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Treatment in a Stroke Unit and Risk Factor Control Reduce Recurrent Stroke Risk

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Keywords

Stroke recurrence · Average attributable fraction · Stroke unit · Risk factor control

Abstract

Introduction: Risk factor control is an important predictor of risk of stroke recurrence. The attributable fraction which estimates the excess risk among the exposed stroke survivors has not been studied previously. We studied the attributable fraction for stroke recurrence in consecutive incident cases of recurrent stroke. ***Methods:*** A case-control study with incident cases of recurrent stroke and controls matched for age and poststroke period was done. A structured interview was done to collect data on sociodemographic variables, lifestyle, and medication adherence. The risk factors, treatment of index stroke, and outcome were collected. Logistic regression analysis was done to find out the factors associated with stroke recurrence. Attributable fraction and average attributable fraction were calculated. ***Results:*** Among the 103 matched pairs, more than 70% were rural residents. Male gender (OR 2.59; 95% CI 1.05–6.42), the presence of depression (OR 8.67; 95% CI 2.80–26.84), memory problem (OR 10.12; 95% CI 2.48–41.34), uncontrolled diabetes (OR 3.19; 95% CI 1.42–7.19), cardioembolic stroke (OR 4.45; 95% CI 1.12–17.62), and index stroke not being treated in a stroke unit (OR 6.60; 95% CI 2.86–15.23) were associated with increased risk of stroke recurrence. The maximum average attributable fraction for stroke recurrence risk was attributed to index stroke not being treated in the stroke unit and uncontrolled diabetes. ***Conclusion:*** The index stroke treated in a comprehensive stroke care unit and control of risk factors can reduce recurrent stroke risk among stroke survivors. This population-attributable risk is important in planning secondary stroke prevention strategies.

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Introduction

Recurrent strokes can occur any time after the index stroke. Despite the evidence-based strategies to prevent recurrent strokes, the recurrence rate is high. The pooled cumulative risk was 3.1% at 30 days, 11.1% at 1 year, 26.4% at 5 years, and 39.2% at 10 years after initial stroke [1]. People suffering from a recurrent stroke have poorer functional outcomes and additional hospitalization costs than the first-ever stroke [2].

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The etiologic subtype of index stroke is an important factor which predicts stroke recurrence with large-artery atherosclerosis having increased risk of recurrence, whereas small-vessel stroke has a lower risk of recurrence [3, 4]. Patients treated in a stroke unit at index stroke had a reduced risk of recurrence [5]. The early recurrence within 1 year is more common in the large atherosclerotic disease subtype [3], but in the subsequent years, recurrences are mainly attributed to risk factors such as diabetes, hypertension, dyslipidemia, and coexisting diseases [6–8].

The risk associated with a particular exposure to cause the disease can be accurately estimated by multiple methods. While the odds ratio estimates the association with the exposure, the attributable fraction (AF) estimates the excess risk among the exposed to get the disease or the risk attributable to a particular exposure. The population attributable risk (PAR) is another method of estimating risk which explains the added risk in the exposed population. It considers the excess risk associated with the exposure and the prevalence of risk factors in the population. The population AF (PAF) is the proportion of cases in the population that can be attributed to the exposure in the population. There are regression models in which the PAF can be directly calculated and adjusted for other variables [9, 10]. The AF for stroke recurrence has not been meticulously studied before. The PAF is an efficient tool from a public health perspective yet underutilized. We studied the AF for stroke recurrence in consecutive incident cases of recurrent stroke.

Methodology

The incident cases of recurrent stroke were recruited from stroke clinics with stroke recurrence after the first episode of stroke, during the data collection period till the calculated sample size was reached. Index stroke was defined as “rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 h or longer or leading to death, with no apparent cause other than of vascular origin” [11]. Based on the noncontrast computed tomography scan findings, the type of stroke was categorized as ischemic stroke (IS) and intracerebral hemorrhage. TIA patients were recruited based on imaging evidence of acute infarct. Sample size for the pair-matched case-control study was calculated using sample size tables for clinical studies software. Sample size was calculated fixing α error = 0.05, power = 0.80, anticipated proportion of discordant pairs = 0.5, anticipated odds ratio = 3 (stroke unit care) and for a two-sided test. The number of matched pairs was estimated to be 61. Considering probability of nonresponse, and for the further multivariate analysis, 103 matched pairs were recruited for this study. The total sample size of 206 was recruited from February 2019 to December 2019. As one incident recurrent stroke case was recruited, an age and poststroke-period-matched control was recruited from the stroke registry. Our hospital-based stroke registry data were examined to get the closest pair of (age ±3, poststroke period ±2 weeks) stroke survivors without stroke recurrence, as the control. In cases where the closest pair was not available, the next eligible control from the list was selected.

Incident cases of recurrent strokes were defined as the incident case of recurrent stroke among survivors of the first episode of IS within 1 month of stroke recurrence. We included patients with ischemic and hemorrhagic strokes. Patients with TIA were included if they had evidence of acute infarct in imaging. The control was defined as age- and poststroke-period-matched survivors of the first episode of IS, hemorrhagic stroke, and transient ischemic attack without a recurrent stroke.

Data collection was done in a home setting for both cases and controls using a pretested structured interview schedule. A clinical information sheet was used to collect information on radiographic, imaging, and clinical details of index stroke from medical records. Standard instruments were used to measure height, weight, waist circumference, and blood pressure. Medication adherence and compliance with other recommended health advice like following a healthy diet, physical activity, tobacco abstinence, and limiting alcohol consumption just prior to the recurrence period were also assessed.

A stroke unit is defined as an organized in-hospital facility that is entirely devoted to care for patients with stroke and is staffed by a multidisciplinary team with special knowledge in stroke care. Self-reported medication adherence was defined as consumption of more than 80% of their medications in the last 2 weeks, based on their last prescription. The data on medication adherence were collected by interviewing the patient and primary caregiver regarding the medication intake history of 2 weeks. A healthy diet was defined as consumption of approximately 350–400 g of vegetables a day; one medium-sized fruit or two small-sized fruit per day; and avoiding extra salts, sweets, and fried foods [12, 13]. Recommended physical activity was at least 30 min of moderate physical activity like walking for at least 3 days a week [12].

The data on risk factors, blood sugar, and lipid levels prior to the recurrence period were also collected from laboratory reports. Risk factor control is defined as achieving the desired levels of blood pressure, blood sugar, and cholesterol. The targets for risk factor control were taken from National Cholesterol Education Program (NCEP) ATP III guidelines [14] for cholesterol (LDL < 100 and TC < 200), American Diabetes Association guidelines (FBS 70–130 and $HbA_1C < 7$) for diabetes control [15], and ASA secondary stroke prevention guidelines [15] for blood pressure (SBP < 140 and DBP < 90).

Statistical Analysis

Bivariate analysis was done with stroke recurrence as an outcome and patient characteristics to find out the factors associated with stroke recurrence. Binary logistic regression analysis was done to find out the independent factors associated with stroke recurrence. The attributable risk of stroke recurrence for the significant variables was calculated using the formula OR−1/OR; where OR is the odds ratio [16]. The PAR was calculated with adjusted and crude odds ratios. The prevalence risk factors were taken from previous studies [17, 18], and PAR of stroke recurrence was calculated using the formula P_e (OR−1)/1 + P_e (OR−1) (Pe – prevalence of exposure in population and OR– odds ratio for that

Table 1. Characteristics of the participants

Variables	Categories	Controls (*N* = 103), *n* (%)	Cases (*N* = 103), *n* (%)
Sex	Male	69 (67.0)	83 (80.6)
	Female	34 (33.0)	20 (19.4)
Age	<50	19 (18.4)	19 (18.4)
	51–60	33 (32.0)	29 (28.2)
	61–70	29 (28.2)	30 (29.1)
	>70	22 (21.4)	25 (24.3)
Type of stroke	Ischemic	100 (97.1)	94 (91.3)
	TIA	3 (2.9)	4 (3.9)
	Hemorrhagic	0 (0.0)	5 (4.9)
TOAST classification*	Large artery atherosclerosis	36 (36.0)	38 (40.4)
	Cardioembolism	5 (5.0)	14 (14.9)
	Small artery atherosclerosis	23 (23.0)	15 (17.0)
	Undetermined causes	32 (32.0)	23 (23.4)
	Other determined causes	4 (4.0)	4 (4.3)

* TIA excluded from cases (*n* = 94) and controls (*n* = 100).

risk factor) [16]. In order to have a more precise estimate of the PAF, the average AF was calculated by sequential logistic regression analysis including significant risk factors in the final model using the Ruckinger method [10].

Results

Out of total 206 participants, 103 cases and 103 age- and poststroke-period-matched controls were recruited over a period of 11 months. The mean age of the cases was 60.73 ± 11.02 years and that of the control was 60.48 ± 10.75 years (age-matched). Females constituted 19.4% of the cases and 33.0% of controls. Around 70% of the cases and controls were rural inhabitants. The recommended physical activity was not followed by 86.4% of cases and 72.8% of controls, while 84.5% of the cases and 62.1% of the controls were not following a healthy diet. The mean cost of medication for controls was 152.2 ± 151.6 INR per week and that of cases was 325.3 ± 167.5 INR per week, and this difference was statistically significant, and the p value was <0.001. The other characteristics of the participants (Table 1) and their effect on stroke recurrence are shown in Table 2.

Male gender (OR 2.59; 95% CI 1.05–6.42), the presence of depression (OR 8.67; 95% CI 2.80–26.84), memory problem (OR 10.12; 95% CI 2.48–41.34), uncontrolled diabetes (OR 3.19; 95% CI 1.42–7.19), cardioembolic stroke (OR 4.45; 95% CI 1.12–17.62), and index stroke not being treated in a stroke unit (OR 6.60; 95% CI 2.86–15.23) were associated with increased risk of stroke recurrence. Multivariate analyses of the factors predicting stroke recurrence risk are shown in Table 3. The attributable risk based on the adjusted odds ratio, PAF based on the adjusted odds ratio, and the average AF are shown in Table 4. The attributable risk for stroke recurrence was highest for the presence of memory problems. The average AF showed 25.19%, 19.33%, 17.74%, 12.23%, 9.90%, and 4.72% of the recurrent stroke risk among stroke survivors can be attributed to index stroke not being treated in a stroke unit, uncontrolled diabetes, male gender, the presence of depression, memory problem, and cardioembolic stroke subtype, respectively.

Discussion

Previous studies have identified many factors associated with stroke recurrence. We in fact studied the PAF which is most relevant at the public health level. In low- and middle-income countries with limited resources, the attributable risk estimation helps planning interventions which can produce maximum public health impact. Our study results showed that 25.19%, 19.33%, 17.74%, 12.23%, 9.90%, and 4.72% of the recurrent stroke risk among stroke survivors can be attributed to index stroke not being treated in a stroke unit, uncontrolled diabetes, male gender, the presence of depression, memory prob-

Table 2. The characteristics of the participants and its effect on stroke recurrence (result of bivariate analysis)

Variable	Categories	Controls (*N* = 103), *n* (%)	Cases (*N* = 103), *n* (%)	Crude odds ratio* (95% CI)	*p* value
Sex	Male Female	69 (67.0) 34 (33.0)	83 (80.6) 20 (19.4)	1 0.49 (0.26–0.93)	0.027
Cost of medication/week	≤250 >250	71 (68.9) 32 (31.1)	43 (41.7) 60 (58.3)	1 3.10 (1.75–5.48)	<0.001
NIHSS	≤15 >15	88 (85.5) 15 (14.6)	99 (97.1) 3 (2.9)	1 0.18 (0.05–0.64)	0.056
Exercise	No Yes	75 (72.8) 28 (27.2)	89 (86.4) 14 (13.6)	1 0.42 (0.21–0.86)	0.015
Diet	No Yes	64 (62.1) 39 (37.9)	87 (84.5) 16 (15.5)	1 0.30 (0.15–0.59)	<0.001
Last health checkup	Within 3 months >3 months	75 (72.8) 28 (27.2)	86 (83.5) 17 (16.5)	1 0.53 (0.27–1.04)	0.064
Anxiety	No Yes	61 (59.2) 42 (40.8)	44 (42.7) 59 (57.3)	1 1.95 (1.12–3.39)	0.018
Depression	No Yes	94 (91.3) 9 (8.7)	65 (63.1) 38 (36.9)	1 6.10 (2.77–13.49)	<0.001
Memory	No Yes	99 (96.1) 4 (3.9)	78 (75.7) 25 (24.3)	1 7.93 (2.65–23.75)	<0.001
Adherence	No Yes	29 (28.2) 74 (71.8)	49 (47.6) 54 (52.4)	1 0.43 (0.24–0.77)	0.004
The presence of valvular heart disease	No Yes	100 (97.1) 3 (2.9)	91 (88.3) 12 (11.7)	1 4.40 (1.20–16.07)	0.016
Blood pressure	Not controlled Controlled	78 (75.7) 25 (24.3)	75 (72.8) 28 (27.2)	–	0.633
Blood sugar	Not controlled Controlled	51 (49.5) 52 (50.5)	71 (68.9) 32 (31.1)	1 0.44 (0.25–0.78)	0.005
Dyslipidemia control	Not controlled Controlled	17 (16.5) 86 (83.5)	32 (31.1) 71 (68.9)	1 0.44 (0.23–0.86)	0.014
Type of index stroke	Ischemic TIA Hemorrhagic	100 (97.1) 3 (2.9) 0 (0.0)	94 (91.3) 4 (3.9) 5 (4.9)	–	0.088
TOAST classification	Others Cardioembolic	97 (94.2) 6 (5.8)	84 (85.7) 14 (14.3)	1 2.69 (0.99–7.32)	0.045
Treatment in the stroke unit	No Yes	20 (19.4) 83 (80.6)	58 (56.9) 44 (43.1)	1 0.18 (0.10–0.34)	<0.001
Days hospitalized, *n*	≤7 days >7 days	73 (70.9) 30 (29.1)	87 (85.3) 15 (14.7)	1 0.42 (0.21–0.84)	0.013
Discharge advice	No Yes	20 (19.4) 83 (80.6)	40 (38.8) 63 (61.2)	1 0.38 (0.20–0.71)	0.002

* χ^2 test was done.

Table 3. Factors associated with stroke recurrence

Variable	Categories	Controls (N = 103), n (%)	Cases (N = 103), n (%)	Adjusted odds ratio* (95% CI)	p value
Sex	Male	69 (67.0)	83 (80.6)	1	0.038
	Female	34 (33.0)	20 (19.4)	0.38 (0.15–0.95)	
Cost of medication/week	≤250	71 (68.9)	43 (41.7)	1	0.162
	>250	32 (31.1)	60 (58.3)	2.48 (1.23–5.01)	
NIHSS	≤15	88 (85.5)	99 (97.1)	1	0.056
	>15	15 (14.6)	3 (2.9)	0.11 (0.01–1.06)	
Depression	No	94 (91.3)	65 (63.1)	1	0.001
	Yes	9 (8.7)	38 (36.9)	7.45 (2.34–23.75)	
Memory	No	99 (96.1)	78 (75.7)	1	0.002
	Yes	4 (3.9)	25 (24.3)	8.83 (2.20–35.40)	
Presence of valvular heart disease	No	100 (97.1)	91 (88.3)	1	0.075
	Yes	3 (2.9)	12 (11.7)	4.14 (0.87–19.76)	
Blood sugar	Not controlled	51 (49.5)	71 (68.9)	1	0.009
	Controlled	52 (50.5)	32 (31.1)	0.34 (0.15–0.76)	
TOAST classification	Others	97 (94.2)	84 (85.7)	1	0.039
	Cardioembolic	6 (5.8)	14 (14.3)	4.26 (1.07–16.94)	
Treatment in the stroke unit	No	20 (19.4)	58 (56.9)	1	<0.001
	Yes	83 (80.6)	44 (43.1)	0.16 (0.07–0.37)	
Days hospitalized, *n*	≤7 days	73 (70.9)	87 (85.3)	1	0.078
	>7 days	30 (29.1)	15 (14.7)	0.41 (0.15–1.11)	
Discharge advice	No	20 (19.4)	40 (38.8)	1	0.074
	Yes	83 (80.6)	63 (61.2)	0.43 (0.19–1.08)	

* Multiple binary logistic regression analysis was done.

Table 4. AF for stroke recurrence

Variable	Prevalence of exposure[1]	Attributable risk, %	PAF for adjusted OR[4]	Average AF[5]
Sex (male)	74.6[2]	61.39	99	17.74
Depression	38.6[2]	88.47	99	12.23
Memory problem	38.6[2]	90.12	99	9.90
Uncontrolled blood sugars	74.0[2]	68.65	99	19.33
Cardioembolic stroke	14.6[2]	77.48	98	4.72
Index stroke not being treated in the stroke unit	64.0[3]	84.85	99	25.19

[1] Prevalence of exposure was taken from previous studies. [2] Shani et al. [17]. [3] Rudd et al. [18]. [4] Calculated using the formula: P_e (OR–1)/1 + P_e (OR–1). [5] Calculated using R statistical software by the Ruckinger method (Ruckinger et al. [10]).

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lem, and cardioembolic stroke subtype, respectively. We found that 70% of the recurrent strokes among the stroke population over a mean poststroke period of around 5 years can be prevented by modifying these five identified modifiable risk factors.

Our study showed that the highest AF was for index stroke not being treated in the stroke unit. The stroke unit is a care area where patients with acute cerebrovascular events are admitted where standardized investigations, treatment regimens, and investigations are applied. Recurrent strokes can be significantly reduced if the index stroke is treated in the stroke unit. Previous studies conducted in developed countries showed that stroke unit care improves functional outcome and survival rate at 5 years and 10 years compared to patients treated in general wards [19, 20]. In low- and middle-income settings, where a limited number of comprehensive stroke units are available, starting primary care stroke units itself can have a huge impact. Treatment in the stroke unit facilitates stroke etiologic evaluation and initiation of appropriate secondary stroke prevention strategies. Individualized discharge planning and patient and family education which are the essential components of stroke unit care help in more awareness among patients regarding the importance of medication adherence and risk factor control. A study by Lee et al. [5] showed that patients treated in stroke units have a reduced risk of recurrence.

Uncontrolled diabetes ranked second in the PAR of stroke recurrence. Previous studies also reported the presence of diabetes, and its poor diabetic control is associated with stroke recurrence [21]. Previous studies also showed that there is a high prevalence of diabetes among the stroke population and only one-fourth achieved desired levels of blood sugars. Diabetic control was associated with medication adherence and was better in patients following recommended physical activity and a healthy diet [17]. Targeted interventions can be initiated at the community level to address the risk factors through prevention clinics at the primary care level to reduce the stroke recurrence.

Our study showed that the presence of memory problems and depression is associated with an attributable risk of around 22% at the population level. Patients with stroke-related medical complications, poststroke depression, and physical disability were less likely to follow preventive measures [22, 23]. Poststroke depression is independently associated with stroke recurrence and is due to poor medication adherence and noncompliance to other secondary stroke prevention strategies [23]. There is a need to screen the stroke survivors for poststroke depression and give timely treatment.

The data on the AF of stroke recurrence are very limited in the literature. The only available report was from a prospective study of 1,500 stroke survivors followed up for a period of 5 years, and they analyzed the factors associated with stroke recurrence. They have reported attributable risk of stroke recurrence for diabetes at 36.93% (−3.10 to 62.63) and atrial fibrillation −19.68% (−34.40 to 52.00) during the first year after the index stroke [24] and a PAF of stroke recurrence for diabetes 9.1% (95% CI, −2.0 to 20.2) and atrial fibrillation 4.9% (95% CI, −7.3 to 17.2). The overall adjusted PAF of first-ever stroke for the risk factors hypertension, hyperlipidemia, diabetes mellitus, coronary heart disease, smoking, heavy episodic alcohol consumption, low physical activity, and obesity was reported as 78.9% in a large nationwide age- and sex-matched case-control study in Germany [25].

The PAF is more important from a public health point of view because it gives excess risk for a particular risk factor in the population. It incorporates both individual associations of risk and the prevalence of risk factors in the population. After considering the value of PAR for selected risk factors, the one with higher value may be most important for planning interventions.

Since stroke is emerging as a major public health issue, the national program is warranted to combat the stroke burden in the community. The future direction for reducing the stroke burden in the community includes not only primary prevention and acute stroke treatment but also having stroke prevention clinics for risk factor control and medication adherence so that stroke recurrence can be prevented.

The strength of our study is the case-control methodology. The importance of risk factor control on stroke recurrence is reinforced by our study. We know that stroke unit care is effective in improving the functional outcome in the acute phase, but this study's results showed that stroke unit care has an implication in the secondary prevention of stroke at the community level also.

One of the major limitations of this study is that we did not use validated scales to assess medication adherence. The data on memory issues and side effects were also collected based on self-report only. With this study being done in a tertiary care center, the findings may not be representative of patients treated in primary- or secondary-level hospitals. We have recruited stroke survivors with stroke recurrence from 1 month to 92 months which is a wide range, but we selected controls without stroke recurrence matched to the same poststroke period.

Conclusion

Stroke unit care and control of risk factors are important in secondary prevention of stroke. Establishing stroke units to cover the entire population and secondary prevention clinics for risk factor control are areas of intervention to reduce the stroke burden.

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Statement of Ethics

This study received permission from the Institute Ethics Committee of the Sree Chitra Tirunal Institute for Medical Sciences and Technology (Ref. No. SCT/IEC/1327/November2019). Informed written consent was obtained from all the participants.

Conflict of Interest Statement

Dr. P.N. Sylaja is an associate editor of *Cerebrovascular Diseases Extra*. All the other coauthors have no conflicts of interest to declare.

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Author Contributions

S.D. Shani: conception and design of the study, data collection, analysis, and drafting of the manuscript. Ravi Prasad Varma: conception and design of the study, analysis, and critical revision of the manuscript. P. Sankara Sarma: statistical analysis and critical revision of the manuscript. R.S. Sreelakshmi: data collection and critical revision of the manuscript. R. Harikrishnan: data collection and critical revision of the manuscript. V. Raman Kutty: conception and design of the study and critical revision of the manuscript. P.N. Sylaja: conception and design of the study and critical revision of the manuscript.

Data Availability Statement

The data that support the findings of this study are not openly available but will be available on demand.

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