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Modifiable Comorbidity as a Risk Factor for DRPs and Unimproved NIHSS Score in Ischemic Stroke Patients

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ABSTRAK

Drug-related problems are problems that are often encountered in stroke patients because of the complex management of stroke therapy due to comorbidities. Research shows that 90% of stroke patients experience drug-related problems (DRPs). However, there was limited information regarding the effect of comorbidity 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 indeed had a significant impact as a risk factor for DRPs and clinical outcomes in hospitalized ischemic stroke patients at a tertiary hospital in Indonesia during January 2020-October 2021. This study was conducted retrospectively using cross-sectional analysis, with the subject being the patient's medical record. This study found no significant relationship between the presence of comorbidities in patients with the incidence of DRPs. Diabetes mellitus was found to have a significant association with no improvement in NIHSS scores in ischemic stroke patients. In patients with diabetes mellitus, 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).
Kata kunci: Comorbid; DRPs; ischemic stroke; NIHSS

INTRODUCTION

Stroke is a condition where there is a focal neurological deficit suddenly and can last for at least 24 hours. Stroke can be classified as an ischemic or hemorrhagic stroke, which is diagnosed by the doctor after the patient undergoes a CT scan or MRI. Risk factors for stroke include age, gender, race, family history, hypertension, atrial fibrillation, cardiovascular disease, diabetes, dyslipidemia, smoking, alcohol, post-menopausal hormone therapy, lifestyle factors such as obesity and diet, and others[1–3].

Apart from being the leading cause of death in the world [4], stroke is also one of the leading causes of disability in the world. Research shows that most post-ischemic stroke patients experience cognitive and functional abnormalities, where 60.44% of patients experience cognitive impairment and 37.37% of patients experience functional disability in the category of moderate to complete dependency [5].

Ischemic stroke is a complex disease and is influenced by many things. So often stroke patients receive therapy with polypharmacy in the management of therapy [6,7]. Based on research, each additional drug in patients can increase the risk of DRP by 7% [3]. So, the potential for DRPs to occur in stroke patients is much higher than in patients with other diseases that do not require polypharmacy. Approximately 90.2% of stroke patients had DRPs, of which each patient had 2,015 DRPs [8]. Another study found 67.7% of ischemic stroke patients had DRPs with a total identified DRPs of 271 DRPs with an average of 1.8 DRPs per patient [9]. However, there was limited information regarding the effect of comorbidity 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 indeed had a significant impact as a risk factor for DRPs and clinical outcomes in hospitalized ischemic stroke patients.

METHODS

This research was conducted retrospectively, using cross-sectional analysis, involving hospitalized ischemic stroke patients at a tertiary hospital in Indonesia from January 2020-October 2021. We used the medical record

as the data source, and included ischemic stroke patients with ages above 18 years old, with a length of stay of more than 2 days. Data extracted from the medical record were age, sex, length of stay, medication regimentation, route of administration, laboratory data, and patient's clinical condition as the subjective data.

DRPs were analyzed using both local guidelines from PERDOSSI and PNPK, and widely used international guidelines from the American Heart Association, American Stroke Association, European Society of Cardiology, and the 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

Continuous variables were described as mean ± SD and categorical variables were described by counts with percentages. Demographic characteristics, including gender and age, were compared between comorbidity groups using the Chi-square test. To investigate the association between comorbidities with both DRPs prevalence and clinical outcome using NIHSS, we performed the Chi-square test. Multivariate binary logistic regression was used to analyze the odd ratio between comorbidity and clinical outcome. The feasibility of the model is tested using Hosmer and Lemeshow test.

RESULTS AND DISCUSSION

Demographic Characteristic

Patients with ischemic stroke were selected based on inclusion and exclusion criteria. The characteristic of patients with comorbidities is summarized in Table I. There was no significant difference in the age group between patients with comorbidities diabetes mellitus and dyslipidemia group; and gender with comorbidities dyslipidemia and hypertension. It was noticeable that patients with hypertension consisted more geriatric significantly (51 vs 23, $p<0,05$) and there was more woman than a man in a patient with diabetes mellitus (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 [10]. Based on the National Diabetes Statistics Report by the CDC and data from the International Diabetic Federation, shows that the prevalence of diabetes mellitus in men is greater than in women [11,12]. Meanwhile, data by Riskesdas 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[13].

As seen in Table I, the average age of the participant was 62,11 years old, which was considered to be a geriatric patient [14], and previous studies also showed that age is one of the risk factors of ischemic stroke prevalence [15]. The average length of stay was 7 days, and 47,7% of patient had improved NIHSS score when discharged, and the rest (52,3%) was categorized as unimproved.

Drug-Related Problems

The prevalence 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 [16].

Although there are studies that state that treatment using polypharmacy is associated with a decrease in clinical outcomes in patients[17–20], not giving therapy when the patient is indicated is not a good reason.

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 II. Association between comorbidities with the incidence of DRPs and clinical outcome

Outcomes	Diabetes Mellitus (n=42)	*p-value*	Dyslipidemia (n=43)	*p-value*	Hypertension (n=74)	*p-value*
DRPs occurrence	38 (90,5)	0,763	37 (86)	0,779	64 (86,5)	0,538
NIHSS status unimprovement	29 (69)	**0,010**	24 (55,8)	0,687	41 (55,4)	0,460

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

Association of comorbidities with DRPs occurrence and clinical outcome

This study found an unsignificant relationship between the presence of comorbidities in patients with the incidence of DRPs. 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 Insulin Therapy Guidelines, ischemic stroke conditions are included in non-diabetic emergencies, where insulin is recommended[21]. 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 and ACCE, with dose adjustment depending on the patient's blood glucose[22,23].

The presence of high blood pressure, with the wrong 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 (SBP 211 mmHg) or low SBP 110 mmHg, were significantly associated with worsening NIHSS scores (p=0.003)[24]. 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, ICH, 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 [25–27].

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 [27].

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 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 [26].

Meanwhile, analysis using the Chi-square method showed that there was unsignificant relationship between comorbidity and un-improving NIHSS status in an ischemic stroke patient, except in patients with comorbid diabetes mellitus (*p-value* = 0.010). This is consistent 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

Table III. Association between comorbidities and 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**	2,987 (1,321-6,757)
Hypertension	33 (29,7)	41 (38,9)	0,463	1,361 (0,598-3,095)
Dyslipidemia	19 (17,1)	24 (21,6)	0,774	1,125 (0,505-2,502)

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

significantly associated with higher mortality, a longer length of stay, and reduced chances of recovery[28]. Another study also stated that persistent hyperglycemic conditions were significantly correlated with increased mortality at 30 days in patients with ischemic stroke[29]. Patients with hyperglycemia had a significantly 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[30].

Although this study did not find a significant relationship between the presence of comorbid hypertension and dyslipidemia with the patient's NIHSS status, many studies have found an increased risk of worsening clinical outcomes in patients with comorbid hypertension and dyslipidemia. The presence of hypertension and dyslipidemia in the patients was associated with a significantly increased risk of stroke recurrence [31,32].

NIHSS unimprovement in patients with comorbidity

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 patients with diabetes mellitus, 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).

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. [33].

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)[34]. 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 outcomes[35]. 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). LDL-c is a strong atherogenic factor and can penetrate the arterial walls and cause oxidative stress, which in turn increases the severity of infarction[36].

Larger scale studies are needed to determine the significance of comorbidities on NIHSS status in patients with ischemic stroke. However, with the limitations that exist in this study, this study found that the presence of comorbid diabetes mellitus is a comorbidity that

has a significant risk of reducing patient clinical outcomes, as indicated by no improvement in the NIHSS status of ischemic stroke patients.

CONCLUSION

This study found unsignificant relationship between the presence of comorbidities in patients with the incidence of DRPs and 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 with increased risk of 2,987-fold.

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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.
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.
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.
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. *J Res Pharm Pract*. 2016;5(3):222-225.
9. Hohmann C, Neumann-Haefelin T, Klotz JM, Freidank A, Radziwill R. Drug-related problems in patients with ischemic stroke in hospital. *Int J Clin Pharm*. 2012;34(6):828-831.
10. 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.
11. CDC. National Diabetes Statistics Report 2020. Estimates of diabetes and its burden in the United States. Published online 2020:32.
12. 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
13. Kemenkes. Tetap Produktif, Cegah dan Atasi Diabetes Mellitus. *Infodatin*. 2020;20(1):6.
14. Kemenkes. *PENYELENGGARAAN PELAYANAN KESEHATAN LANJUT USIA DI PUSAT KESEHATAN MASYARAKAT*. Vol 1663.; 2015:7.
15. Yousufuddin M, Young N. Aging and ischemic stroke. *Aging (Albany NY)*. 2019;11(9):2542-2544.
16. Westberg SM, Derr SK, Weinhandl ED, et al. Drug Therapy Problems Identified by Pharmacists Through Comprehensive Medication Management Following Hospital Discharge. *J Pharm Technol*. 2017;33(3):96-107.

17. Appleton SC, Abel GA, Payne RA. Cardiovascular polypharmacy is not associated with unplanned hospitalisation: evidence from a retrospective cohort study. *BMC Fam Pract*. 2014;15:58.
18. von Lueder TG, Atar D. Comorbidities and polypharmacy. *Heart Fail Clin*. 2014;10(2):367-372.
19. Scott IA, Hilmer SN, Reeve E, et al. Reducing inappropriate polypharmacy: the process of deprescribing. *JAMA Intern Med*. 2015;175(5):827-834.
20. 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.
21. PERKENI. Petunjuk Praktis Terapi Insulin pada Pasien Diabetes Mellitus. *PB PERKENI*. 2021;2:70.
22. American Diabetes Association. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2021. *Diabetes Care*. 2021;44(Suppl 1):S15-S33.
23. 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.
24. 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 Neurol*. 2016;16:27.
25. Kemenkes. *PEDOMAN NASIONAL PELAYANAN KEDOKTERAN TATA LAKSANA STROKE*. Vol 342.; 2019:1-82.
26. 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).
27. 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.
28. Levetan CS. Effect of hyperglycemia on stroke outcomes. *Endocr Pract*. 2014;10 Suppl 2:34-39. doi:10.4158/ep.10.s2.34
29. 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.
30. 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.
31. 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.
32. Rouch L, Xia F, Bahorik A, Olgin J, Yaffe K. Atrial Fibrillation is Associated With Greater Risk of Dementia in Older Veterans. *Am J Geriatr Psychiatry*. 2021;29(11):1092-1098.
33. 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.
34. 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. *Neurol Sci*. 2021;42(6):2371-2378. doi:10.1007/s10072-020-04791-x
35. 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).
36. 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. *Sci Rep*. 2020;10(1):7645. doi:10.1038/s41598-020-64715-9