kitmeridou S, *et al.* The clinical utility of leukoaraiosis as a prognostic indicator in ischemic stroke patients. Neurol Int 2022; 14(4):952-80. https://doi.org/10.3390/neurolint14040076
19. Xue J, Wu Z, Gong S, Qin S, Gu A. High-dose atorvastatin improves vascular endothelial function in patients with leukoaraiosis. J Clin Lab Anal 2020; 34(3):e23081. https://doi.org/10/1002/jcla.23081
20. Vedala K, Nagabandi AK, Looney S, Bruno A. Factors associated with leukoaraiosis severity in acute stroke patients. J Stroke Cerebrovasc Dis 2019; 28(7):1897-1901. https://doi.org/10.1016/j.jstrokecerebrovasdis.2019.04.003
21. Park K, Yasuda N, Toyonaga S, Yamada SM, Nakabayashi N, Nakasato M, *et al.* Significant association between leukoaraiosis and metabolic syndrome in healthy subjects. Neurology 2007; 69(10):974–8. https://doi.org/10.1212/01.wnl.0000266562.54684.bf
22. Chen Y, Bian Y. Overview-research progress of leukoaraiosis. J Behav Brain Sci 2022; 12:599-26. https://doi.org/10.4236/jbbs.2022.1211036