Pharmacology and Clinical Pharmacy Research
Volume 8 No. 1 April 2023
ISSN:2527-7322 | e-ISSN: 2614-0020
doi: 10.15416/pcpr.v4i3.38919

Correlation of Polypharmacy and Comorbidity with NIHSS Status in Ischemic Stroke Patient

Firdha A. Wardhani[1,2]
[1]Faculty of Pharmacy, Gadjah Mada University. Yogyakarta - Indonesia
[2]Faculty of Pharmacy, dr. Soebandi University. Jember District, East Java - Indonesia

Abstract

Drug-related problems are a common problem among stroke patients due to comorbidities resulting from the complex management of stroke treatment leading to polypharmacy management. Studies show that 90% of stroke patients have drug-related problems (DRPs). However, there is limited information on the impact of comorbidities as risk factors for DRP prevalence and unfavorable prognosis in patients with ischemic stroke. This study aimed to determine the risk factors for DRP and clinical outcomes as modifiable comorbidities in ischemic stroke patients admitted to a tertiary hospital between January 2020 and October 2021 were indeed significant influences. The study was conducted retrospectively using a cross-sectional analysis of patient's medical records. The study found no significant association between the presence of comorbidities and polypharmacy in patients with the incidence of DRP, although we found that the DRPs occurrence was found more in a patient with comorbidities and polypharmacy. Diabetes mellitus was found to have a significant association with no improvement in NIHSS scores in ischemic stroke patients. We found that diabetes mellitus patient had an increased risk of non-improvement NIHSS score 2,987 times compared to patients without diabetes mellitus. The second increased risk was the presence of comorbid hypertension (OR 1.352), the third was the occurrence of polypharmacy (OR 1,175), and the fourth was dyslipidemia (OR 1.138).

Keywords: Comorbid, DRPs, ischemic stroke, NIHSS

Introduction

Stroke is defined as a sudden onset of focal neurological deficit that persists for at least 24 hours. Stroke can be classified as ischemic or hemorrhagic and is diagnosed by a doctor after a patient has undergone a CT (Computed Tomography) scan or MRI (Magnetic Resonance Imaging).

Age, sex, race, family history; and comorbidities such as hypertension, atrial fibrillation, cardiovascular disease, diabetes, dyslipidemia, obesity; and other factors like smoking, alcohol, postmenopausal hormone therapy, and lifestyle factors such as diet are a few of stroke risk factors.[1–3]

Stroke is not only the major cause of death, but also one of the leading causes of disability worldwide.[4] Studies have shown that most ischemic stroke patients have cognitive and functional abnormalities, of which 60.44% have cognitive impairment and 37.37% have moderate-to-complete category-dependent functional impairment.[5]

Corresponding Author: Firdha Aprillia Wardhani, Master of Clinical Pharmacy, Faculty of Pharmacy, Gadjah Mada University. Yogyakarta - Indonesia. Email : firdhaaprillia@mail.ugm.ac.id
Received: 15 April 2022 **Revised**: 8 August 2022 **Published:** 5 April 2023

Ischemic stroke is a complex disease affected by many factors. Stroke patients often receive multiple medications in their treatment management.[6,7] According to research, each additional drug increases a patient's risk of DRPs (Drug-Related Problems) by 7%.[3] Therefore, stroke patients are much more likely to develop DRPs than patients with other diseases that do not require multidrug therapy. Approximately 90.2% of stroke patients had DRPs, with 2,015 DRPs per patient.[8]

However, there was limited information regarding the effect of comorbidity and polypharmacy as both a risk factor for DRPs prevalence and worse outcomes in an ischemic stroke patient. This research was conducted to see whether modifiable comorbidities and polypharmacy indeed had a significant impact as a risk factor for DRPs and clinical outcomes, using NIHSS (National Institution of Health Stroke Scales) as a sensitive parameter to detect the clinical outcome in hospitalized ischemic stroke patients.

Methods

This study was retrospectively conducted with a cross-sectional analysis of ischemic stroke patients admitted to a tertiary hospital in Yogyakarta, Indonesia from January 2020 to October 2021. Using medical records as a data source, we included adult patients (> 18 years old) diagnosed with ischemic stroke, and NIHSS analyzed both when patient admitted and discharged. Subjects would be excluded if they had length of stay less than 2 days or had incompletion of medical record. The data extracted from the medical records were age, gender, length of hospital stay, medication regimen, route of administration, laboratory data, and the clinical status of patients as subjective data.

DRP was analyzed using local guidelines from PERDOSSI (Perhipunan Dokter Saraf Indonesia-Indonesian Neurologist Association) and PNPK (Pedoman Nasional Pelayanan Kedokteran-National Guidelines for Medical Services), as well as international guidelines widely used by the AHA (American Heart Association), ASA (American Stroke Association), ESC (European Society of Cardiology), and the NICE (National Institute for Health and Care Excellence). Drug interactions were checked and analyzed using Lexicomp's Drug Interaction Checker, with at least risk modified D with alternative therapy as patient's management, or X with a contraindication. Patients were categorized as improved based on a reduced NIHSS score of at least 2 points, and unimproved if the discharged NIHSS score was reduced by less than 2 points, stay at the same value as admission, or death.

Statistical Analysis

Mean ± SD were used to described the continuous variables and percentages were used to count the categorical variables. Demographic characteristics, such as gender and age, were compared between comorbidity groups using the Chi-square test. To discover the association between comorbidities with both DRPs prevalence and clinical outcome using NIHSS, we performed multivariate binary logistic regression. The feasibility of the model is tested using Hosmer and Lemeshow test.

Results and Discussion

A total of 111 ischemic stroke patients were included. The characteristic of patients with comorbidities is summarized in Table 1. We found no significant difference in the age group between patients with comorbidities diabetes mellitus and dyslipidemia group; and gender with comorbidities dyslipidemia and hypertension. There was unsignificant difference in the age group with diabetes and dyslipidemia; sex with dyslipidemia and

hypertension. Notably, hypertensives were older (51 vs 23, p<0,05), and more women than men were diabetic (29 vs 13, p<0,05).

This result is following research that has been done, which states that the prevalence of hypertension is significantly associated with older age 9. Based on the National Diabetes Statistics Report by the CDC (Centers for Disease Control and Prevention) and data from the International Diabetic Federation, shows that the prevalence of diabetes mellitus in men is greater than in women.[10,11] Meanwhile, data by Riskesdas (Riset Kesehatan Dasar-Basic Health Research) Indonesia shows that in 2018 the prevalence of diabetes mellitus in women was higher than in men (1.78% vs. 1.21%), which has increased since 2013 (1.7% vs. 1.4%). In the last 5 years, the prevalence of diabetes mellitus in women has shown an increase, while the prevalence in men has decreased.[12]

As shown in Table 1, the average age of the participants was 62.11 years old, that were considered elderly patients. The previous studies have also shown that age is one of the risk factors for ischemic stroke prevalence.[13-14] The presence of comorbidities in patients is a risk factor for ischemic stroke, meanwhile the most common aging change in older adult is stiffness of the arteries, causing hypertension. Total cholesterol and LDL (Low-Density Lipoprotein) showed an increasing trend with age. Those two factors combined produce an increased risk in the occurrence of ischemic stroke in older adult.[15,16]
The average length of stay was 7 days, 47.7% of patients had improved NIHSS scores at discharge, and the remainder (52.3%) were classified as not improving. Patients were categorized as improved based on a reduced NIHSS score of at least 2 points, and unimproved if the discharged NIHSS score was reduced by less than 2 points, stay at the same value as admission, or death.

Drug-Related Problems
The occurrence of DRPs in 111 patients observed was 88,3%, with the most common DRPs observed were "patient needs additional therapy" with 74,8%, followed by "dosage too low" (48,6%), "ineffective drug therapy" (33,3%), and "adverse drug reaction" (9,9%) respectively. This finding is supported by previous research, in which "patients need additional drugs" and "dosages too low" were the most commonly found DRPs in patient.[17]

Conditions where patients require additional therapy are mostly found in patients with diabetes mellitus with hyperglycemia that has not been controlled until the patient is discharged from the hospital. While the condition where the patient received less effective therapy was when the patient

Table 1. Demographic Characteristic of Patients

Characteristic	Overall	Diabetes Mellitus (n=42)	*P*	Dyslipidemia (n=43)	*P*	Hypertension (n=74)	*P*
Age group	62,11 ± 14,048 (29-92)						
Geriatric	66 (59,5)	29	0,160	27	0,711	51	**0,008**
Non-geriatric	45 (40,5)	13		16		23	
Gender							
Woman	60 (54,1)	29	**0,023**	24	0,920	41	0,840
Man	51 (45,9)	13		19		33	

We bold the value that statistically significant
We presented the variables as n (%) in nominal data; mean ± SD in continuous data

received antihypertensive therapy within 24 hours, when the patient's neurological condition was not yet stable. The condition in which the patient receives drug therapy with a dose that is too low is in a condition where the patient receives antihypertensives in a stable condition, with blood pressure until discharge from the hospital is still above the target of therapy. And lastly, the type of unwanted effect due to therapy that is most commonly found in patients is the occurrence of liver injury due to drugs.

Clinical Outcome

We found that 53 (47,7%) patients in this study had a reduced NIHSS score of at least 2 points and were categorized as improved patients when discharged, and 58 (52,3%) patients were categorized as unimproved. (Table 2).

DRPs that are often found in patients with diabetes mellitus in this study are hyperglycemic conditions of patients who have not been controlled, either using insulin or oral antidiabetic. Based on the PERKENI (Perhimpunan Endokrinologi Indonesia-Indonesian Endocrinologist Association) Insulin Therapy Guidelines, ischemic stroke conditions are included in non-diabetic emergencies, where insulin is recommended.[18]

Initiation of insulin can be done using prandial insulin 5 – 10 IU/8 hours or a combination of basal and prandial based on the recommendations of the ADA (American Diabetic Association) and ACCE (American Association of Clinical Endocrinology), with dose adjustment depending on the patient's blood glucose.[19,20]

The presence of high blood pressure, with the ineffective therapy; or the presence of a decrease in blood pressure in patients without an indication of a decrease in blood pressure, are the types of DRPs found in patients with hypertension. Although lowering blood pressure is recommended in post-acute stroke patients, excessive blood pressure reduction is associated with worsening NIHSS scores.

The study showed that patients with very high SBP (Systolic Blood Pressure) (SBP 211 mmHg) or low SBP 110 mmHg, were significantly associated with worsening NIHSS scores ($p=0.003$).[21] Based on PNPK Stroke, AHA/ASA, and ESO, blood pressure reduction is recommended immediately if there are comorbidities such as acute coronary syndrome, acute heart failure, aortic dissection, intracerebral hemorrhage, or preeclampsia or eclampsia. However, if there are no comorbidities, then the blood pressure is reduced by about 15% in the first 24 hours if the patient's blood pressure is > 220/120 mmHg.[22–24]

Table 2. Association between Comorbidities and the Incidence of DRPs

Comorbidity	DRPs (n=98)	Without DRPs (n=13)	P value
Polypharmacy	90 (81)	12 (10,9)	0,913
Diabetes mellitus	38 (34,2)	4 (3,6)	0,498
Hypertension	64 (57,6)	10 (9)	0,410
Dyslipidemia	37 (33,3)	6 (5,4)	0,544

We bold the value that statistically significant
We presented the variables as n (%) in nominal data; mean ± SD in continuous data

ESO explains that optimal blood pressure is different in patients with ischemic stroke who do not meet the eligibility for reperfusion therapy, where lowering blood pressure can reduce the risk of hemorrhagic transformation and edema, but high blood pressure has benefits in maintaining cerebral blood flow when the autoregulation process is imbalanced with the presence of ischemic stroke. Thus, both European (ESO) and American (AHA/ASA) guidelines do not recommend reducing blood pressure in ischemic stroke patients for at least 24 hours, unless the patient's blood pressure is extreme (> 220/120 mmHg), and certain comorbidities have been described. previously.[24]

Inadequate lowering lipid profile in dyslipidemia patients, especially LDL-c is a problem found in patients with dyslipidemia. According to the AHA/ASA, one of the clinical conditions of ASCVD (Atherosclerotic Cardiovascular Disease) is stroke, and in patients aged 75 years it is recommended to use a high-intensity statin with a target for LDL-c reduction of 50%, or use a moderate-intensity statin if high-intensity therapy is contraindicated or produces significant undesirable effects. In patients >75 years of age, initiation of moderate-high intensity statins is recommended.[23]

Polypharmacy was found in 102 patients (91,9%), with the average medicine used in each patient being 9,98 medicines. This founding is aligned with our hypothesis that ischemic stroke patients have more chance to be treated in polypharmacy management, and one of the causes is the existence of comorbidities that are often followed or diagnosed before the acute stroke onset. It was also proven with the similar proportion between polypharmacy and comorbidities occurrence in this study, that show comorbidities are also found in most patients, to be exact in 83,8% of patients.

This study found no significant relationship between the presence of comorbidities in patients with the incidence of DRPs. However as shown in Table 2, the occurrence of DRPs was found more in a patient with polypharmacy and comorbidities. A study with a larger population is needed to define a more significant relationship between polypharmacy and comorbidities, with DRPs occurrence in an ischemic stroke patient.

Correlation of Comorbidities and Polypharmacy with NIHSS Improvement

In this study, it was found that all comorbidities contributed to the occurrence of non-improved outcomes, which was indicated by no decrease in the NIHSS score. A significant risk was found in the presence of comorbid diabetes mellitus in these patients. Diabetes mellitus was found to have a significant association with no improvement in NIHSS scores in ischemic stroke patients. In diabetes mellitus patients, there is an increased risk of non-improvement NIHSS score 2,987 times compared to patients without diabetes mellitus. The second increased risk was the presence of comorbid hypertension (OR 1.361, 95% CI 0.598-3.095, p-value = 0.463), and the third was dyslipidemia (OR 1.125, 95% CI 0.505-2.502, p-value 0.774). (Table 3).

This is reciprocal with a previous study, in which patients with hyperglycemic diabetes were significantly associated with increased NIHSS scores. The literature states that hyperglycemia during acute stroke, both in patients with or without a history of diabetes mellitus, is significantly associated with higher mortality, a longer length of stay, and reduced chances of recovery.[25].

Another study also stated that persistent hyperglycemic conditions were significantly correlated with increased mortality at 30 days in patients with ischemic stroke.[26]

Table 3. Correlation between Comorbidities with NIHSS Improvement

Comorbidity	Improvement (n=53)	No improvement (n=58)	P value	OR (95% CI)
Diabetes mellitus	13 (11,7)	29 (26,1)	**0,009**	2,960 (1,304-6,720)
Hypertension	33 (29,7)	41 (38,9)	0,474	1,352 (0,593-3,082)
Dyslipidemia	19 (17,1)	24 (21,6)	0,754	1,138 (0,508-2,548)

Statistically significant values are given in bold
Variables are presented as n (%) in nominal data; mean ± SD in continuous data

Table 4. Correlation between Polypharmacy with NIHSS Improvement

Condition	Improvement (n=53)	No improvement (n=58)	P value	OR (95% CI)
Polypharmacy	48 (43,2)	54 (48,6)	0,825	1,175 (0,280 4,929)

Statistically significant values are given in bold
Variables are presented as n (%) in nominal data; mean ± SD in continuous data

Hyperglycemia patients had a higher NIHSS (14.9 vs 7.8, p=0.000), higher mortality (65.9 vs 5, p<0.001), and a longer LoS (12.5 vs.3,p<0.001) compared to normoglycemia.[27] The presence of high glucose exposure in hyperglycemic patients associated with mitochondrial dysfunction, inflammation, and oxidative stress that triggers endothelial apoptosis, and has the potential to increase infarct volume, decrease recanalization, and increase the risk of ischemic stroke transformation into hemorrhagic stroke.[26]

The association between comorbid hypertension and NIHSS scores is also consistent with studies showing that blood pressure correlates with clinical outcomes in ischemic stroke patients. The study found that higher post-stroke blood pressure in patients (blood pressure 48 hours post-onset), was significantly associated with decreased neurologic improvement and increased neurological and functional deterioration.[28] The presence of hypertension in these patients was also associated with a significantly increased risk of stroke recurrence.[29,30]

.

The association between comorbid dyslipidemia and clinical outcome in ischemic stroke patients is supported by several studies showing that LDL-c levels in dyslipidemia patients have an association with an increase in NIHSS scores. The study found that an increase in LDL-c was significantly correlated with an increase in NIHSS (p=0.033), and when compared with patients with low LDL-c values, there was an increased risk of an increase in stroke severity based on NIHSS data, as much as 2.9-fold (95% CI 1.48-5.74)31. The study found a correlation between LDL and HDL ratios and patients' NIHSS outcomes, where the LDL and HDL ratios could predict 31% of patients' NIHSS outcomes32. Another study found that the presence of LDL-c levels independently predicted NIHSS values (OR 1.537, 95% CI 0.134-2.878, p=0.042), with the mean LDL-c levels in patients with mortality outcomes being significantly higher than in patients without mortality (1.04 vs 0.88, p=0.017).[33]

This study has limitations, including the study design in this study which was cross-sectional which identified an association but not a causal relationship. Although we found no significant association, polypharmacy also contributed to the risk of unimproved NIHSS score in a patient with ischemic stroke (OR

1,175) (Table 4). Studies have found that the increase in drug number has been associated with negative outcomes in health, including a more frequent hospitalization and DRPs occurrence.[34–37] However, it should be noted that both unnecessary drugs and patient needs for additional therapy, are included in DRPs. When indeed polypharmacy increased the risk of DRPs occurrence, and as known, the DRPs occurrence contributed to the unimproved clinical outcome; reducing the necessary medication is not an alternative. If treatment is needed by the patient, then reducing the amount of medication received by the patient is not an option, in order to reduce polypharmacy. Polypharmacy does not always mean that the therapy received by the patient is irrational, but clinical pharmacy needs to ensure that the polypharmacy received by the patient is rational and does not cause problems, which we refer to as DRPs.

Clinical pharmacists need to be more vigilant when finding patients with polypharmacy and comorbidities. Supervision and monitoring of therapy also need to be more stringent, to ensure that DRPs do not occur in these patients. A combined approach with skill integration from different health care professionals, especially from both clinicians and clinical pharmacies are needed to address medical complexity in an ischemic stroke patient, and eventually brought a positive effect on the patient's health outcomes.

Conclusion

This study found no significant relationship between the presence of comorbidities in patients with the incidence of DRPs, but all comorbidities contributed to the occurrence of non-improved outcomes, which was indicated by no decrease in the NIHSS score. A significant risk was found in the presence of comorbid diabetes mellitus in these patients. Diabetes mellitus was found to have a significant association with no improvement in NIHSS scores in ischemic stroke patients.

Acknowledgment

None.

Funding

This research is included in the research funded by LPDP.

Conflict of Interest

None declared.

References

1. Khaku AS, Tadi P. Cerebrovascular Disease. In: StatPearls. StatPearls Publishing; 2021. Accessed July 20, 2021. *http://www.ncbi.nlm.nih.gov/books/NBK430927/*
2. Vos T, Lim SS, Abbafati C, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *The Lancet*. 2020;396(10258):1204-1222. doi:10.1016/S0140-6736(20)30925-9
3. Viswam S, Nair G, Thomas B, Shivashankar V. A Prospective Observational Study on Polypharmacy in Geriatrics at A Private Corporate Hospital. *Journal of Applied Pharmaceutical Science*. 2017;7:162-167. doi:10.7324/JAPS.2017.71024
4. Permatasari N. Perbandingan Stroke Non Hemoragik dengan Gangguan Motorik Pasien Memiliki Faktor Resiko Diabetes Melitus dan Hipertensi. *Jurnal Ilmiah Kesehatan Sandi Husada*. 2020;11(1):298-304.
5. Nahrowi NS, Ong PA, Adam A. Cognitive and Functional Outcome of Patients with Ischemic Stroke at Dr. Hasan Sadikin Hospital Bandung. *Althea Medical Journal*. 2018;5(2):82-86.
6. DiPiro JT, Yee GC, Posey M, Haines ST, Nolin TD, Ellingrod V, eds. Stroke. *In:*

Pharmacotherapy: A Pathophysiologic Approach, 11e. 11th ed. McGraw-Hill Education; 2020:38. Accessed March 10, 2021. https://accesspharmacy.mhmedical.com/book.aspx?bookID=2577
7. Kose E, Maruyama R, Okazoe S, Hayashi H. Impact of Polypharmacy on the Rehabilitation Outcome of Japanese Stroke Patients in the Convalescent Rehabilitation Ward. *Journal of Aging Research*. 2016;2016:1-8. 5
8. Kanagala VS, Anusha A, Rao BS, Challa SR, Nalla KS, Gadde RS. A study of medication-related problems in stroke patients: A need for pharmaceutical care. *Journal of Pharmacy Practice and Research*. 2016;5(3):222-225.
9. Shukuri A, Tewelde T, Shaweno T. Prevalence of old age hypertension and associated factors among older adults in rural Ethiopia. *IBPC*. 2019;12:23-31.
10. CDC. National Diabetes Statistics Report 2020. *Estimates of diabetes and its burden in the United States*. Published online 2020:32.
11. IDF. Diabetic Prevalencies : Fact and Figures. IDF : About Diabetes. Published 2021. Accessed April 1, 2022. *https://idf.org/aboutdiabetes/what-is-diabetes/facts-figures.html*
12. Kemennterian Kesehatan Republik Indonesia. 2020. *Tetap Produktif, Cegah dan Atasi Diabetes Mellitus.* Infodatin. 2020;20(1):6.
13. Kementerian Kesehatan Republik Indonesia. *Penyelenggaraan Pelayanan Kesehatan Lanjut Usia di Pusat Kesehatan Masyarakat.* Vol 1663; 2015:7.
14. Yousufuddin M, Young N. Aging and ischemic stroke. *Aging (Albany NY).* 2019;11(9):2542-2544.
15. Feng L, Nian S, Tong Z, et al. Age-related trends in lipid levels: a large-scale cross-sectional study of the general Chinese population. BMJ Open. 2020;10(3):e034226.
16. Roy-O'Reilly M, McCullough LD. Age and Sex Are Critical Factors in Ischemic Stroke Pathology. *Endocrinology.* 2018;159(8):3120-3131.
17. Westberg SM, Derr SK, Weinhandl ED, et al. Drug Therapy Problems Identified by Pharmacists Through Comprehensive Medication Management Following Hospital Discharge. *Journal of Pharmacy Technology.* 2017;33(3):96-107.
18. PERKENI. *Petunjuk Praktis Terapi Insulin pada Pasien Diabetes Mellitus*. PB PERKENI. 2021;2:70.
19. American Diabetes Association. 2. *Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2021*. Diabetes Care. 2021;44(Suppl 1):S15-S33. doi:10.2337/dc21-S002
20. Garber AJ, Handelsman Y, Grunberger G, et al. Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm – 2020 Executive Summary. *Endocrine Practice*. 2020;26(1):107-139.
21. Liu CH, Wei YC, Lin JR, et al. Initial blood pressure is associated with stroke severity and is predictive of admission cost and one-year outcome in different stroke subtypes: a SRICHS registry study. *BMC Neurology*. 2016;16:27.
22. Kemennterian Kesehatan Republik Indonesia. *Pedoman Nasional Pelayanan Kedokteran Tata Laksana Stroke.* Vol 342.; 2019:1-82.
23. Powers WJ, Rabinstein AA, Ackerson T, et al. *Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart*

Association/American Stroke Association. Stroke. 2019;50(12).
24. Sandset EC, Anderson CS, Bath PM, et al. European Stroke Organisation (ESO) guidelines on blood pressure management in acute ischaemic stroke and intracerebral haemorrhage. *European Stroke Journal.* Published online May 11, 2021:239698732110121.
25. Levetan CS. Effect of hyperglycemia on stroke outcomes. *Endocrine Practice.* 2014;10 Suppl 2:34-39.
26. Mi D, Wang P, Yang B, Pu Y, Yang Z, Liu L. Correlation of hyperglycemia with mortality after acute ischemic stroke. *Therapeutic Advances in Neurological Disorders.* 2018;11.
27. Al-Weshahy A, El-Sherif R, Selim KAAW, Heikal A. Short term outcome of patients with hyperglycemia and acute stroke. *The Egyptian Journal of Critical Care Medicine*. 2017;5(3):93-98.
28. Ishitsuka K, Kamouchi M, Hata J, et al. High Blood Pressure After Acute Ischemic Stroke Is Associated With Poor Clinical Outcomes. *Hypertension.* 2014;63(1):54-60.
29. Ding M, Fratiglioni L, Johnell K, et al. Atrial fibrillation, antithrombotic treatment, and cognitive aging: A population-based study. *Neurology*. 2018;91(19):e1732-e1740.
30. Rouch L, Xia F, Bahorik A, Olgin J, Yaffe K. Atrial Fibrillation is Associated With Greater Risk of Dementia in Older Veterans. *The American Journal of Geriatric Psychiatry*. 2021;29(11):1092-1098.
31. Zhang A, Deng W, Zhang B, et al. Association of lipid profiles with severity and outcome of acute ischemic stroke in patients with and without chronic kidney disease. *Neurological Sciences.*2021;42(6):2371-2378.
32. Elberta F, Ghofir A, Rusdi I. LDL/HDL ratio association with out-patient NIHSS score and Dyslipidemic Drug intake status as Metabolic Syndrome Criteria of ischemic stroke patients at RSUP Dr. Sardjito, Yogyakarta. *Journal of the Medical Sciences (Berkala Ilmu Kedokteran)*. 2018;50(1).
33. Yao T, Long Q, Li J, et al. Small dense low-density lipoprotein cholesterol is strongly associated with NIHSS score and intracranial arterial calcification in acute ischemic stroke subjects. *Scientific Reports*.2020;10(1):7645.
34. Appleton SC, Abel GA, Payne RA. Cardiovascular polypharmacy is not associated with unplanned hospitalisation: evidence from a retrospective cohort study. *BMC Family Practice.* 2014;15:58.
35. von Lueder TG, Atar D. Comorbidities and polypharmacy. *Heart Failure Clinics.*2014;10(2):367-372.
36. Scott IA, Hilmer SN, Reeve E, et al. Reducing inappropriate polypharmacy: the process of deprescribing. *JAMA Internal Medicine.* 2015;175(5):827-834.
37. Onder G, van der Cammen TJM, Petrovic M, Somers A, Rajkumar C. Strategies to reduce the risk of iatrogenic illness in complex older adults. *Age Ageing*. 2013;42(3):284-291.