Research Article

Correlation between Atherogenic Index of Plasma and Lipid Profile with Cognitive Function and Their Effect on Outcome in Ischemic Stroke Patients

Fasihah I. Fitri,* Muhammad Zulfikri

Department of Neurology Faculty of Medicine Universitas Sumatera Utara-Adam Malik General Hospital, Medan

*Corresponding author: fasihah.irfani@usu.ac.id
Received 13 March 2023; Accepted 25 July 2023
https://doi.org/10.23886/ejki.11.264.102

Abstract

Dyslipidemia is one of the main risk factors for both ischemic stroke and cognitive impairment. Atherogenic index of plasma (AIP) has been shown to correlate with mortality and clinical outcomes in stroke, but studies about its association with cognitive impairment in ischemic stroke is still limited. We aimed to determine the correlation between AIP and lipid profile and cognitive function and their effect on outcome in ischemic stroke patients. A cross-sectional study involving 50 ischemic stroke patients in the Haji Adam Malik General Hospital was conducted from August 2021 to March 2022. We measured the cholesterol level and calculated the AIP then divided them into 3 risk categories which were high (AIP>0.21); intermediate (AIP>0.11and ≤0.21) and low (≤0.11). We performed cognitive assessment and stroke outcome at the 7th day of stroke onset. Data analysis was conducted with Spearman correlation test. The subjects were predominantly male (60%) with median age of 55 (34-68) years. Most of the subjects had AIP level of high risk (54%) and were cognitively impaired (66%). There was no significant association between AIP and both global cognition and each cognitive domain. However, there were significant negative correlations between total cholesterol (r=-0.31, p=0.03) and LDL-C level (r=-0.30, p=0.03) and attention. There was also a significant negative correlation between cognitive function and stroke outcome (r=-0.61, p=0.01). Higher total cholesterol and LDL-C levels showed negative correlation with cognitive function, mainly attention. Poorer cognitive function correlated with worse outcome in ischemic stroke patients.

Keywords*: atherogenic index of plasma, cognitive function, lipid profile, clinical outcome.*

Korelasi Indeks Aterogenik Plasma dan Profil Lipid dengan Fungsi Kognitif dan Pengaruhnya terhadap Luaran Klinis Pasien Stroke Iskemik

Abstrak

Dislipidemia merupakan salah satu faktor risiko utama stroke iskemik dan gangguan kognitif. Indeks aterogenik plasma (IAP) berkorelasi dengan mortalitas dan luaran klinis stroke, tetapi penelitian mengenai hubungannya dengan gangguan kognitif pada stroke iskemik masih terbatas. Tujuan penelitian ini adalah menentukan korelasi antara IAP, profil lipid dengan fungsi kognitif dan pengaruhnya terhadap luaran klinis pada pasien stroke iskemik. Studi potong-lintang melibatkan 50 pasien stroke iskemik dilakukan di Rumah Sakit Umum Haji Adam Malik pada bulan Agustus 2021 - Maret 2022. Kadar kolesterol diukur dan IAP dihitung kemudian dibagi menjadi 3 kategori risiko yaitu tinggi (IAP>0,21), sedang (IAP>0,11 dan <0,21) dan rendah (IAP<0,11). Penilaian fungsi kognitif dan luaran klinis dilakukan pada hari ke-7 onset stroke. Data dianalisis dengan uji korelasi Spearman. Subjek didominasi laki-laki (60%) dengan rerata usia 55 (34-68) tahun. Sebagian besar subjek memiliki IAP risiko tinggi (54%) dan gangguan kognitif (66%). Tidak terdapat hubungan bermakna antara IAP dengan kognitif global dan masing-masing domain kognitif. Namun, terdapat korelasi negatif antara kolesterol total (r=-0,31, p=0,03) dan kadar LDL-C (r=-0,30, p=0,03) dan atensi. Terdapat korelasi negatif antara fungsi kognitif dan luaran klinis stroke (r=-0.61, p=0,01). Kadar kolesterol total dan K-LDL yang lebih tinggi menunjukkan korelasi negatif dengan fungsi kognitif, terutama atensi. Fungsi kognitif yang lebih buruk berkorelasi dengan luaran klinis lebih buruk pada pasien stroke iskemik.

Kata kunci*: indeks aterogenik plasma, fungsi kognitif, profil lipid, luaran klinis.*

Introduction

Stroke is the leading cause of disability and the second leading cause of death in developed countries after ischemic heart disease or the third largest cause of death if malignancy is included. Ischemic stroke is the most common type of stroke with an incidence of 300-500 per 100,000 population.[1] The prevalence of stroke in Indonesia in 2013 to 2018 increased from 7 to 10.9/mil.[2] Stroke is also the second most common cause of cognitive impairment that results in disability, increased mortality, and decreased quality of life for patients. Stroke can cause non-somatic symptoms such as cognitive impairment, known as vascular cognitive impairment that range from mild cognitive impairment to vascular dementia. Ischemic stroke patients have a higher risk of suffering from cognitive impairment.[3,4] Cognitive impairment can occur either immediately or as later complications after stroke onset.[5] There are several contributing factors for cognitive impairment in stroke.[6]

Previous studies showed that dyslipidemia play an important role as risk factors for both ischemic stroke and cognitive impairment[7] mainly by promoting the development of atherosclerosis of extracranial and intracranial blood vessels[8,9] A study in 2017 stated an increase in LDL-C levels and a decrease in HDL-C levels as risk factors for carotid artery atherosclerosis and coronary heart disease that can cause secondary complications of cognitive impairment.[10] Al Fawal et al[11] found that an increase in LDL-C levels and a decrease in HDL-C levels caused white matter abnormalities in stroke patients. In contrast, another study in 2020 stated that non-HDL cholesterol levels did not have a significant relationship with cognitive function in ischemic stroke patients with mild neurological deficits.[4] Study in 2021 showed cognitive impairment can affect the clinical outcome of stroke, so assessment of cognitive status at an early stage and identifying stroke risk factors are very important predictors of cognitive impairment.[12] Atherogenic index of plasma (AIP) is the logarithmically transformed ratio of molar concentrations of triglycerides to HDL-cholesterol and has a sensitivity to predict coronary heart disease and cardiovascular disease,[13,14] however studies about its association with cognitive impairment in ischemic stroke remains limited. This study aimed to determine the correlation between AIP and lipid profile and cognitive function and their effect on outcome in acute ischemic stroke patients.

Methods

Setting, Participants and Ethics

This was a cross sectional study involving 50 acute ischemic stroke patients treated at Adam Malik General Hospital Medan North Sumatra, Indonesia on August 2021 to March 2022 and recruited subjects using consecutive non-random sampling method. We included patients with a modified Rankin scale (mRS) score of 0-2 indicating mild stroke, had normal level of consciousness, and were able to speak, read and write in Bahasa Indonesia (Indonesian language) fluently. The exclusion criteria were patients with recurrent ischemic stroke, history of dementia before the onset of stroke, metabolic disease, delirium, depression or previous psychiatric disorders, heart disease and patients who were using antihyperlipidemic drugs before admission.

All patients were well informed about the nature of the study as well as the procedure and gave written informed consent before participating in the study. Information was clearly given to make it clear that the choice to give consent or not would not affect the treatment given. Participants remained anonymous by replacing their names with individual identifying numbers before the statistical procedures started. The study followed the ethics principles of the Declaration of Helsinki. Formal research protocol registration and ethical approval was obtained from the Faculty of Medicine Universitas Sumatera Utara Ethical Committee number 1088/KEP/USU/2021.

Measures

The lipid profile measured were total cholesterol, triglyceride, high density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) levels in blood. About 5 ml of venous blood samples were collected after an overnight fast (12 hours). The AIP values were calculated from logarithms (serum triglycerides/ serum HDL-C) and categorized based on the level of risk for cardiovascular diseases into: high (AIP>0.21); intermediate (AIP>0.11and ≤0.21) and low (≤0.11).[15] Cognitive function was assessed using Montreal Cognitive Assessment-Indonesian Version (MoCA-INA) at the 7th day of onset or at discharge if hospitalized for less than 7 days. The MoCA-INA has been developed and validated in Indonesia so that it can be used as a cognitive screening tool.[16,17] It assesses several cognitive domains which are visuospatial/executive, naming, memory, attention, language, abstraction, delayed recall and orientation (to time and place).

Visuospatial abilities are assessed using a clock-drawing task and a trail-making task. Attention, concentration and working memory are evaluated using a sustained attention task (target detection using tapping), a serial subtraction task and digits forward and backward. Its score range is 0-30, higher score indicates better cognitive performance, and a cut off of more than 26 is considered normal. The MoCA adds one point for those whose educational level is 12 or fewer years.[16,18] Demographic, clinical and radiologic variables were collected including: age, sex, marital status, education, employment, the presence of comorbidities including dyslipidemia and type 2 diabetes mellitus (T2DM), stroke type based on classification from the trial ORG 10172 in the treatment of acute stroke (TOAST), stroke severity and outcome using the National Institutes of Health Stroke Scale (NIHSS) score[19] and modified Rankin Scale (mRS)[20] score stroke type based on classification from the trial ORG 10172 in the treatment of acute stroke (TOAST).[21]

Statistical Analysis

Descriptive statistics were used to describe the median, mean and percentage. The Kolmogorov-Smirnov test was used to test for normality of the data. The Spearman correlation test was used to determine the correlation between AIP and lipid profile with global cognition and each cognitive domain as well as between the cognitive function and stroke outcome. The level of significance was set at $\alpha = 0.05$. All statistical procedures were performed with Statistical Package for the Social Sciences (SPSS).

Results

A total of 50 subjects were included in this study, consisted of 30 males (60%) and 20 females (40%). The median age was 55 (34-68) years. Most of the subjects had completed senior high school level of education (58%) and were self-employed (42%). The median MoCA-Ina score was 24 and more than half of the subjects had abnormal score (54%). All subjects had small vessel occlusion type of stroke based on TOAST classification. Only 14% of subjects presented with no comorbidities, either dyslipidemia or T2DM. The mean AIP value was 0.24±0.23 and most of the subjects had high risk based on the AIP value (54%). The characteristics of the subjects are shown in Table 1.

Using the Spearman correlation test, there were no correlations between AIP and global cognition nor which each of the cognitive domains. Regarding the correlation between lipid parameters and cognitive function, we found negative correlations between total cholesterol (r=-0.31, p=0.03) and LDL-C level (r=-0.30, p=0.03) and attention. Details on correlation between AIP, lipid profile and cognitive function can be seen in Table 2. We also found a negative correlation between cognitive function and NIHSS scores (and r=-0.61, p=0.01) as shown in Figure 1.

Tabel 1. Subject Characteristics

Characteristics	n (50)	%
Age (years) *	55 (34-68)	
34-45	11	22
46-57	23	46
58-69	16	32
Gender		
Male	30	60
Female	20	40
Educational Level		
Elementary and Junior high school	3	6
Senior high school	29	58
University	18	36
Occupation		
Self-employed	21	42
Government employees	10	20
Housewive and Unemployed	19	38
Moca-Ina scores*	24 (12-29)	
Normal	17	34
Abnormal	33	66
Cognitive Domains		
Visuospatial/executive	4 (1-5)	
Naming*	3 (1-3)	
Delayed recall *	3 (0-5)	
Attention *	5 (2-6)	
Language *	2 (0-3)	
Abstraction *	1 (0-2)	
Orientation *	6 (5-6)	
Lipid Profile,mg/dl		
Total cholesterol**	180.66 ± 49.97	
LDL-C**	123.92 ± 43.01	
Triglycerides*	134 (63-407)	
HDL-C*	36 (22-64)	
AIP**	0.24 ± 0.23	
Low risk	17	34
Moderate risk	6	12
High risk	27	54
Comorbidities		
No T2DM or dyslipidemia	7	14
Dyslipidemia	20	40
Dyslipidemia and T2DM	23	46

*Data is presented in the form of median and minimum-maximum values (data not normally distributed), ** Data is presented in the form of mean and standard deviation (normally distributed data).

Table 2. Correlations between AIP and Lipid Profile and Cognitive Domains

Characteristics	Global cognition	Visuospatial/ Executive	Naming	Delayed Recall	Attention	Language	Abstract thinking	Orientation
AIP	r=0.10 p=0.94	r=-0.10 p=0.48	r=0.18 p=0.23	r= -0.11 p=0.94	r=0.06 p=0.70	r=0.05 p=0.76	r=0.13 p=0.36	r=-0.79 p=0.59
Total cholesterol	r=-0.21 p=0.14	r= -0.21 p=0.14	r=0.11 p=0.46	r=-0.10 p=0.49	r=-0.31 p=0.03*	r=-0.20 p=0.17	r=0.01 p=0.97	r=-0.02 p=0.91
LDL-C	r=-0.19 p=0.18	r=-0.22 p=0.13	r=0.09 p=0.55	r=-0.10 p=0.50	r=-0.30 p=0.03*	r=-0.24 p=0.10	r=0.04 p=0.81	r=-0.02 p=0.90
Triglyceride	r -0.08 p=0.61	r=-0.17 p=0.24	r=0.10 p=0.51	r=-0.02 p=0.91	r=-0.03 p=0.86	r=0.02 p=0.88	r=0.03 p=0.86	r=-0.05 p=0.73
HDL-C	r=-0.07 p=0.62	r=-0.04 p=0.77	r=-0.08 p=0.56	r=0.04 p=0.76	r=-0.12 p=0.40	r=0.01 p=0.95	r= -0.12 p=0.41	r=0.11 p=0.44

Spearman correlation test, *p < 0.05 = significant
AIP; *atherogenic index of plasma*; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol

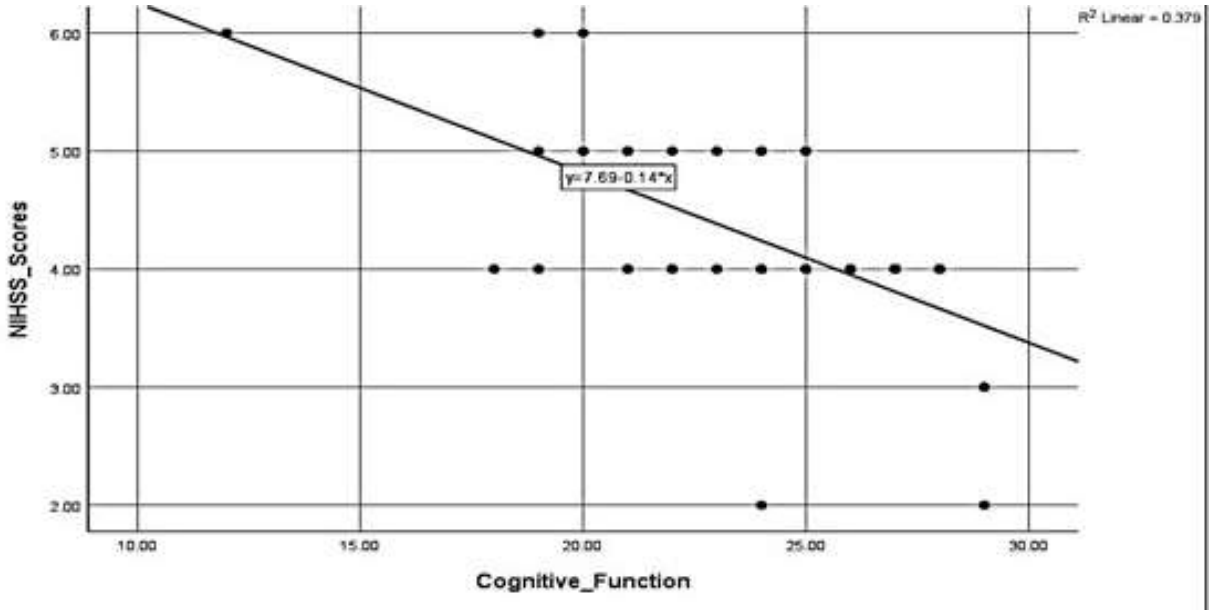

Figure 1. Correlation between Cognitive Function and NIHSS Scores

Discussion

This study characterized impairment across multiple cognitive domains during the acute phase of ischemic stroke and found that most of our subjects (54%) had abnormal cognitive function. Considering that we excluded patients with previous history of dementia and cognitive impairment before the stroke onset, our finding suggested that ischemic stroke was associated with cognitive dysfunction. This finding is consistent with a previous study conducted in 115 acute ischemic stroke patients in Jakarta which also found that as high as 70.4% subjects had cognitive impairment that was also assessed using MoCA-INA. Similar to our study, most of their subjects (30.4%) also had senior high school level of education.[4] Li et al[22] also found high prevalence of cognitive impairment (88.1%) at acute stage of stroke among these patients. Nys et al[23] found that cognitive impairment was common in the first weeks after stroke in 190 acute stroke patients, with executive and perceptual disorders were the most common domains affected. A recent systematic review about longitudinal effect of stroke cognition found that stroke was associated with an increased risk of cognitive decline and several factors related with this decline included sociodemographic status, health-related comorbidity, stroke history and clinical features.[3] Srithumsuk et al[5] found that the presence of cognitive impairment at baseline was

associated with cognitive decline after 3-year follow up. Cognitive impairment can occur immediately or as later complications after stroke onset, known as post stroke cognitive impairment (PSCI). The prevalence of PSCI is reported to be quite high and varies from various studies across different countries and depends on the diagnostic criteria used. Several risk factors for the occurrence of PSCI include demographic factors such as age, education and occupation, as well as vascular risk factors and factors related to stroke characteristics such as the location and volume of the lesion. The mechanisms underlying PSCI include vascular cognitive impairment due to neuroanatomical lesions in strategic areas and cerebral microbleeds as a result of small vessel disease as well as combined pathology of AD and stroke.[24,25]

Our study did not find any significant correlation between AIP and cognitive function, both global and each cognitive domain. This is in contrast to a previous study in which there was a significant relationship between AIP and cognition in the older adults with heart failure.[26] This might be due to the different population and vascular risk factor characteristics. The previous study included older subjects (most were aged 60-64 years) and most presented with one or more chronic cardiovascular complications, hypertension, hypercholesterolemia and diabetes mellitus, which related more to the presence of metabolic syndrome. AIP is associated significantly with metabolic syndrome which itself was correlated with an increased risk of developing cognitive impairment.[27,28]

Of all the lipid parameters we only found that higher levels of total cholesterol and LDL-C were correlated significantly with worse attention. There has been an extensive amount of studies looking at the association between lipid profiles and cognitive function across different population with various results. Comparable to our findings, a cross-sectional study in China involving 1,762 participants showed that only those with high levels of total cholesterol and LDL-C, but not HDL and TG, were at risk for cognitive impairment, and the authors suggested that the association depended on gender and age.[29] Lysandra et al showed no significant relationship between non-HDL cholesterol levels with cognitive function in ischemic stroke patients with mild neurological deficits.[4] Srithumsuk et al[5] found that dyslipidemia together with higher educational level were protective factors for cognitive decline after stroke during the 3-year follow-up.

In contrast, several previous studies found negative association between lipid parameters and cognitive function in various populations as mentioned in a recent review by Appleton et al[10] Our previous study also found an inverse relationship between lipid parameters and cognitive function in T2DM patients.[30] The association between lipid profile and stroke, cognitive impairment and subsequent dementia remain complex and not yet fully understood. High levels of LDL-C and low levels of HDL-C are risk factors for carotid atherosclerosis and coronary heart diseases that may contribute to cognitive impairment due to impaired cerebral hypoperfusion or embolism. Lipid plasma is also related to oxidative stress and lipid peroxidation which have an important role in the development of vascular dementia. The brain is also particularly susceptible to oxidative lipid damage due to its high content of fatty acids.[10] Increase in LDL-C levels and a decrease in HDL-C levels caused white matter abnormalities in stroke patients which also a factor in developing cognitive dysfunction.[11] High serum LDL-C and total cholesterol also increase the deposition of amyloid and activity of β-secretase which also contribute to the development of AD.[29]

This study found that lower NIHSS score was significantly correlated with better cognitive function. This is in line with a previous study by Li et al[22] that showed early cognitive impairment was associated with higher risk of disability and poor daily living activity among Chinese acute ischemic stroke patients. The plausible mechanisms between cognitive dysfunction after stroke and poor functional outcomes may partly be explained by the neuroanatomical lesions. Large infarct volume and high vascular territorial involvement, as well as subcortical infarcts are associated with worsening cognitive function.[6] There might also be an overlap in the pathomechanism underlying the cognitive changes between degenerative and vascular components that could not be separated exclusively in our study. Major limitation of our study is due to the inability to exclude other confounding factors that might also contribute to cognitive impairment and stroke outcome, such as advanced age, socioeconomic status, other vascular risk factors or comorbidities such as hypertension and lifestyle factors such as smoking.

Conclusion

Higher total cholesterol and LDL-C levels showed negative correlation with cognitive function, mainly attention. Poorer cognitive function

correlated with worse outcome in ischemic stroke patients. This findings highlight the importance to address dyslipidaemia as factors contributing to poor outcome in acute ischemic stroke patients. Further longitudinal studies are needed to clarify the association between lipid parameters and cognition.

References

1. Fitri FI. Stroke Iskemik pada lanjut usia. In: Turana IY, Fitri FI, eds. Buku ajar neurogeriatrik. Edition I. Kelompok studi neurogeriatrik Perhimpunan Dokter Spesialis saraf Indonesia, 2021. Indonesian.
2. RISKESDAS. Riset Kesehatan Dasar. Badan Penelitian dan Pengembangan Kesehatan Kementerian Kesehatan R.I tahun 2018. Available from: https://labdata.litbang.kemkes.go.id/ images/download/laporan/RKD/2018/Laporan_Nasional_RKD2018_FINAL.pdf. Indonesian.
3. Tang EY, Amiesimaka O, Harrison SL, Green E, Price C, Robinson L, et al. Longitudinal effect of stroke on cognition: a systematic review. J Am Heart Assoc. 2018;7:1-9. doi: 10.1161/JAHA.117.006443.
4. Lysandra A, Wreksoatmodjo BR, Widayanti JR. Hubungan kolesterol non-HDL terhadap fungsi kognitif pada pasien stroke iskemik dengan defisit neurologis ringan. Majalah Kedokteran Neurosains Perhimpunan Dokter Spesialis Saraf Indonesia. 2020;37:1-7. Indonesian. doi: 10.52386/neurona.v37i3.163.
5. Srithumsuk W, Kabayama M, Gondo Y, Masui Y, Akagi Y, Klinpudtan N, et al. The importance of stroke as a risk factor of cognitive decline in community dwelling older and oldest peoples: the SONIC study. BMC geriatrics. 2020;20:1-10. doi: 10.1186/s12877-020-1423-5.
6. Dichgans M, Leys D. Vascular cognitive impairment. CIRCRE. 2017;120:573-91. doi: 10.1161/CIRCRESAHA.116.308426.
7. Putri H, Rambe AS, Surbakti KP. Hubungan dan besar risiko kadar lipid serum terhadap gangguan fungsi kognitif pada pasien stroke iskemik dan non stroke [tugas akhir]. Medan: Universitas Sumatera Utara; 2016. Available from https://repositori.usu.ac.id/handle/123456789/42518. Indonesian.
8. Boehme AK, Esenwa C, Elkind MS. Stroke risk factors, genetics, and prevention. CIRCRE. 2017;120:472-95. doi: 10.1161/CIRCRESAHA. 116.308398.
9. Wu J, Chen S, Liu L, Gao X, Zhou Y, Wang C, et al. Non-high-density lipoprotein cholesterol vs low-density lipoprotein cholesterol as a risk factor for ischemic stroke: a result from the Kailuan study. Neurol Res. 2013;35:505–11. doi: 10.1179/1743132813Y.0000000206.
10. Appleton JP, Scutt P, Sprigg N, Bath PM. Hypercholesterolaemia and vascular dementia. Clin Sci. 2017;131:1561-78. doi: 10.1042/CS20160382.
11. Menet R, Bernard M, El-Ali A. Hyperlipidemia in stroke pathobiology and therapy: Insights and perspectives. Front Physiol. 2018;9:488. doi: 10.3389/fphys.2018.00488.
12. Al-Fawal B, Ibrahim A, Elhamed MA. Post-stroke dementia: frequency, predictors, and health impact. Egypt J Neurol Psychiatry Neurosurg. 2021;57. doi: 10.1186/s41983-021-00270-y.
13. Soška V, Jarkovský J, Ravčuková B, Tichý L, Fajkusová L, Freiberger T. The logarithm of the triglyceride/HDL-cholesterol ratio is related to the history of cardiovascular disease in patients with familial hypercholesterolemia. Clin Biochem. 2012;45:96–100. doi: 10.1016/j.clinbiochem.2011.11.001.
14. Sujatha R, Kavitha S. Atherogenic indices in stroke patients: a retrospective study. Iran J Neurol. 2017;16:78-82. PMID: 28761629, PMCID: PMC5526781.
15. Fernández-Macías JC, Ochoa-Martínez AC, Varela-Silva JA, Pérez-Maldonado IN. Atherogenic index of plasma: novel predictive biomarker for cardiovascular illnesses. Arch Med Res. 2019;50:285-94. doi: 10.1016/j.arcmed.2019.08.009.
16. Husein N, Silvia L, Yetty R, Herqutanto. Uji validitas dan reabilitas montreal cognitive assessment versi Indonesia (MoCA-Ina) untuk skrining gangguan fungsi kognitif. Neurona Neuro Sains. 2010;27:15-22.
17. Fitri FI, Rambe AS, Ong PA, Gultom IM. Correlation between The Indonesian Versions of Montreal Cognitive Assessment (MoCA-INA) and Visual Cognitive Assessment Test (VCAT-INA) as cognitive screening tools. IJHHS. 2022;6:47-54. doi: 10.31344/ijhhs.v6i1.376.
18. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005;53:695-9. doi: 10.1111/j.1532-5415.2005.53221.x.
19. Chalos V, van der Ende NA, Lingsma HF, Mulder MJ, Venema E, Dijkland SA, et al, National Institutes of Health Stroke Scale: an alternative primary outcome measure for trials of acute treatment for ischemic stroke. Stroke. 2020;51:282-90. doi: 10.1161/STROKEAHA.119.026791.
20. Banks JL, Marotta CA. Outcomes validity and reliability of the modified rankin scale: implications for stroke clinical trials: a literature review and synthesis. Stroke. 2007;38:1091-6. doi: 10.1161/01.STR.0000258355.23810.c6
21. Adams Jr HP, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in acute stroke treatment. Stroke. 1993:24:35-41. doi: 10.1161/01.STR.24.1.35.
22. Li J, Wang J, Wu B, Xu H, Wu X, Zhou L, et al. Association between early cognitive impairment and midterm functional outcomes among chinese acute ischemic stroke patients: a longitudinal study. Front Neurol. 2020;11:20. doi: 10.3389/fneur.2020.00020.
23. Nys GM, van Zandvoort MJ, de Kort PL, Jansen BP, de Haan EH, Kappelle LJ. Cognitive disorders in acute stroke: prevalence and clinical determinants. Cerebrovasc Dis. 2007;23:408–16. doi: 10.1159/000101464.

24. Sun JH, Tan L, Yu JY. Post-stroke cognitive impairment: epidemiology, mechanisms and management. Ann Transl Med. 2014;2:80. doi: 10.3978/j.issn.2305-5839.2014.08.05.
25. Hu GC, Chen YM. Post-stroke dementia: epidemiology, mechanisms and management. IJGE . 2017;12:210-14. doi: 10.1016/j.ijge.2017.07.004.
26. Arifin H, Fitri FI, Nasution IK. Hubungan indeks aterogenik plasma dan fraksi ejeksi dengan fungsi kognitif pada pasien lanjut usia dengan gagal jantung {tugas akhir}. Medan: Universitas Sumatera Utara; 2021. Available from https://repositori.usu.ac.id/bitstream/handle/123456789/38021.
27. Li YW, Kao TW, Chang PK, Chen WL, Wu LW. Atherogenic index of plasma as predictors for metabolic syndrome, hypertension and diabetes mellitus in Taiwan citizens: a 9-year longitudinal study. Sci Rep. 2021;11:1–8. doi: 10.1038/s41598-021-89307-z.
28. Yaffe K, Weston AL, Blackwell T, Krueger KA. The metabolic syndrome and development of cognitive impairment among older women. Arch Neurol. 2009;66:324–8. doi: 10.1001/archneurol.2008.566.
29. Zhao B, Shang S, Li P, Chen C, Dang L, Jiang Y, et al. The gender- and age- dependent relationships between serum lipids and cognitive impairment: a cross-sectional study in a rural area of Xi'an, China. Lipids Health Dis. 2019;518:4. doi: 10.1186/s12944-018-0956-5.
30. Simanjuntak P, Fitri FI, Rambe AS. Hubungan profil lipid dengan fungsi kognitif pada pasien diabetes melitus tipe 2 {tugas akhir}. Medan: Universitas Sumatera Utara; 2021. Available from https://repositori.usu.ac.id/bitstream/handle/123456789/36531/187041124.