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2-Analysis_of_stroke_risk_factors_

ANALYSIS OF STROKE RISK FACTORS ON THE FREQUENCY OF RECURRENT STROKE EVENTS IN ACUTE ISCHEMIC STROKE PATIENTS

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Online-ISSN 2623-2723
Print ISSN 2338-0373
Journal of Widya Medika Vol. 10 No. 2 October 2024
https://doi.org/10.33508/jwm.v10i2.6033

ANALYSIS OF STROKE RISK FACTORS ON THE FREQUENCY OF RECURRENT STROKE EVENTS IN ACUTE ISCHEMIC STROKE PATIENTS

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ABSTRACT

Introduction: Ischemic strokes making up over three quarters of all cases are a major global cause of disability and mortality. Survivors face a 15% risk of recurrence within two years, with recurrent strokes often resulting in more severe neurological damage and increasing the risk of death and long-term disability.

Methods: This retrospective cross-sectional study analyzed medical records from Gotong Royong Hospital in Surabaya from January 2023 to June 2024, selecting patients with acute ischemic stroke and a history of prior strokes. The data were descriptively analyzed and further examined using bivariate analysis to identify correlations with recurrent stroke episodes, followed by a multivariate regression analysis.

Results: The study recruited 87 participants, predominantly male (64.4%), with an average age of 63.2 years and varying medical histories, including hypertension (79.3%), diabetes mellitus (46%), and dyslipidemia (31%). Bivariate analysis revealed no significant correlations between hypertension, diabetes, dyslipidemia, random blood glucose, HbA1C, and the number of previous strokes, although significant positive correlations were found between systolic and diastolic blood pressures, LDL cholesterol, and triglycerides with the number of previous strokes. The multivariate analysis showed that while systolic and diastolic blood pressures, LDL, and triglyceride levels collectively predicted the number of previous strokes (F-value of 6.851 and a p-value < 0.01), only the initial systolic ($t = 3.887$, $p < 0.01$) and diastolic blood pressures ($t = 2.029$, $p = 0.046$) were independently correlated with an increased number of strokes.

Conclusions: Systolic and diastolic blood pressures were independently associated with frequency of recurrent stroke.

Keywords: Ischemic Stroke, Recurrent Stroke, Hypertension, Dyslipidemia, Diabetes Melitus

ABSTRAK

Pendahuluan: Stroke iskemik merupakan lebih dari tiga perempat dari semua kasus penyebab utama kecacatan dan kematian secara global. Para penderita memiliki risiko rekurensi sebesar 15% dalam dua tahun, yang seringkali mengakibatkan kerusakan neurologis yang lebih parah dan meningkatkan risiko kematian serta kecacatan jangka panjang.

Metode: Penelitian retrospektif ini menganalisis rekam medis dari Rumah Sakit Gotong Royong di Surabaya sejak Januari 2023 hingga Juni 2024, dengan memilih pasien stroke iskemik akut yang memiliki riwayat stroke sebelumnya. Data kemudian dianalisis secara deskriptif serta menggunakan analisis bivariat untuk mengidentifikasi korelasi dengan episode stroke berulang, dan dilanjutkan oleh analisis regresi multivariat.

Hasil: Terdapat 87 pasien, dengan sebagian besar laki-laki (64,4%), dengan usia rata-rata 63,2 tahun dan riwayat penyakit sebelumnya seperti hipertensi (79,3%), diabetes melitus (46%), dan dislipidemia (31%). Analisis bivariat menunjukkan bahwa tidak ada korelasi signifikan antara hipertensi, diabetes, dislipidemia, gula darah acak, HbA1C, terhadap jumlah riwayat stroke sebelumnya, meskipun ditemukan korelasi positif secara signifikan antara tekanan darah sistolik dan diastolik, kolesterol LDL, dan trigliserida dengan jumlah riwayat stroke sebelumnya. Analisis multivariat menunjukkan bahwa meskipun tekanan darah sistolik dan diastolik, kadar LDL, dan trigliserida secara kolektif dapat memprediksi jumlah stroke sebelumnya (nilai $F = 6.851$ dan p-value < 0.01), hanya tekanan darah sistolik ($t = 3.887$, $p < 0.01$) dan diastolik ($t = 2.029$, $p = 0.046$) yang secara independen berkorelasi dengan jumlah riwayat stroke berulang.

Kesimpulan: Tekanan darah sistolik dan diastolik secara independen berhubungan dengan frekuensi stroke berulang

Kata Kunci: Stroke Iskemik, Stroke Berulang, Hipertensi, Dislipidemia, Diabetes Melitus

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Online-ISSN 2623-2723
Print ISSN 2338-0373
Journal of Widya Medika Vol. 10 No. 2 October 2024
https://doi.org/10.33508/jwm.v10i2.6033

INTRODUCTION

Stroke represents a predominant factor contributing to both disability and mortality on a global scale, with ischemic strokes comprising approximately 85% of all recorded stroke incidents. The fundamental pathophysiological mechanism associated with ischemic stroke is primarily thrombotic, largely initiated by the process of atherosclerosis.[1,2] The worldwide impact of stroke is profound, not only regarding health-related outcomes but also in terms of its economic ramifications, particularly in low- and middle-income nations where an increasing population of stroke survivors exacerbates the financial burden associated with treatment and rehabilitation services.[3]

Stroke is predominantly regarded as a result of sustained exposure to lifestyle-associated risk determinants. The alteration of these risk determinants can significantly affect the prevalence of strokes and the degree of disability associated with such events.[4] Ischemic thrombotic stroke risk factors are generally classified into two categories: modifiable and non-modifiable, with non-modifiable factors encompassing gender, age, ethnicity, and race, while modifiable factors consist of hypertension, dyslipidemia, diabetes mellitus, and tobacco use.[4,5]

Given that risk factors and lifestyles vary across different regions and populations, it is essential to explore stroke risk factors and their clinical manifestations within specific populations. This is particularly important for patients who have experienced recurrent strokes, as these events pose significant health risks and can be fatal.[6] Preventing recurrent strokes is vital to reducing the high costs associated with treatment and rehabilitation, and requires a comprehensive understanding of the underlying risk factors.[5]

Individuals who endure an initial ischemic stroke face a substantial risk of recurrence, as evidenced by the fact that 15% to 30% of such individuals experience a subsequent stroke within the first two years post-event.[7] Recurrent stroke is a major cause of death, re-hospitalization, and long-term disability, and often results in more severe neurological impairment than the first stroke. Therefore, secondary prevention strategies are crucial to reducing the risk of recurrence. However, the factors contributing to the high risk of recurrent stroke are still not fully understood. While epidemiological studies have identified several predictors of stroke recurrence, such as age, hypertension, atrial fibrillation, diabetes mellitus, and hyperlipidemia, it is possible that other, yet unidentified, risk factors also play a role in stroke recurrence.[5,8] The purpose of the study is to understand the factors influencing stroke recurrence, aiming to develop targeted

prevention strategies for patients at high risk of subsequent, more severe strokes.

METHODS

This study utilized an analytical observational research design characterized by a cross-sectional retrospective methodology. The sample was collected from the medical records of Gotong Royong Hospital in Surabaya, using a total sampling technique from January 2023 to June 2024. The inclusion criteria for this study were patients in the emergency department of Gotong Royong Hospital with acute ischemic stroke who had a prior history of stroke. Recurrent ischemic stroke was characterized by the emergence of a new neurological impairment occurring following a phase of clinical stability and showing new ischemic evidence confirmed through Computed Tomography (CT)or Magnetic Resonance Imaging (MRI) of the brain.[9] The collected data were processed and analyzed descriptively, focusing on the frequency distribution of each characteristic, including age, gender, history of hypertension, diabetes mellitus, dyslipidemia, and the number of previous stroke episodes. Laboratory tests conducted included random blood glucose, glycated hemoglobin or hemoglobin A1c (HbA1C), Low Density Lipoprotein (LDL) cholesterol levels, and triglycerides. Patients failing to meet the inclusion criteria were systematically excluded from the study.

Bivariate analysis was performed utilizing the Mann-Whitney test in order to elucidate the correlation between the history of hypertension, diabetes mellitus, and dyslipidemia with the number of previous stroke episodes. The Spearman correlation coefficient was employed to evaluate the association between systolic and diastolic blood pressure, random blood glucose, HbA1C, LDL cholesterol levels, and triglycerides with the number of recurrent stroke episodes. Multivariate analysis was performed using multiple linear regression. The analysis of data was executed employing SPSS software version 24.0.

RESULT

Characteristics of recruited participants

The study recruited a total of 87 participants, with the majority being male (64.4%). The participants had an average age of 63.2 years, ranging from 29 to 87 years, with the largest age distribution being 51-60 years (34.5%). In terms of medical history, the majority of the participants had hypertension (79.3%), while 46% had a history of diabetes mellitus, and 31% had dyslipidemia. Regarding initial blood pressure, the average systolic pressure was 161.2 mmHg and the diastolic pressure averaged 93.2

Online-ISSN 2623-2723
Print ISSN 2338-0373
Journal of Widya Medika Vol. 10 No. 2 October 2024
https://doi.org/10.33508/jwm.v10i2.6033

mmHg. The participants had an average random blood glucose level of 183.18 mg/dL, with a wide range from 84 to 704 mg/dL. The mean HbA1C level was 6.6%, with values ranging from 3.9% to 15.1%. The average LDL cholesterol level was 115.9 mg/dL, and triglycerides averaged 159.3 mg/dL.

Table 1. Characteristics of recruited participants

Variable	N (%)	Mean	Median (min-max)
Sex			
Male	56 (64.4%)	-	-
Female	31 (35.6%)	-	-
Age			
≤ 50 years	11 (12.6%)	63.2 ± 11.8	62 (29-87)
51-60 years	30 (34.5%)		
61-70 years	22 (25.3%)		
> 70 years	24 (27.6%)		
Medical History			
Hypertension	69 (79.3%)	-	-
Diabetes Mellitus	40 (46%)	-	-
Dyslipidemia	27 (31%)	-	-
Initial Blood Pressure			
Systolic	-	161.2 ± 34.5	160 (90-260)
Diastolic	-	93.2 ± 16.2	90 (60-160)
Random blood glucose	-	183.18 ± 104	154 (84-704)
HbA1C	-	6.6 ± 2.2	5.9 (3.9-15.1)
LDL	-	115.9 ± 43.2	117 (43-217)
Triglycerides	-	159.3 ± 115.1	124 (35-668)
Number of Previous Stroke History	-	1.6 ± 0.8	1 (1-4)

Bivariate analysis of risk factor and the number of previous stroke episodes

The relationship between past medical history and the number of previous stroke episodes was analyzed using the Mann-Whitney test (Table 2). The results indicated that there was no statistically significant association between a history of hypertension and the number of previous strokes (p = 0.857). Similarly, the analysis showed no significant relationship between a history of diabetes mellitus and the number of previous stroke episodes (p = 0.754). Additionally, the presence of dyslipidemia was not significantly associated with the number of previous stroke (p = 0.71). These findings suggest

that these past medical conditions do not have a significant impact on the recurrence of stroke episodes in this study population.

Table 2. Relationship between

Variables	Number of Previous Stroke History	
	r	*p*
Past medical history		
Hypertension	-	0.857*
Diabetes mellitus	-	0.754*
Dyslipidemia	-	0.71*
Systole	0.413	< 0.001**
Diastole	0.275	0.01**
Random blood glucose	0.74	0.495**
HbA1C	0.94	0.384**
LDL	0.22	0.04**
Triglyseride	0.225	0.036**

* Mann-Whitney U test; ** Spearman test

The bivariate analysis using Spearman's correlation was performed to examine the relationship between various clinical parameters and the number of previous stroke (Table 3). The analysis revealed a significant positive correlation between systolic blood pressure and the number of previous stroke ($r = 0.413$, $p < 0.001$), indicating that higher systolic blood pressure is associated with an increased number of stroke episodes. Similarly, diastolic blood pressure showed a significant positive correlation with the number of previous stroke ($r = 0.275$, $p = 0.01$).

In contrast, no significant correlations were found between the number of previous stroke and random blood glucose ($r = 0.74$, $p = 0.495$) or HbA1C levels ($r = 0.94$, $p = 0.384$). However, LDL cholesterol levels ($r = 0.22$, $p = 0.04$) and triglyceride levels ($r = 0.225$, $p = 0.036$) were both significantly correlated with the number of previous strokes, suggesting that higher levels of these lipids are also associated with an increased recurrence of stroke episodes. The bivariate analysis showed that the relationship between systolic and diastolic blood pressure, as well as LDL and triglycerides, with the number of previous strokes, had a $p < 0.25$. Therefore, these four independent variables can be analyzed together using multiple linear regression.

Table 4. Multiple linear regression analysis

Variable	Number of Previous Stroke			
	F	*p*	*t*	*p*
Systole	6.851	< 0.01	3.887	< 0.01
Diastole			2.029	0.046
LDL			0.213	0.832
Triglyserides			1.627	0.108

Multivariate analysis of risk factor and the number of previous stroke episodes

Online-ISSN 2623-2723
Print ISSN 2338-0373
Journal of Widya Medika Vol. 10 No. 2 October 2024
https://doi.org/10.33508/jwm.v10i2.6033

A multiple linear regression analysis was conducted to assess the independent effects of systolic blood pressure, diastolic blood pressure, LDL cholesterol levels, and triglyceride levels on the number of previous strokes (Table 4). The overall model was statistically significant, with an F-value of 6.851 and a p-value < 0.01, indicating that the combination of these variables significantly predicts the number of previous strokes. Both systolic blood pressure (t = 3.887, p < 0.01) and diastolic blood pressure (t = 2.029, p = 0.046) emerged as statistically significant predictors, suggesting that higher systolic and diastolic blood pressure are independently associated with an increased number of previous stroke.

However, the analysis revealed that neither LDL cholesterol levels (t = 0.213, p = 0.832) nor triglyceride levels (t = 1.627, p = 0.108) were significantly associated with the number of previous strokes in this regression model. These findings indicate that while both systolic and diastolic blood pressure have a significant impact, the effects of LDL cholesterol and triglycerides on stroke recurrence are less pronounced when other factors are simultaneously considered.

DISCUSSION

Our study indicates a lack of significant correlation between a previous history of hypertension and the occurrence of recurrent ischemic strokes. In contrast, a study conducted at RS Al-Islam Bandung identified a significant correlation between hypertension and recurrent ischemic stroke, with an odds ratio of 4.03. This finding suggests that individuals with hypertension are over four times more likely to experience a recurrent ischemic stroke compared to those without hypertension.[10] Hypertension not only elevates the risk of recurrent strokes but also impacts the functional outcomes of stroke patients. Although some studies have found no statistically significant association between hypertension and functional outcomes, there is evidence suggesting that hypertensive ischemic stroke patients are at an increased risk of poor functional recovery.[11]

This study also demonstrates that a history of diabetes mellitus does not show a significant relationship with the number of previous strokes. Hyperglycemia, commonly associated with diabetes, doubles the risk of recurrent stroke and raises the likelihood of death or disability following an ischemic stroke. The underlying mechanisms include endothelial dysfunction, increased arterial stiffness, and systemic inflammation.[12] Diabetes mellitus is extensively acknowledged as a considerable risk factor for ischemic stroke, with individuals diagnosed with diabetes

exhibiting a 1.5 to 3 fold increased likelihood of experiencing a stroke in comparison to their non-diabetic counterparts. This elevated risk is largely due to the progression of atherothrombotic cerebrovascular lesions in diabetic patients.[13]

Dyslipidemia, marked by abnormal lipid levels in the blood, serves as an acknowledged risk factor not just for the emergence of ischemic strokes but also for their future recurrence. The correlation between dyslipidemia and the recurrence of strokes is complex, involving various lipid components and their interactions with other cardiovascular risk factors.[14] Atherosclerotic dyslipidemia significantly elevates the long-term probability of stroke recurrence, especially among individuals who receive intravenous thrombolysis for acute ischemic stroke. This probability is particularly pronounced in patients characterized by the Large-Artery Disease (LAD) subtype.[15]

In the Spearman analysis, initial systolic and diastolic blood pressure in the emergency room, as well as LDL and triglyceride levels, were found to have a significant relationship ($P<0.05$) with the number of previous strokes. In contrast, random blood glucose and HbA1c levels did not show a significant association. Further analysis using multivariate techniques was conducted to identify the variables most influential in predicting recurrent stroke events. The multivariate analysis revealed that, although systolic and diastolic blood pressure, along with LDL and triglyceride levels, collectively significantly predicted the number of recurrent strokes, it was determined that only the initial systolic and diastolic blood pressure measurements were independently correlated with an increased number of previous strokes.

Previous research by Ristonilassius also demonstrated a significant relationship between systolic and diastolic blood pressure and the occurrence of recurrent strokes.[16] Another study in China indicated that patients exhibiting systolic blood pressure levels equal to or exceeding 160 mmHg were significantly correlated with an elevated likelihood of recurrent cerebrovascular accidents in subjects suffering from non-lacunar infarct strokes. Independently, systolic blood pressure was determined to serve as a predictive factor for stroke recurrence within the cohort of patients experiencing non-lacunar infarction (HR 1.65, 95% CI 1.01–2.67; P = .04).[17] The Systolic Hypertension in the Elderly Program (SHEP) trial elucidated that individuals with Diastolic Blood Pressure (DBP) less than 70 mmHg within the blood pressure control group experienced a reduced incidence of cerebrovascular accidents. Moreover, in

Online-ISSN 2623-2723
Print ISSN 2338-0373
Journal of Widya Medika Vol. 10 No. 2 October 2024
https://doi.org/10.33508/jwm.v10i2.6033

individuals over the age of 60, rigorous management of DBP to a target of 68 mmHg was associated with a lower risk of stroke compared to the placebo group, which maintained a DBP of 72 mmHg (with a relative risk of 0.64; 95% confidence interval, 0.50–0.82; p = 0.0003).[18] In contrast to our results, a 2020 study conducted by Chen et al. indicated that diastolic blood pressure levels below 80 mmHg were markedly correlated with an elevated risk of stroke, implying that the relationship between diastolic blood pressure and stroke occurrence is non-linear in nature.[19]

In this study, the blood glucose profile, including random blood glucose and HbA1c levels, did not show a significant relationship with the occurrence of recurrent ischemic stroke. The mean random blood glucose level in the study sample was within the normal range (mean = 183.18 ± 104), while the mean HbA1c level indicated an increase from the normal value (6.6 ± 2.2). Hyperglycemia is frequently seen in acute stroke patients and is linked to larger infarct sizes and worse outcomes. This association is observed in both diabetic and non-diabetic individuals, underscoring the impact of stress-induced hyperglycemia on stroke prognosis.[20] Contrary to our result, a study from India showed that elevated HbA1c levels are generally associated with an increased risk of stroke recurrence. This is particularly evident in patients with diabetes, where poor glycemic control (HbA1c > 7%) is linked to higher stroke severity and recurrence rates.[21] However, the relationship is not straightforward, as some studies suggest that HbA1c alone may not be a strong predictor of stroke recurrence compared to other markers like the Stress Hyperglycemia Ratio (SHR). This ratio, which takes into account both random blood glucose measurements and levels of HbA1C, has been proposed as a prognostic instrument. Elevated SHR values are associated with poorer functional outcomes and heightened mortality rates, indicating that stress hyperglycemia observed at the time of admission may serve as a predictor of unfavorable outcomes in individuals suffering from ischemic stroke.[22]

A research conducted by Pan et al. revealed that increased levels of LDL are correlated with a 35% higher risk of experiencing a recurrent stroke within a three-month interval. In contrast, the implementation of lipid-lowering therapeutic interventions following the occurrence of a stroke was linked to a diminished risk of subsequent ischemic stroke in patients exhibiting elevated baseline LDL cholesterol concentrations.[23] Individuals exhibiting LDL cholesterol concentrations beneath 120 mg/dL throughout therapeutic intervention

demonstrated a 29% reduction in the occurrence of recurrent cerebrovascular incidents, including stroke and Transient Ischemic Attack (TIA), in contrast to those whose LDL cholesterol levels were at or exceeding 120 mg/dL (event rate 2.20 vs 3.11 per 100 person-years).[24]

Previous research on the relationship between triglyceride levels and the number of previous strokes has not yielded consistent results. Triglycerides have shown paradoxical associations with recurrent stroke, varying by age. In middle-aged individuals (40-64 years), elevated triglyceride levels are associated with an increased risk of recurrent stroke, whereas in older age groups (≥ 65 years), they do not significantly impact stroke recurrence. In fact, high triglyceride levels in older patients are linked to smaller infarct volumes and better outcomes after ischemic stroke, possibly due to age-related changes in triglyceride metabolism.[25] Additionally, low triglyceride levels in older individuals may reflect poor nutrition, which could paradoxically increase stroke risk, although the exact mechanism remains unclear. Interestingly, higher triglyceride levels have also been associated with less severe ischemic strokes and better short-term outcomes. A recent study in 20204 involving 6,558 patients found that those with elevated triglyceride levels experienced less severe strokes and had a lower likelihood of poor outcomes at discharge and 90 days post-stroke. This suggests that while high triglyceride levels are generally considered a risk factor for stroke, they may paradoxically be linked to less severe initial strokes and better immediate recovery outcomes.[26]

Triglycerides, frequently evaluated in conjunction with glucose concentrations via the Triglyceride-Glucose (TyG) index, have been demonstrated to influence the outcomes and recurrence of strokes. The TyG index, which serves as an indicator of insulin resistance, has been associated with an increased probability of recurrent strokes. A research investigation conducted by the Xi'an Stroke Registry revealed that a elevated TyG index correlated with a greater risk of recurrent stroke within a one-year timeframe, particularly among the female cohort. This non-linear association implies that the TyG index may function as a prognostic biomarker for stroke recurrence, particularly when the index exceeds specific thresholds.[27] In nondiabetic patients with small vessel occlusion, an elevated TyG index was correspondingly linked to an increased probability of ischemic stroke recurrence, thereby suggesting its utility as a significant biomarker for evaluating recurrence risk in distinct subpopulations of stroke patients.[28]

The limitations of this study include a limited sample size and the fact that it was

Online-ISSN 2623-2723
Print ISSN 2338-0373
Journal of Widya Medika Vol. 10 No. 2 October 2024
https://doi.org/10.33508/jwm.v10i2.6033

conducted at a single research site. Further large-scale studies are needed to explore additional risk factors and to assess the impact of these risk factors on patient outcomes, such as stroke severity and disability levels.

CONCLUSION

This study highlights the significant role of systolic and diastolic blood pressure as predictors of recurrent ischemic stroke, underscoring the importance of stringent blood pressure and lipid level management in secondary prevention strategies. Although hypertension, diabetes, and dyslipidemia are known risk factors for stroke, their direct impact on recurrence was not statistically significant in our cohort, suggesting a complex interplay of risk factors that may differ from those affecting initial stroke events. The findings call for further multicenter studies to confirm these results and explore new biomarkers, aiming to refine prevention strategies for recurrent strokes.

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Online-ISSN 2623-2723
Print ISSN 2338-0373
Journal of Widya Medika Vol. 10 No. 2 October 2024
https://doi.org/10.33508/jwm.v10i2.6033

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