ACADEMIC HOSPITAL JOURNAL

Volume 4, No. 1, March 2022

ISSN 2615-6253 (ONLINE)
ISSN 2615-6245 (PRINT)

Hypertension as Risk Factor of Poor Functional Outcome in First-Ever Ischemic Stroke Patients

Siti Aisyah[1], Astuti Prodjohardjono[2], Abdul Gofir[2], Probosuseno Probosuseno[3], Noor Alia Susianti[5,6], Sri Sutarni[2], Ismail Setyopranoto[2]

[1]Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia
[2]Department of Neurology, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia
[3]Department of Internal Medicine, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia
[5]Neurology Research Office, Department of Neurology, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia
[6]PPDS, Department of Neurology, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia

*Correspondency: saffiati@gmail.com

Submitted: January Reviewed: February-March Publish: March 2022

Abstract

Background: Survival rate of ischemic stroke has been improving which increases long-term disability in consequences. Global Burden of Disease (GBD) 2017 shows stroke as the third most common cause of morbidity. Hypertension is the most common risk factor for ischemic stroke incidence and affecting long-term functional outcome. Therefore, hypertension control in ischemic stroke is expected to improve functional outcome and quality of life. Therefore, this study was conducted to know the role of hypertension as risk factor of poor functional outcome in first-ever ischemic stroke patients.

Methods: Study was conducted by observational retrospective cohort from May 2018 until April 2019 in 7 hospitals in Special Region of Yogyakarta. Functional outcome of first-ever ischemic stroke patients was assessed by physician at day 30 by using Barthel Index. Bivariate analysis was analyzed by using Chi-Square with 95% CI and *p*-value <0.05 indicated statistical significance.

Results: Based on the study, there were increased risk for having dependent functional outcome in hypertension (RR=1.1, 95% CI=0.7-1.7), diabetes mellitus (RR=1.0, 95% CI=0.7-1.5) but these results were not statistically significant (p>0.05).

Conclusion: From the study it can be concluded that hypertension is one of the most common risk factors of stroke but hypertension has no role in predicting functional outcome. However, hypertension increases risk for having poor functional outcome in ischemic stroke patients.

Keywords: *Ischemic Stroke, Hypertension, Risk Factor, Poor Functional Outcome, Barthel Index*

1. Introduction

Stroke is characterized by neurological deficit attributed to an acute focal injury of the central nervous system which divided into ischemic and hemorrhagic stroke. There were 5.5 million of death due to stroke and more than half of them were having ischemic stroke diseases.[1,2] Stroke prevalence in Indonesia has reached 12.1 per mil.[3] On the other hand, stroke prevalence and incidence may increase as life expectancy gets higher. It is proven by Special Region Yogyakarta as the province in Indonesia with highest life expectancy and placed as the second highest stroke prevalence in Indonesia.[3,4]

Although mortality caused by stroke can be decreased by early stroke detection and advanced therapies, stroke disability still cannot be eliminated. It is shown by Global Burden of Disease (GBD) 2017 that stroke placed as the third most common cause of morbidity globally. In Indonesia, at 12,9%, stroke is leading cause of death after coronary heart disease.[5] Disability caused by stroke prolongs medical care and rehabilitation makes economic burdens for patients and their family. Activity daily living is one of the most important components of quality of life in elderly which can be limited due to disability. Barthel Index evaluates functional outcome in terms of dependency when performing daily life activity. It has been widely use in clinical practice as it is one of the simplest tool with adequate validity to assess functional outcome.[6,7]

Disability caused by stroke can be predicted and prevented by early detection of stroke risk factors. Hypertension is the most common risk factors for ischemic stroke.[8] In Yogyakarta, among 13,605 total subjects, 197 stroke incidences were recorded (1.4%) and most of them were having hypertension.[9] Previous evidences show hypertension as one of the risk factors that may affect its functional outcome.[10] But it is still debatable because the study conducted by Nakibuuka *et al.,* (2015) and Kusumaningsih *et al.*, (2017) show contradictory result that hypertension is not associated with stroke functional outcome.[11,12]

Consequently, control hypertension in ischemic stroke patients can decrease long-term poor functional outcome. This will impact to better patients' and families' quality of life. Therefore, information about the ability of hypertension in predicting stroke functional outcome is very important. The controversial results open opportunity for further research about the role of hypertension in predicting stroke functional outcome.

2. Materials and Methods

Research design

This research is an observational retrospective cohort study conducted from February until November 2019 by accessing patients' medical reports of first-ever ischemic stroke patients who were hospitalized Dr. Sardjito General Hospital, Hardjolukito Central Air Force Hospital, UGM Academic Hospital, Rajawali Citra Hospital Bantul, Bethesda Hospital, Panti Rapih Hospital, Panembahan Senopati Hospital from May 2018 until April 2019. Patients' functional outcome data were obtained from physicians' examination during

the follow up at 30 days after stroke onset using Barthel Index (BI) and classified as independent (BI score ≥ 85) and non-independent (BI score <85).[6] The inclusion criteria in this study were: (1) adult patients (26-65 years old), (2) patients diagnosed with first-ever ischemic stroke, (3) no prior history of significant disability, (4) *compos mentis* or fully alert, and (5) getting pharmacotherapy which suitable with stroke guideline. Meanwhile, the exclusion criteria in this study were: (1) patients' data were incomplete, (2) patients with history of organic CNS damage (e.g trauma, malignancies, CNS infections), or history of serious infection (e.g hepatitis, HIV), and (3) patients with disease that can influence activity daily living, such as congestive heart failure, atrial fibrillation, coronary arterial disease, chronic renal failure, chronic obstructive pulmonary disease, and bronchial asthma.

Proportional values in both groups were taken based on the study conducted by Kusumaningsih *et al.,* (2017), which included proportion of effect in exposed group as 0.7 and proportion of effect in non-exposed group as 0.4 with value of 95% confidence interval (CI) and power value of 80%. Subjects needed for each group was 40.7 ≈ 41, therefore total subjects needed for both groups were 82 subjects.

Statistical analysis

Data statistical used IBM SPSS Statistics® version 24 computer software. Bivariate analysis of categorical data used Chi-Square. Bivariate analysis of numerical data used T-test; or else, Mann-Whitney test was used. This research used 95% CI and *p*-value <0.05 indicated statistical significance

Ethical Clearance

All ethical considerations in this study were approved and supervised by Medical and Health Research Ethics Committee of Faculty of Medicine, Public Health and Nursing Universitas Gadjah Mada (EC No. KE/FK/0682/EC/2020). The authors declared that there are no conflicts of interests throughout the study.

3. Results

Patients' baseline characteristics assessed in this research consisted of demographic characteristics, risk factors, and functional outcome. This research assessed age and sex as demographic characteristics. Hypertension and diabetes mellitus risk factor were also assessed in this research. The functional outcome was assessed using BI and classified as dependent (score <85) and independent (score ≥85). The result for each characteristic is presented in Table 1.

Table 1. Baseline characteristics

	n	%	Median (Q1-Q3)
Demographic characteristics			
Age (year)			58 (52-61)
Sex			
Male	50	59.5	
Female	34	40.5	
Risk factors			
Hypertension			
Yes	58	69.0	
No	26	31.0	
Diabetes Mellitus			
Yes	25	29.8	
No	59	70.2	
Functional outcome			
Barthel Index			
Dependent	49	58.3	
Independent	35	41.7	

Characteristic homogeneity between hypertension and non-hypertension group was analyzed prior to the study (Table 2). There was no significant difference between the two groups ($p>0.05$). This finding means the two groups had similar characteristics.

Table 2. Data homogeneity

	Hypertension		Non-hypertension		RR (95% CI)	*p*
	n	%	n	%		
Demographic characteristics						
Age (year) *	58.0 (52.0-61.0)		57.5 (52.0-61.7)		-	0.9
Sex**						
Male	34	68.0	16	32.0	0.9	0.8
Female	24	70.6	10	29.4	(0.7-1.3)	
Risk factors						
Diabetes Mellitus**						
Yes	19	76.0	6	24.0	1.2	0.4
No	39	66.1	20	33.9	(0.9-1.5)	

*Mann-Whitney test (median (Q1-Q3)), **Chi-squared test, statistically significant if $p<0.05$

Table 3 shows there were no significant relations between all variables to functional outcome measured by BI ($p>0.05$). Thus, hypertension risk factor, diabetic risk factor, sex, and age have no role in predicting 30 days functional outcome after first-ever ischemic stroke. However, there were increased risk of dependency in older, female, hypertensive, and diabetic ischemic stroke patients.

Table 3. Bivariate analysis

	Dependent outcome		Independent outcome		RR (95% CI)	*p*
	n	%	n	%		
Demographic characteristics						
Age (year)*	58.0 (38.0-64.0)		57.0 (40.0-64.0)		-	0.5
Sex**						
Male	25	50.0	25	50.0	0.7	0.06
Female	24	70.6	10	29.4	(0.5-1.0)	
Risk factors						
Hypertension**						
Yes	35	60.3	23	39.7	1.1	0.7
No	14	53.8	12	46.2	(0.7-1.7)	
Diabetes Mellitus**						
Yes	15	60.0	10	40.0	1.0	0.8
No	34	57.6	25	42.4	(0.7-1.5)	

***** Mann-Whitney test (median (minimum-maximum)), ******Chi-squared test, statistically significant if $p<0.05$

4. Discussion

Poor functional outcome associated with age is caused by oxidative stress and reactive oxygen species (ROS) through aging which decreases bioactivity of nitric oxide (NO). Less NO leads to inability for the arteries to vasodilate and therefore impair cerebral blood flow during stroke.[13] Bindawas *et al.*, (2017), showed that older adults have less functional outcome improvement after stroke with mean age of 59 years old.[14] It is also showed in this research that dependent functional outcome in ischemic stroke patients have median age of 58 years old, with youngest age was 38 years old and oldest age was 64 years old.

Stroke prevalence in Indonesia was higher in males compared to females which corresponds to this research result.[3] The relationship of higher stroke prevalence in males is because of other risk factors that occur in males such as high systolic blood pressure and biologically, males have atherosclerotic phenotype that is more prone to rupture.[3,15,16] Less percentage of female suggested to be caused by the presence of estrogen that has role as protective factor to cardiovascular system.[17] However, females have higher dependency rate (70.6%) because they have greater age onset compare to males which was shown by increased incidence of stroke in females after 85 years old.[18] Greater post-stroke depression also can be seen in females which impair stroke recovery, so the functional outcome in females are poorer than their male counterparts.[19]

In Indonesia, the two factors that were most associated with stroke are hypertension and diabetes mellitus.[11] Hypertension, as one of the most risk factors was found 69.0% of all patients in this research. Yudiarto *et al.*, (2014)

also found that hypertension is one of the most common risk factor for ischemic stroke.[8] Banerjee *et al.*, (2017) explained that hypertension promotes to hypertrophy, thickening, arterial stiffness and dysfunction of arterial wall that leading to atherosclerosis formation.[20] Meanwhile, there were 29.8% of ischemic stroke patients with diabetes. Diabetes mellitus increases risk for having stroke through vascular dysfunction caused by inactivation of NO which caused by hyperglycemia induced accumulation of ROS.[21,22]

Although there was no significant role of hypertensive status to predict dependency in ischemic stroke patients, the risk for having dependent functional outcome after stroke in hypertensive patients increased by 1.1 times. In hypertensive ischemic stroke patients, there would be cerebral blood flow disturbance after stroke and worsening of stroke through atherosclerosis-thrombosis formation due to functional hyperemia, cerebrovascular, and endothelial dysregulation caused by persistent high blood pressure. Functional hyperemia is the regulation of cerebral vessels to vasodilate towards activated lobe. Vessels remodeling and hypertrophy in hypertension results in reduced vascular lumen and increased vascular resistance which leads to lack of CBF during stroke. Furthermore, high pressure of CBF leads to edema due to increase of vascular permeability in hypertension.[23]

Other vascular risk factor accompanying hypertension may have significant role in predicting stroke functional outcome. Oh *et al.,* (2014) showed similar result that high blood pressure alone is not a significant predictor for ischemic stroke functional outcome. On the other hand, metabolic syndrome (MetS) which based on The National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATP III) defined by having three or more of the following constellation of vascular risk factors: central obesity, elevated triglycerides, diminished high-density lipoprotein (HDL cholesterol), increased blood pressure, and elevated fasting glucose, can predict functional outcome in ischemic stroke patients. Metabolic abnormalities in MetS impairs fibrinolytic and pro-inflammatory activities and causes endothelial dysfunction. These states aggravate ischemic injury and disrupt arterial recanalization of atherothrombotic occlusion.[24]

5. Conclusion

This study showed that hypertension is one of the most common risk factors of stroke but has no role in predicting ischemic stroke functional outcome. However, hypertension increases risk for having poor functional outcome in ischemic stroke patients. It is suggested for clinicians that early detection and control of blood pressure in hypertension are still necessary to prevent ischemic stroke disease and poor functional outcome. Performing stroke rehabilitation such as physiotherapy as soon as possible is also essential to pursue delay of functional recovery. For families and communities, it is crucial to prevent hypertension by performing healthy lifestyle, early detection, control of

hypertension, and control management of blood pressure in ischemic stroke disease.

6. Acknowledgment

The authors would like to thank Department of Neurology, Universitas Gadjah Mada for the help during the study; Kol. Kes. dr. Wahyu Wihartono, M.Kes, Sp.S as the neurologist in Hardjolukito Central Air Force Hospital; dr. Farida Niken Astari Nugraha Hati, M.Sc., Sp.S and dr. Fajar Maskuri, M.Sc., Sp.S as the neurologists in UGM Academic Hospital; dr. Setyaningsih, Sp.S as the neurologist in Rajawali Citra Bantul Hospital; Prof. dr. Harsono, Sp.S(K), dr. Laksmi Asanti, Sp.S(K), FAAN, dr. Sugianto, Sp.S, M.Kes, Ph.D, dr. Kriswanto Widyo, Sp.S, Dr. dr. Rizaldy T. Pinzon, Sp.S, M.Kes, and dr. Yohan Budi Hartanto, M.Sc., Sp.S as neurologist in Bethesda Hospital; dr. Esdras Ardi P, Sp.S, M.Sc, dr. Mchael Agus Prasetyo,Sp.S., M.Si, Med, dr. Djoko Rijanto D., Sp.S, dr. Baruno Adi C, Sp.S, and dr. Tommy Rachmat Setyawan,Sp.S, FINS as neurologist in Panti Rapih Hospital; dr. Intan Rahayu, Sp.S, dr. Sherlyta T., Sp.S, and dr. Rita Fitriani, Sp.S as neurologists in Panembahan Senopati Bantul Hospital.

REFERENCES

1. Feigin VL, Krishnamurthi R V, Parmar P, Norrving B, Mensah GA, Bennett DA, *et al.* Update on the Global Burden of Ischemic and Hemorrhagic Stroke in 1990-2013: The GBD 2013 Study. *Neuroepidemiology*. 2015/10/28. 2015;45(3):161–76. doi:10.1159/000441085
2. Metrics GH. Erratum: Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017 (The Lancet (2018). *Lancet*. 2019;393(10190):e44. doi:10.1016/S0140-6736(19)31047-5
3. Kementerian Kesehatan RI Badan Penelitian dan Pengembangan. Hasil Utama Riset Kesehatan Dasar [Internet]. *Kementrian Kesehatan Republik Indonesia*. 2018. p. 1–100. Available from:http://www.depkes.go.id/resources/download/info-terkini/hasil-riskesdas-2018.pdf
4. Dinas Kesehatan D.I.Yogyakarta. Profil Kesehatan Provinsi Daerah Istimewa Yogyakarta Tahun 2017 [Internet]. *Dinas Kesehatan D.I.Yogyakarta*. 2017. Available from:http://www.depkes.go.id/resources/download/profil/PROFIL_KES_PROVINSI_2017/14_DIY_2017.pdf
5. Kemenkes RI. Penyakit Jantung Penyebab Kematian Tertinggi, Kemenkes Ingatkan CERDIK [Internet]. 2017. Available from:https://www.kemkes.go.id/article/view/17073100005/penyakit-jantung-penyebab-kematian-tertinggi-kemenkes-ingatkan-cerdik-.html
6. Rajsic S, Gothe H, Borba HH, Sroczynski G, Vujicic J, Toell T, *et al.* Economic burden of stroke: a systematic review on post-stroke care. *Eur J Heal Econ*. 2019 Feb 16;20(1):107–34. doi:10.1007/s10198-018-0984-0
7. Schulc E, Pallauf M, Mueller G,

Wildbahner T, Them C. Is the Barthel Index an Adequate Assessment Tool for Identifying a Risk Group in Elderly People Living at Home? *Int J Nurs Clin Pract*. 2015;2(1). doi:10.15344/2394-4978/2015/140

8. Yudiarto F, Machfoed M, Darwin A, Ong A, Karyana M, Siswanto. Indonesia Stroke Registry (S12.003) [Internet]. Vol. 82, *Neurology*. 2014. p. S12.003. Available from:http://n.neurology.org/content/82/10_Supplement/S12.003.abstract
9. Setyopranoto I, Bayuangga HF, Panggabean AS, Alifaningdyah S, Lazuardi L, Dewi FST, *et al.* Prevalence of stroke and associated risk factors in sleman district of Yogyakarta Special Region, Indonesia. *Stroke Res Treat*. 2019;2019. doi:10.1155/2019/2642458
10. Ishitsuka K, Kamouchi M, Hata J, Fukuda K, Matsuo R, Kuroda J, *et al.* High Blood Pressure After Acute Ischemic Stroke Is Associated With Poor Clinical Outcomes. *Hypertension*. 2014 Jan;63(1):54–60. doi:10.1161/HYPERTENSIONAHA.113.02189
11. Kusumaningsih W, Rachmayanti S, Werdhani RA. Relationship between risk factors and activities of daily living using modified Shah Barthel Index in stroke patients. *J Phys Conf Ser*. 2017;884(1). doi:10.1088/1742-6596/884/1/012151
12. Nakibuuka J, Sajatovic M, Nankabirwa J, Ssendikadiwa C, Furlan AJ, Katabira E, *et al.* Early mortality and functional outcome after acute stroke in Uganda: prospective study with 30 day follow-up. *Springerplus*. 2015 Dec 25;4(1):450. doi:10.1186/s40064-015-1252-8
13. El Assar M, Angulo J, Vallejo S, Peiró C, Sánchez-Ferrer CF, Rodríguez-Mañas L. Mechanisms Involved in the Aging-Induced Vascular Dysfunction. *Front Physiol*. 2012;3. doi:10.3389/fphys.2012.00132
14. Bindawas SM, Vennu V, Mawajdeh H, Alhaidary H. Functional outcomes by age after inpatient stroke rehabilitation in Saudi Arabia. *Clin Interv Aging*. 2017 Oct;Volume 12:1791–7. doi:10.2147/CIA.S145402
15. Wang Y, Dai Y, Zheng J, Xie Y, Guo R, Guo X, *et al.* Sex difference in the incidence of stroke and its corresponding influence factors: results from a follow-up 8.4 years of rural China hypertensive prospective cohort study. *Lipids Health Dis*. 2019 Dec 25;18(1):72. doi:10.1186/s12944-019-1010-y
16. 16. Fairweather D. Sex Differences in Inflammation during Atherosclerosis. *Clin Med Insights Cardiol*. 2014 Jan 19;8s3:CMC.S17068. doi:10.4137/CMC.S17068
17. Zhang G, Li C, Zhu N, Chen Y, Yu Q, Liu E, *et al.* Sex differences in the formation of atherosclerosis lesion in apoE-/-mice and the effect of 17β-estrodiol on protein S-nitrosylation. *Biomed Pharmacother*. 2018 Mar;99:1014–21. doi:10.1016/j.biopha.2018.01.145
18. Feigin VL. Global, Regional, and Country-Specific Lifetime Risks of Stroke, 1990 and 2016. *N Engl J Med*. 2018 Dec

20;379(25):2429–37. doi:10.1056/NEJMoa1804492

19. Gall SL, Tran PL, Martin K, Blizzard L, Srikanth V. Sex Differences in Long-Term Outcomes After Stroke. *Stroke*. 2012 Jul;43(7):1982–7. doi:10.1161/STROKEAHA.111.632547
20. Banerjee C, Chimowitz MI. Stroke Caused by Atherosclerosis of the Major Intracranial Arteries. *Circ Res*. 2017 Feb 3;120(3):502–13. doi:10.1161/CIRCRESAHA.116.308441
21. Boehme AK, Esenwa C, Elkind MSV. Stroke Risk Factors, Genetics, and Prevention. *Circ Res*. 2017 Feb 3;120(3):472–95. doi:10.1161/CIRCRESAHA.116.308398
22. Chen R, Ovbiagele B, Feng W. Diabetes and Stroke: Epidemiology, Pathophysiology, Pharmaceuticals and Outcomes. *Am J Med Sci*. 2016 Apr;351(4):380–6. doi:10.1016/j.amjms.2016.01.011
23. Iadecola C, Davisson RL. Hypertension and Cerebrovascular Dysfunction. *Cell Metab*. 2008 Jun;7(6):476–84. doi:10.1016/j.cmet.2008.03.010
24. Oh MY, Ko SB, Lee SH, Kim C, Ryu WS, Kim CH, *et al.* Association between metabolic syndrome and functional outcome in patients with acute ischaemic stroke. *Eur J Neurol*. 2014 Jan;21(1):177–9. doi:10.1111/ene.12128