



EVALUATION OF ETIOLOGY, RISK FACTORS AND PROGNOSIS OF RECURRENT STROKE AT TERTIARY CARE FACILITY, RAJASTHAN

General Medicine

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ABSTRACT

Introduction: Recurrent strokes are an important cause of morbidity and mortality. Identification of etiology, type and risk factors associated with recurrent stroke, may play an essential role in the prevention of further stroke. **Objective:** Assessment of etiology, risk factors and prognosis of recurrent stroke at 3 months follow-up. **Methods:** It was a hospital based observational prospective study conducted at a tertiary care facility, Jaipur for one year duration. Total 55 patients with radiologically confirmed diagnosis of recurrent stroke were included in our study. Data related to history, demography, risk factors and imaging were collected. Modified rankin scale was calculated on admission and at 3 month follow up. Data were analyzed using 't' test and chi-square test. **Result:** Most common type of recurrent stroke was ischemic stroke (91%). In cases of recurrent ischemic stroke, small vessel occlusion was most common (26%) subtype. The frequent risk factors were hypertension (89%), sedentary life style (78%) and dyslipidemia (71%). Maximum cases had ischemic to ischemic (83.6%) pattern of recurrence. Majority of patients (51%) had recurrence after 12 months of their previous stroke. Most common reason for stroke recurrence was non-compliance to medication (58%). Mortality was significantly higher in hemorrhagic group (60%), than ischemic group, at 3 months follow-up (p value<0.05). **Conclusion:** Recurrent stroke can be preventable to a much extent, by controlling vascular risk factors. This can be achieved with ensuring better compliance to medications and secondary lifestyle modifications along with proper workup to find stroke etiology.

KEYWORDS

Hemorrhagic stroke, Hypertension, Ischemic stroke, Recurrent stroke, Small Vessel Occlusion.

INTRODUCTION

Recurrent Stroke (RS) is defined as any stroke occurring within 24 hours after the onset of incident stroke in a different vascular territory and any stroke occurring in the same territory after 21 days of the incident stroke.^{1,2} The risk for a recurrent stroke has been reported to be about 4% in the first month, about 12% in the first year after stroke and 4% every year thereafter.¹ Recurrent stroke events during the 1st year are in a majority of the cases attributable to atherosclerosis of the large arteries.³ There is an elevated risk of recurrent stroke of 30% by 5 years.¹

Recurrent stroke was classified mainly into two types, first Ischemic stroke and the second was Hemorrhagic stroke. Stroke recurrence rates, including both ischemic and hemorrhagic strokes, in various stroke registries show 3-year cumulative risk of stroke recurrence as 6% in Malmo⁴, 18% in Perth⁵ and 25% in Oxfordshire¹

Risk factors for recurrence after stroke can be divided into non-modifiable and modifiable risk factors.⁶⁻¹⁰ Most important modifiable risk factors for stroke recurrence are hypertension, dyslipidemia, diabetes mellitus, smoking, ischemic heart disease and atrial fibrillation.¹¹ Advance age and male gender are important non-modifiable risk factors.¹¹ Majority of patients have more than one risk factors.¹² Smoking, alcohol abuse and physical inactivity are lifestyle related risk factors for stroke recurrence. Life style modifications, including tobacco cessation, decrease alcohol intake and increase physical activity, are also important in prevention of stroke recurrence.¹³

The incidence of stroke recurrence is high despite development of primary and secondary preventive treatment.¹¹ The risk of stroke recurrence is highest in immediate period after index stroke (early stroke recurrence <12 months).¹ Although some studies shows higher late stroke recurrence (>12 months).¹⁴ This emphasizes that efforts at secondary stroke prevention should be initiated as soon as possible and continued for several years thereafter to gain greatest benefit. Currently there is an ongoing PREVENT Trial, which included physical inactivity as an important risk factor for stroke recurrence along with other modifiable risk factors.

This Current Study Was Conducted With The Following Objective-

- To find out the etiology and risk factors associated with recurrent stroke.

- To find out the short-term prognosis at 3 months of follow-up among patients of recurrent stroke.
- To find out the pattern of recurrence in patient with recurrent stroke.

MATERIALS AND METHODS

This hospital based cross-sectional analytical study was conducted at neurology department of tertiary care facility at Jaipur, Rajasthan. This study was conducted for a period of one year from June 2020 to July 2021 after clearance from the Institutional Ethical Committee and research review board of the institution. Patients were enrolled from June 2020 to February 2021 and last included patient in our study was assessed for prognosis after three months of enrolment. And then another 3 months were required for data compilation, statistical analysis processing and writing which was finished in July 2021. During the study period total of 62 cases of recurrent stroke was admitted in the department out of them 55 fulfilling inclusion and exclusion criteria were included in our study.

Inclusion & Exclusion Criteria

Patients of recurrent stroke, diagnosis confirmed by CT or MRI brain, aged >18 years who gave informed consent were included in our study. And patients of <18 years of age, or with Metabolic encephalopathy or with extra-dural hemorrhage (EDH), sub-dural hemorrhage (SDH), Subarachnoid hemorrhage (SAH) and traumatic Intracranial hemorrhage (ICH) were excluded from the study.

METHODOLOGY

The patients enrolled in the study were subjected to a detailed clinical history and clinico-radiological examination. Ischemic strokes were classified as per Causative Classification of Stroke system¹⁵ [CCS]-TOAST. Hemorrhagic strokes were classified according to etiological-H-ATOMIC¹⁶ classification. Risk factor details were obtained from patients (history), general practitioners and records. To evaluate the differences of proportion of stroke patients by age, we divided age into three groups, young age was < 45 years, middle age was 45-64 years, and old age was ≥65 years. Duration between previous and recent stroke was divided in <1 month, 1 to <4 month, 4-12 months and >12 months. Early and late recurrence were defined as within 12 months and >12 months, respectively. History regarding compliance to drugs and secondary lifestyle modifications was obtained.

Risk Factors

Hypertension- defined according to World Health Organization

criteria: systolic blood pressure (SBP) ≥ 140 mm Hg, diastolic blood pressure (DBP) ≥ 90 mm Hg, or the patient on antihypertensive treatment.¹⁷

Diabetes Mellitus- if fasting plasma glucose (FPG) ≥ 126 mg/dl or glycosylated hemoglobin (HbA1c) $\geq 6.5\%$.¹⁸

Anemia- Hb (Hemoglobin) <13 g/dl for men, and Hb <12 g/dl for women.¹⁹

Dyslipidemia- previously diagnosed, receiving lipid lowering drugs or total cholesterol ≥ 240 mg/dl or low density lipoprotein ≥ 160 mg/dl.²⁰

Blood investigations done were Complete Blood Count, Lipid profile, INR, random blood sugar, fasting blood sugar and HbA1c. To define prognosis of patients at 3 months, modified Rankin scale (mRS)²¹ was used. mRS score was calculated at admission and at 3 months.

Statistical Analysis

Data was entered in excel spreadsheet. Continuous data was summarized in form of mean and standard deviation. Discrete data was expressed in form of proportions and difference in proportions was analysed using chi-square test. The level of significance was kept at 95% for all statistical analysis.²²

Results

Our study included 55 patients of recurrent stroke with mean age of 64.95 ± 1.67 years (range 20-85 years). Table I depicts demographic profile and types of previous & recent stroke. More than half (56.4%, 31/55) of cases were of ≥ 65 years age group. Majority (61.8%, 34/55) of cases were male. Most of the cases (85.5%, 47/55) had ischemic type of previous stroke. Most common type of recurrent stroke was ischemic stroke in 50 (91%) patients, and hemorrhagic stroke in five (9%) patients. Among ischemic stroke, most common TOAST subtype found was small vessel occlusion in 13(26%), followed by cardioembolic in 12(24%). Among hemorrhagic stroke group most common subtype was hypertensive bleed (60%).

Figure I showed the proportion of risk factors in patients with recurrent stroke. Hypertension (HTN) was the most common risk factor in 49(89%) patients, followed by sedentary life style in 43(78.2%) and least common was vasculitis in three(5.5%). In this study 21(38.2%) patients were diabetic, 19(34.5%) were prediabetic and 15(27.2%) were non-diabetic.

Figure II presenting the mRS score at admission and at 3 month follow up. Association of mRS score at admission and at 3 months follow-up was statistically significant ($X^2=24.00$, Df=3, $p<0.001$). At 3 month follow up nine (16.4%) patients had mortality.

Table II shows distribution of time period between previous and recent stroke occurrence. In our study more than half of patients (50.9%, 28/55) had their stroke recurrence after 12 months from the index stroke, while only one(1.8%) patient had their recurrences within one month of previous stroke. Most common reason for recurrence was non-compliance to medications in 32(58.2%) patients, followed by non-compliance to secondary life style modifications (including smoking & alcohol cessation and/or physical inactivity) in 17(30.9%) patients and least common reason associated with recurrence was poor monitoring of treatment response (7.3%) and different etiology for recent stroke (5.5%).

In present study, most common pattern of stroke recurrence was 'ischemic (previous) to ischemic (recent)' in 83.6% patients, followed by 'hemorrhagic to hemorrhagic' and 'hemorrhagic to ischemic' each in 7.3% patients. Least common pattern of recurrence seen in our study was 'ischemic to hemorrhagic' in 1.8% patients only.

Table III is presenting association of outcome at 3 months with type of recurrent stroke. Hemorrhagic recurrent stroke had higher mortality compared to recurrent ischemic stroke at 3 month follow up and this difference in mortality with type of recurrent stroke was found to be statistically significant ($p=0.033$).

DISCUSSION

Recurrent stroke is associated with greater damage to patients and a more serious burden on families as compared with the first stroke. In our study, maximum number of patients were in ≥ 65 years age group (56.4%), and minimum (5.5%) were in <45 years age group. According to a study done by Rothwell PM et al²³, age is the most important non-modifiable risk factor for all stroke types and is also one

of the significant independent predictors of recurrent stroke. In this study 65% of all strokes occur in individuals over the age of 65 years. In our study, males were predominant (61.8%) as compared to females (38.2%). In previous studies, prevalence of males was more compared to females.^{4,5} In our study, history of previous ischemic stroke (85.5%) was more compared to previous hemorrhagic stroke (14.5%). These findings were similar to a study done by Leoo T et al¹⁴, in which previous ischemic stroke was found in 90% cases. Lee JD et al²⁴ et al also found higher stroke recurrence rates in patients with previous ischemic stroke. In our study, among 55 cases of recurrent stroke, maximum had recurrent ischemic stroke (91%), as compared to (9%) recurrent hemorrhagic stroke. This finding is concordant with previous studies done by, Leoo T et al¹⁴ et al and El-Gohary TM et al¹² shows that most common subtype of recurrent stroke was ischemic stroke (91% and 84% respectively). Among recurrent ischemic stroke patients, according to TOAST subtypes, we found most common etiology was small vessel occlusion (26%), followed by cardioembolic (24%), and other determined etiology in 14% cases. In a study done by Leoo T et al¹⁴ most common TOAST subtype was small vessel occlusion (34%) and least common was other determined (2%).

In our study, most common risk factor of recurrent stroke was hypertension in 89% cases, followed by sedentary life style in 78.2% cases, dyslipidemia (71%) and diabetes mellitus (38.2%). Results are consistent with previous literature like study done by El-Gohary TM et al¹², where most common risk factor associated was hypertension (90.2%), followed by DM (62.5%). In our study association of patients falling in different mRS score at admission and at 3 month was statistically significant ($p<0.001$). Thus, patients were improving with time and continuity of treatment.

In our study, most patients (51%) had their stroke recurrence after 12 months (late recurrence) from previous stroke, while only few (1.8%) occurring in less than 1 month from previous stroke. Results were like a study done by Leoo T et al¹⁴, in which maximum number (75%) of patients had their recurrence >12 months after the previous stroke. This long term stroke recurrence may be explained as people generally do not remain adherent to the preventive measures for long duration.

Non-adherence to medications and life style modifications are major issues in secondary stroke prevention. In the study done by Shankari G et al⁷, non-compliance to secondary life style modifications was studied, which shows non-adherence to smoking cessation and physical activity, in 29% and 21.5% patients, post stroke. Our study concluded combined results of non-compliance to secondary life style modifications (31%), which included non-compliance to smoking cessation, physical activity and/or alcohol cessation. Thus, stroke recurrence is preventable to much extent by increasing compliance to medications and secondary lifestyle modifications. In our study, among five (9%) patients no workup was done at the time of previous stroke, due to lesser availability of medical services in rural areas and false beliefs of people towards stroke refraining them from seeking medical attention. There was a significant proportion (18.2%) of cases in which reasons for stroke recurrence was unexplained.

In our study, most common pattern of stroke recurrence was 'ischemic to ischemic' in 83.6% cases, followed by 'hemorrhagic to hemorrhagic' in 7.3%. Similar results were reported by Modrego PJ et al²⁵, most common pattern of recurrence was 'ischemic to ischemic' in 75.5% cases.

In our study overall mortality at 3-month after recurrent stroke was 16.4%. Mortality in hemorrhagic recurrent stroke patients was higher than ischemic recurrent stroke patients (60% and 12% respectively). This association of mortality with types of recurrent stroke was statistically significant ($p=0.033$). Results were comparable with study done by Modrego PJ et al²⁵, in which overall hospital fatality rate for recurrent stroke was 16.3% and mortality in hemorrhagic and ischemic stroke groups were 40% and 17% respectively. Different mortalities after recurrent stroke in these studies may be due to the difference in the home care facilities; lack of autopsy findings as deaths occurring outside, our hospital area; genetic and environmental variations among study population.

Limitation and Recommendation

This study had been performed at a tertiary care level private hospital and the results cannot be generalized to the general population. So, large multi-centric study in Indian population is needed to significantly correlate reasons for recurrence found in our study. In view of

multifactorial cause of stroke recurrence, search for other risk factors should be done in long follow up.

Table I: Demographic Distribution Of Patients And Types Of Recurrent Stroke

Variable		Frequency (n)	Percentage (%)
Age Groups (In Years)	<45	3	5.5
	45-64	21	38.2
	≥65	31	56.4
Sex	Female	21	38.2
	Male	34	61.8
Type of previous stroke	Ischemic	47	85.5
	Hemorrhagic	8	14.5
Type of recent stroke (n=50)	Large artery atherosclerosis	9	18
	Cardio embolic	12	24
	Small vessel occlusion	13	26
	Others (Determined)	7	14
	Undetermined	9	18
	Hemorrhagic (n=5)		
	Hypertensive	3	60
	Cerebral amyloid angiopathy	1	20
	Oral anticoagulants	1	20

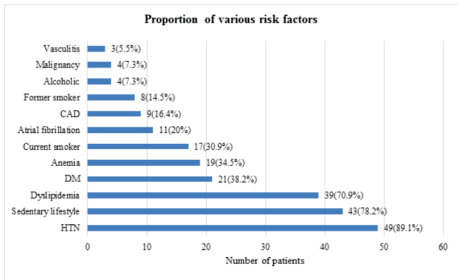


Figure I: Proportion Of Various Risk Factors Among Patients Of Recurrent Stroke

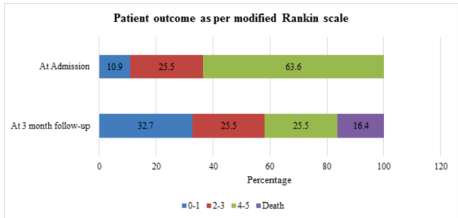


Figure II: Modified Rankin Scale At Admission And At 3-month Follow-up In Patients Of Recurrent Stroke

Table II: Time Period Between Recurrent & Previous Stroke And Reasons Of Recurrent Stroke

Variables	Frequency (n)	Percentage (%)	
Time period between recurrent and previous stroke	<1 months	1	1.8
	1-<4 months	3	5.5
	4-12 months	23	41.8
	>12 months	28	50.9
Reason for recurrence	Non-compliance to medication	32	58.2
	Non-compliance to secondary life style modification	17	30.9
	Inadequate management for prevention of secondary stroke	8	14.5
	Poor monitoring of treatment response	4	7.3
	No workup done for previous stroke	5	9.1
	Different etiology for recent event	3	5.5
	Unexplained	10	18.2

Table III- Association Of Outcome At 3 Months With Type Of Recurrent Stroke

Outcome at 3 months	Type of recurrent stroke		P value
	Ischemic	Hemorrhagic	

Alive	44(88)	2(40)	X ² =4.547, Df=1, P value= 0.033
Death	6(12)	3(60)	
Total	50(100)	5(100)	

CONCLUSION

Recurrent stroke can be preventable to a much extent, by controlling vascular risk factors. In index stroke patients we should focus more on risk factors related to previous stroke, to prevent chances of recurrent stroke. As the majority of recurrence were late recurrences, so more focus should be on formulating strategies to increase compliance to medications and secondary lifestyle modifications along with proper workup to find stroke etiology. Physicians need to formulate strategies to confirm patients' compliance on follow up visits and ensuring regular interval follow up.

REFERENCES

1. Burn J, Dennis M, Bamford J, Sandercock P, Wade D, Warlow C. Long-term risk of recurrent stroke after a first-ever stroke. The Oxfordshire Community Stroke Project. Stroke. 1994 Feb;25(2):333-7.
2. Hankey GJ, Jamrozik K, Broadhurst RJ, Forbes S, Burvill PW, Anderson CS, et al. Long-Term Risk of First Recurrent Stroke in the Perth Community Stroke Study. Stroke. 1998 Dec;29(12):2491-500.
3. Lovett JK, Coull AJ, Rothwell PM. Early risk of recurrence by subtype of ischemic stroke in population-based incidence studies. Neurology. 2004 Feb 24;62(4):569-73.
4. Elneihum AM, Göransson M, Falke P, Janzon L. Three-year survival and recurrence after stroke in Malmö, Sweden: an analysis of stroke registry data. Stroke. 1998 Oct;29(10):2114-7.
5. Hankey GJ, Jamrozik K, Broadhurst RJ, Forbes S, Burvill PW, Anderson CS, et al. Long-term risk of first recurrent stroke in the Perth Community Stroke Study. Stroke. 1998 Dec;29(12):2491-500.
6. Bailey RR. Lifestyle Modification for Secondary Stroke Prevention. American Journal of Lifestyle Medicine. 2018 Mar;12(2):140-7.
7. Shankari G, Ng SC, Goh SY, Woon FP, Doshi K, Wong PS, et al. Modifiable Factors Associated with Non-Adherence to Secondary Ischaemic Stroke Prevention Strategies. J Stroke Cerebrovasc Dis. 2020 Dec;29(12):105395.
8. Sunprasert N, Tantirithsak T. Impact of risk factors for recurrent ischemic stroke in Prasat Neurological Institute. J Med Assoc Thai. 2011 Sep;94(9):1035-43.
9. Fu G, Yuan W, Du W, Yang Z, Fu N, Zheng H, et al. Risk Factors Associated with Recurrent Strokes in Young and Elderly Patients: A Hospital-based Study. International Journal of Gerontology. 2015 Jun;9(2):63-6.
10. Sun Y, Lee SH, Heng BH, Chin VS. 5-year survival and rehospitalization due to stroke recurrence among patients with hemorrhagic or ischemic strokes in Singapore. BMC Neurol. 2013 Dec;13(1):133.
11. Kocaman G, Dürüyhen H, Koçer A, Asil T. Recurrent Ischemic Stroke Characteristics and Assessment of Sufficiency of Secondary Stroke Prevention. NoroPsikiyatrArs. 2015 Jun;52(2):139-44.
12. El-Gohary TM, Alshenqiti AM, Ibrahim SR, Khaled OA, Ali ARH, Ahmed MS. Risk factors and types of recurrent stroke: a Saudi hospital based study. J Phys Ther Sci. 2019 Oct;31(10):743-6.
13. Gupta A, Grover S, Sakrawal K, Kumar A, Meena S, Rathore M, Kumawat P. Prevalence, Patterns, and Predictors of Tobacco Consumption among Adolescents: An Observational Study from a Rural area of Rajasthan. Indian J Community Med. 2023 Sep-Oct;48(5):748-754.
14. Loo T, Lindgren A, Petersson J, von Arbin M. Risk factors and treatment at recurrent stroke onset: results from the Recurrent Stroke Quality and Epidemiology (RESQUE) Study. Cerebrovasc Dis. 2008;25(3):254-60.
15. Ay H, Benner T, Arsava EM, Furie KL, Singhal AB, Jensen MB, et al. A computerized algorithm for etiologic classification of ischemic stroke: the Causative Classification of Stroke System. Stroke. 2007 Nov;38(11):2979-84.
16. Martí-Fàbregas J, Prats-Sánchez L, Martínez-Domeño A, Camps-Renom P, Marin R, Jiménez-Varrié E, et al. The H-ATOMIC Criteria for the Etiologic Classification of Patients with Intracerebral Hemorrhage. PLoS One. 2016;11(6):e0156992.
17. Oh JS, Bae HG, Oh HG, Yoon SM, Doh JW, et al. The Changing Trends in Age of First-Ever or Recurrent Stroke in A Rapidly Developing Urban Area during 19 Years. J Neurol Neurosci. 2017 July 10; 8(4): 206.
18. Swami V, Yadav SK, Saxena P, Sharma A, Dash CK, Gupta A. Study of Glycemic Variability in Well-controlled Type 2 Diabetic Patients Using Continuous Glucose Monitoring System. Journal of the Association of Physicians of India. 2024 Jan;72(1):19.
19. Chang JY, Lee JS, Kim BJ, Kim JT, Lee J, Cha JK, et al. Influence of Hemoglobin Concentration on Stroke Recurrence and Composite Vascular Events. Stroke. 2020 04;51(4):1309-12.
20. Sridharan SE, Unnikrishnan JP, Sukumaran S, Sylaja PN, Nayak SD, Sarma PS, et al. Incidence, types, risk factors, and outcome of stroke in a developing country: the Trivandrum Stroke Registry. Stroke. 2009 Apr;40(4):1212-8.
21. Broderick JP, Adeoye O, Elm J. Evolution of the Modified Rankin Scale and Its Use in Future Stroke Trials. Stroke. 2017 07;48(7):2007-12.
22. Sakrawal K, Meena G, Gupta A, Malav K, Grover S. Knowledge, attitude, and practice about cervical cancer among adult women in rural Jaipur: An observational analysis. J Family Med Prim Care. 2023 Oct;12(10):2379-2384.
23. Rothwell PM, Coull AJ, Silver LE, Fairhead JF, Giles MF, Lovelock CE, et al. Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories (Oxford Vascular Study). Lancet. 2005 Nov 19;366(9499):1773-83.
24. Lee JD, Hu YH, Lee M, Huang YC, Kuo YW, Lee TH. High Risk of One-year Stroke Recurrence in Patients with Younger Age and Prior History of Ischemic Stroke. CurrNeurovasc Res. 2019;16(3):250-7.
25. Modrego PJ, Pina MA, Fraj MM, Llorens N. Type, causes, and prognosis of stroke recurrence in the province of Teruel, Spain. A 5-year analysis. Neurol Sci. 2000 Dec;21(6):355-60.