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A Retrospective Cohort Study Comparing Stroke Recurrence Rate in Ischemic Stroke Patients With and Without Acupuncture Treatment

Chun-Chuan Shih, MD, PhD, Chien-Chang Liao, PhD, MPH, Mao-Feng Sun, MD, PhD, Yi-Chang Su, MD, PhD, Chi-Pang Wen, MD, PhD, Donald E. Morisky, ScD, Fung-Chang Sung, PhD, MPH, Chung Y. Hsu, MD, PhD, and Jaung-Geng Lin, MD, PhD

Abstract: Little was known about the effects of acupuncture on stroke recurrence. The aim of this study is to investigate whether ischemic stroke patients receiving acupuncture treatment have a decreased risk of stroke recurrence.

A retrospective cohort study of 30,058 newly diagnosed cases of ischemic stroke in 2000 to 2004 was conducted based on the claims of Taiwan National Health Insurance Research Database. The use of acupuncture treatment and stroke recurrence were identified during the follow-up period from 2000 to 2009. This study compared the risk of stroke recurrence between ischemic stroke cohorts with and without acupuncture treatment by calculating adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of acupuncture associated with stroke recurrence in the Cox proportional hazard model.

The stroke recurrence rate per 1000 person-years decreased from 71.4 without to 69.9 with acupuncture treatment ($P < 0.001$). Acupuncture treatment was associated with reduced risk of stroke recurrence (HR

0.88; 95% CI 0.84–0.91). The acupuncture effect was noted in patients with or without medical treatment for stroke prevention but its impact decreased with aging of stroke patients. Compared with stroke patients without acupuncture treatment and medication therapy, the hazard ratios of stroke recurrence for those had medication therapy only, acupuncture only, and both were 0.42 (95% CI 0.38–0.46), 0.50 (95% CI 0.43–0.57), and 0.39 (95% CI 0.35–0.43), respectively.

This study raises the possibility that acupuncture might be effective in lowering stroke recurrence rate even in those on medications for stroke prevention. Results suggest the need of prospective sham-controlled and randomized trials to establish the efficacy of acupuncture in preventing stroke.

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Abbreviations: CI = confidence interval, HR = hazard ratio, ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification, NHI = National Health Insurance.

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From The School of Chinese Medicine for Post-Baccalaureate, I-Shou University, Kaohsiung (CCS); Ph.D. Program for the Clinical Drug Discovery from Botanical Herbs, Taipei Medical University (CCS); Department of Anesthesiology, Taipei Medical University Hospital, Taipei (CCL); School of Chinese Medicine, (CCL, MFS, YCS, JGL); Graduate Institute of Clinical Medical Science, China Medical University, Taichung, Taiwan (CPW, CYH); Fielding School of Public Health University of California, Los Angeles, California (DEM); Department of Public Health, China Medical University (FCS); and Department of Neurology, China Medical University Hospital, Taichung, Taiwan (CYH).

Correspondence: Jaung-Geng Lin, School of Chinese Medicine, China Medical University, 91 Hsueh-Shih Road, Taichung 404, Taiwan (e-mail: jglin@mail.cmu.edu.tw).

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INTRODUCTION

Stroke remains a leading cause of death and the leading cause of disability worldwide.¹ The costs of stroke to the family and the society underscore the importance of stroke prevention and management. Secondary stroke prevention remains a top priority in treating patients after the first stroke^{2–6} and is a key performance indicator in the American Heart Association/American Stroke Association Get With The Guidelines Stroke program,⁷ which have been followed in Taiwan.⁸ The mainstay in stroke prevention for patients with ischemic stroke in the Get With The Guidelines Stroke program is antithrombotic therapy.⁷

In addition to antithrombotics for stroke prevention, rehabilitation is an important therapy for facilitating functional recovery after stroke.⁹ Other than rehabilitation, stroke patients in Taiwan have the option of receiving complementary and alternative therapies including acupuncture that is approved for reimbursement by the National Health Insurance (NHI) in Taiwan.¹⁰

Acupuncture has been in practice among Chinese for more than 2000 years and has been increasingly integrated into the mainstream healthcare programs including those in the United States.¹¹ In addition to various pain syndromes,^{9,12,13} acupuncture has increasingly attracted attention in treating stroke patients with mixed results.^{10,11,14–18} Meta-analyses suggest that the efficacy of acupuncture remains to be established.^{15,17} Despite the lack of solid evidence to support its clinical utility, acupuncture is a safe, low-cost, and viable alternative therapy, especially for patients with stroke-related disorders that do not respond to conventional medical or rehabilitative measures.

Favorable rehabilitation outcome aided by acupuncture in some stroke patients may increase physical activity to reduce stroke recurrence risk.^{19,20} Acupuncture may also have salutary actions on vascular function by increasing nitric oxide level, improving lipid profile, and lowering blood pressure.^{21–25} Pretreatment of electroacupuncture may reduce infarct size, improved neurological outcome in patients with cerebral infarction.²⁶ Based on these ancillary effects of acupuncture that may all lead to lower stroke risk in stroke patients who receive acupuncture, we explore whether the incidence of stroke recurrence was lowered in stroke patients receiving acupuncture as compared with those without based on population-based claims in the National Health Insurance Research Database.

METHODS

Data Sources

Reimbursement claims in the NHI database were used in the present study. NHI has been implemented since March 1995, covering more than 99% of the 23 million population.^{27–30} The electronic database was encrypted with patient identifications scrambled to protect privacy of all subjects. This study was exempted from the review by the Internal Review Board. All beneficiaries' inpatient and outpatient medical services such as simple demographics (gender, birth date, low-income status, and urbanization of living area), primary and secondary diagnoses with the International Classification of Diseases 9th Revision Clinical Modification (ICD-9-CM), procedures, prescriptions, and medical expenditures are recorded in the National Health Insurance Research Database established by the National Health Research Institutes.^{28–30}

Ethics Approval

Insurance reimbursement claims used in this study were from Taiwan's National Health Insurance Research Database. For protection of personal privacy, the electronic database was decoded with patient identifications scrambled for further public access for research. This study was evaluated and approved by Taiwan's National Health Research Institutes (NHIRD-100–122) and the Institutional Review Board of E-DA Hospital, Kaohsiung, Taiwan (2014012); this organization's regulations do not require informed consent because patient identification has been decoded and scrambled.^{28–30} This study was conducted in accordance with the Declaration of Helsinki.

Study Population

In this cohort, 30058 adults (age ≥ 30 years) with ischemic stroke diagnosed for the first time in 2000–2004 were identified. Patients were then divided into 2 groups, without or with acupuncture therapy after stroke. We further randomly selected from those without acupuncture to constitute a control group that was matched by age, sex, and key variables with the acupuncture group, applying propensity score. Patients with ischemic stroke who were included in the acupuncture group received at least 6 sessions of acupuncture treatment. Only acupuncturists who are certified traditional Chinese medical doctor with acupuncture specialty fulfilling the yearly continuing acupuncture education requirements are qualified for filing NHI claims for acupuncture reimbursement.

Patients with and without acupuncture treatment were followed from the index event until the end of 2009 to identify the incidence of stroke recurrence. Comorbidities including hypertension, diabetes, and hyperlipidemia were identified as the key stroke risk factors that might contribute to stroke

recurrence and compound the effectiveness of acupuncture treatment. Effects of medications for stroke prevention including antiplatelet agents, anticoagulants, and lipid-lowering agents on stroke recurrence were also assessed.

Criteria and Definition

ICD-9-CM was used to define ischemic stroke (ICD-9-CM 430–434). Hypertension (ICD-9-CM 401–405), diabetes (ICD-9-CM 250), hyperlipidemia (ICD-9-CM 272.0, 272.1, 272.2), liver cirrhosis (ICD-9-CM 571), mental disorder (ICD-9-CM 290–319), ischemic heart disease (ICD-9-CM 410–414), and renal dialysis (administration code D8, D9) were also identified.

Statistical Analysis

The chi-square tests were used to compare the distribution of age, sex, comorbidities, and medication in reference to stroke recurrence between groups with and without acupuncture treatment. The incidences (per 1000 person-years) of stroke recurrence and incidence rate ratio with 95% confidence intervals (CIs) were derived and compared between groups. Stroke severity was assessed based on length of stay and hospitalization expenditure reimbursed by the NHI. The Kaplan–Meier plot was applied to measure stroke recurrence over time and the Cox proportional hazards model to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). All statistical analyses were performed using SAS software version 9.1 (SAS Institute Inc., Cary, NC) with 2-sided $P < 0.05$ being taken to represent statistical significance.

RESULTS

Overall, there were 30,058 newly diagnosed cases of ischemic stroke. After matching with propensity score, there was no difference in age, sex, comorbidities relevant to stroke and medications for stroke prevention. In follow-up to the end of 2009, 4639 (30.9%) in the acupuncture group experienced stroke recurrence as compared with 5749 patients (38.3%) in the group without acupuncture ($P < 0.001$) (Table 1). The length of stay and hospitalization expenditure, 2 parameters that might reflect stroke severity, were not different between groups.

The stroke recurrence rate per 1000 person-years was 71.4 in the group without and 69.9 with acupuncture treatment, respectively ($P < 0.001$) (Table 2). The reduced risk of stroke recurrence was associated with acupuncture treatment (HR 0.88, 95% CI 0.84–0.91). Acupuncture treatment appeared to reduce stroke recurrence rate in both sexes and across the age groups. Its effect was noted in patients with or without comorbidities relevant to ischemic stroke including hypertension, diabetes, or hyperlipidemia. Acupuncture effect in stroke prevention appeared to be more apparent among those not on medications for stroke prevention. Table 3 presents interaction of medication for stroke prevention and acupuncture treatment. The HR was also significantly lower in those with only acupuncture treatment. Compared with stroke patients without acupuncture treatment and medication therapy, the hazard ratios of stroke recurrence for those had medication therapy only, acupuncture only, and both were 0.42 (95% CI 0.38–0.46), 0.50 (95% CI 0.43–0.57), and 0.39 (95% CI 0.35–0.43), respectively. Compared with stroke patients with medication therapy but without acupuncture treatment, the HR of stroke recurrence for those with both acupuncture treatment and medication therapy was 0.93 (95% CI 0.89–0.97). In Table 4, the risk of stroke recurrence was associated with numbers of package of acupuncture treatment ($P < 0.0001$).

TABLE 1. Characteristics of Stroke Patients With and Without Acupuncture Treatment*

	Acupuncture Treatment		P Value
	No (N = 15029)	Yes (N = 15029)	
Sex	n (%)	n (%)	1.00
Female	6502 (43.3)	6502 (43.3)	
Male	8527 (56.7)	8527 (56.7)	
Age, yr			1.00
30–39	160 (1.1)	160 (1.1)	
40–49	1087 (7.2)	1087 (7.2)	
50–59	2896 (19.3)	2896 (19.3)	
60–69	5170 (34.4)	5170 (34.4)	
70–79	4773 (31.8)	4773 (31.8)	
≥80	943 (6.3)	943 (6.3)	
Mean ± SD	65.7 ± 10.4	65.7 ± 10.4	
Low income	191 (1.3)	191 (1.3)	1.00
Coexisting medical conditions			
Diabetes mellitus	6404 (42.6)	6404 (42.6)	1.00
Hypertension	12,763 (84.9)	12,763 (84.9)	1.00
Hyperlipidemia	6093 (40.5)	6093 (40.5)	1.00
Liver cirrhosis	729 (4.9)	729 (4.9)	1.00
Mental disorder	4759 (31.7)	4759 (31.7)	1.00
Ischemic heart disease	2779 (18.5)	2779 (18.5)	1.00
Renal dialysis	219 (1.5)	219 (1.5)	1.00
Medication use			
Antiplatelet agents	14,086 (93.7)	14,086 (93.7)	1.00
Anticoagulants	687 (4.6)	687 (4.6)	1.00
Lipid-lowering agents	6490 (43.2)	6490 (43.2)	1.00
Admission to ICU	457 (3.0)	457 (3.0)	1.00
Length of hospital stay, days	7.69 ± 5.08	7.77 ± 5.21	
Rehabilitation	8678 (57.7)	8678 (57.7)	1.00
Stroke recurrence	5749 (38.3)	4639 (30.9)	<0.0001

ICU = intensive care unit.

* Match factor of propensity score are sex, age, low income, coexisting medical conditions, medication use, length of stay, and rehabilitation.

The Kaplan–Meier model showed that, during the follow-up period to the end of 2009, ischemic stroke patients with acupuncture treatment had lower cumulative rate of recurrent stroke than those without acupuncture treatment (log-rank $P < 0.0001$) (Figure 1).

DISCUSSION

Using claims data from the National Health Insurance Research Database, we conducted a nationwide, population-based, propensity score-matched, retrospective cohort study that investigated the lower risk of recurrent stroke in ischemic stroke patients with acupuncture treatment than those without acupuncture treatment. The present study also showed that the biological gradient relationship between the numbers of package acupuncture treatment and reduced recurrent stroke. This is the first large-scale investigation reporting the effectiveness of acupuncture treatment on reducing the stroke recurrence in ischemic stroke patients.

Antithrombotic therapies, including antiplatelet agents and oral anticoagulants, are the mainstay in the primary and secondary stroke prevention.^{5,6,31–34} Acupuncture is a widely used procedure in Chinese medicine for patients with various diseases.^{12–18,21–25} Acupuncture has also been applied to stroke patients for reducing spasticity and pain and for improving

motor function.^{10,14–18} Although systematic reviews on the effect of acupuncture, as a supplement therapy for rehabilitation in stroke patients, show mixed results,^{14–18} the infarct size and neurological outcome was improved after the treatment with electroacupuncture in patients with cerebral infarction.²⁶ Overall, acupuncture has not been shown in well-designed sham-controlled and randomized trials to be effective in improving functional outcomes after stroke.^{14,17} Acupuncture is accepted by NHI in Taiwan for caring several diseases including stroke. More than 18% of patients with ischemic stroke in Taiwan received acupuncture for at least 6 sessions to qualify for NHI reimbursement. We noted that among those receiving acupuncture, the stroke recurrence rate was lower than those without.

After the matching procedure by propensity score, there was no significant difference in age, sex, coexisting medical conditions, medications, and length of stay or hospitalization expenditure for the first stroke admission between stroke patients with and without acupuncture treatment. Age is the most important stroke risk factor.^{35,36} If there is any impact of age, the acupuncture group has a slighter higher mean age than the control group. These observations make it unlikely that difference in age can be accounted for lower stroke recurrence rate in the acupuncture group. It is worth noting that there appears to have an age-dependent effect on incidence rate ratio that is significantly lower in younger stroke patients (Table 3).

TABLE 2. Stroke Recurrence Rates Based on Demographic, Comorbidity, and Therapy Profiles With and Without Acupuncture

	Non-Acupuncture (N = 15029)				Acupuncture (N = 15029)				HR (95% CI) [†]
	N	Events	Person-Years	Incidence*	N	Events	Person-Years	Incidence*	
All	15,029	5749	80,497	71.4	15,029	4639	66,325	69.9	0.88 (0.84–0.91)
Sex									
Female	6502	2407	35,624	67.6	6502	1823	29,285	62.3	0.83 (0.79–0.89)
Male	8527	3342	44,873	74.5	8527	2816	37,040	76.0	0.91 (0.86–0.95)
Age, y									
30–39	160	69	743	92.9	166	29	721	40.2	0.35 (0.22–0.54)
40–49	1087	428	5743	74.5	1096	262	4954	52.9	0.61 (0.52–0.71)
50–59	2896	1078	15,688	68.7	2907	809	12,694	63.7	0.81 (0.74–0.89)
60–69	5170	2056	27,989	73.7	5188	1612	23,048	69.9	0.85 (0.80–0.91)
70–79	4773	1797	25,522	70.4	4733	1592	20,924	76.1	0.99 (0.92–1.06)
≥80	943	321	4902	65.5	939	335	3985	84.1	1.15 (0.98–1.34)
Diabetes mellitus									
No	8625	3440	44,623	77.1	8625	2704	37,130	72.8	0.83 (0.79–0.87)
Yes	6404	2309	35,874	64.4	6404	1935	29,196	66.3	0.96 (0.90–1.02)
Hypertension									
No	2266	1182	9041	130.7	2266	890	8519	104.5	0.67 (0.62–0.74)
Yes	12,763	4567	71,456	63.9	12,763	3749	57,806	64.9	0.94 (0.90–0.98)
Hyperlipidemia									
No	8936	3924	43,614	90.0	8963	3213	37,487	85.7	0.84 (0.81–0.88)
Yes	6093	1825	36,882	49.5	6093	1426	28,839	49.4	0.97 (0.90–1.04)
Antiplatelet agents									
No	943	537	3295	163.0	943	341	3474	98.2	0.49 (0.43–0.56)
Yes	14,086	5212	77,202	67.5	14,086	4298	62,852	68.4	0.93 (0.89–0.97)
Anticoagulants									
No	14,342	5456	76813	71.0	14342	4427	63,255	70.0	0.88 (0.85–0.92)
Yes	687	293	3684	79.5	687	212	3070	69.1	0.81 (0.68–0.97)
Lipid-lowering agents									
No	8539	3788	41,728	90.8	8539	3061	35,908	85.2	0.83 (0.79–0.87)
Yes	6490	1961	38,768	50.6	6490	1578	30,417	51.9	0.98 (0.92–1.05)

* Per 1000 person-years.

† Adjustment in the multivariate Cox proportional hazard model. There was an interaction between age and acupuncture treatment ($P < 0.0001$) in the Cox proportional hazard regression.

However, among those receiving medical treatment, acupuncture treatment appears to lower the stroke recurrence rate as well (Table 4). The finding that the effect of acupuncture in reducing stroke recurrence rate was still noted up to 10 years in follow-up is interesting. This long-lasting acupuncture effect is

worth exploring to establish evidence-based acupuncture reduction of stroke recurrence.

A question can also be raised concerning potential difference in stroke severity between groups. Table 2 shows that there was no significant difference in length of stay or hospitalization

TABLE 3. Incidence and Hazard Ratio of Stroke Recurrence Among Different Therapy Groups

Acupuncture	Medication*	n	Events	Person-Years	Incidence [†]	HR	(95% CI) [‡]
No	No	826	486	2743	187.0	1.00	(Reference)
No	Yes	14,203	5263	77,754	67.7	0.42	(0.38–0.46) [§]
Yes	No	826	302	3032	101.9	0.50	(0.43–0.57)
Yes	Yes	14,203	4337	63,293	68.7	0.39	(0.35–0.43) [§]

CI = confidence interval; HR = hazard ratio.

* Medication included antiplatelet agents, anticoagulants, and lipid-lowering agents.

† Per 1000 person-years.

‡ Adjusted for age, sex, low income, intensive care unit stay, liver cirrhosis, mental disorder, ischemic heart disease, renal dialysis, rehabilitation, and length of stay. The P of interaction between acupuncture and medication is < 0.0001 .

§ Compared with stroke patients with medication therapy but without acupuncture treatment, the HR of stroke recurrence for those with both acupuncture treatment and medication therapy was 0.93 (95% CI = 0.89–0.97).

TABLE 4. Risk of Stroke Recurrence in Association With Numbers of Package of Acupuncture Treatment

Numbers of Package	n	Events	Person-Years	Incidence*	HR	(95% CI) [†]
0	15,029	5749	80,497	71.4	1.00	(Reference)
1	4378	1462	16,194	90.3	1.03	(0.97–1.09)
2	2309	723	9744	74.2	0.91	(0.84–0.98)
3	1505	467	6497	71.9	0.89	(0.81–0.98)
4	1062	320	4813	66.5	0.85	(0.76–0.95)
≥5	5775	1667	29,076	57.3	0.77	(0.73–0.81)

* Per 1000 person-years.

[†] Adjusted for age, sex, low income, intensive care unit stay, diabetes mellitus, hypertension, hyperlipidemia, liver cirrhosis, mental disorder, ischemic heart disease, renal dialysis, rehabilitation, antiplatelet agents, anticoagulants, lipid-lowering agents, and length of stay.

expenditure for the first stroke, 2 indirect indicators of stroke severity. Figure 1 shows that the probability for being free of a second stroke was significantly higher among those with acupuncture treatment than those without. The validity of the data presented in this retrospective study is also supported by the finding that those receiving medical treatment fared better than those without as presented in Table 4.

Based on the findings of this study, we proposed some possible explanations for clarifying the effectiveness of acupuncture treatment on stroke recurrence. While systematic reviews failed to establish that acupuncture is a valid rehabilitative measure in improving functional outcome in stroke patients, there are a number of publications showing acupuncture was indeed effective in improving neurological function or physical capability among stroke patients.^{15,16} Increased physical activities have been shown to reduce stroke risk.³⁷ We have also shown that physical activity is effective in reducing stroke mortality.¹⁹ These findings together raise the possibility that acupuncture may have impact through improved physical activity to reduce the risk of recurrent stroke. The salutary effect of acupuncture may not be restricted to improvement in physical activity. It has been shown that acupuncture is useful in lowering blood pressure,^{21,22} reducing the expression

of inflammatory mediators,³⁸ and improving lipid profile.^{24,25} It is believed that lower blood pressure, lipid profile, and less inflammation mediators may lead ischemic stroke patients with acupuncture treatment to have decreased risk of recurrent stroke.

This study has some limitations. First, as we used retrospective medical claims data from health insurance that lacked detailed patient’s information in detail on lifestyle as well as physical, psychiatric, and laboratory examinations, we were unable to differentiate whether these factors influenced the effects of acupuncture treatment on stroke patients. Second, we used ICD-9-CM codes claimed by physicians for the stroke without clarifying the severity of disease, our study would have been improved if we had information of National Institute of Health Stroke Scale. Third, our study could not show the acupuncture points used in patient care due to the limited information from National Health Insurance Research Database. While acupuncture treatment for NHI reimbursement has been closely monitored with strict regulatory accreditation guidelines, the acupuncture protocols were not controlled as in clinical trial settings. Finally, another limitation is that stroke patients who chose acupuncture might have been more motivated to improve post-stroke complications than those did not. Our additional analysis (not shown in the tables) also showed that receiving Chinese herbal medicine (1 of subtypes of traditional Chinese medicine that was also covered in the Taiwan’s National Health Insurance) was associated with reduced risk of recurrent stroke in both stroke patients with (HR 0.73, 95% CI 0.68–0.78) and without (HR 0.63, 95% CI 0.59–0.67) receiving acupuncture treatment.

CONCLUSIONS

In this nationwide retrospective cohort study of ischemic stroke patients, the reduced risk of recurrent stroke was found in the cohorts with acupuncture treatment. Patients with ischemic stroke underwent medication and acupuncture treatment had the lowest risk of stroke recurrence. However, the potential beneficial effects of acupuncture as a supplement measure to reduce stroke recurrence deserve further exploration in well designed clinical trials with stringent acupuncture protocols and sham control in a blinded fashion.

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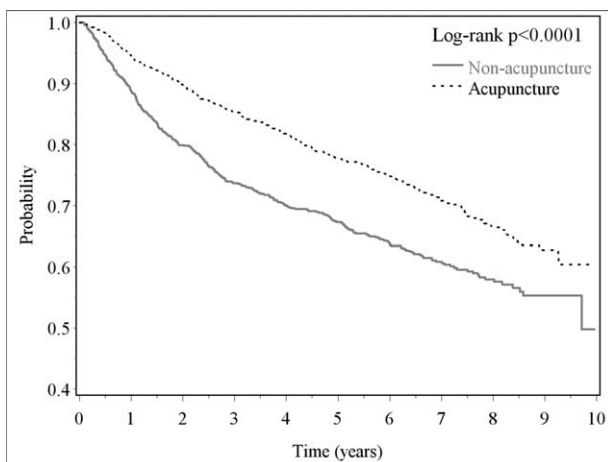


FIGURE 1. Kaplan–Meier analysis for stroke recurrence in ischemic stroke patients newly diagnosed in 2000 to 2004 with and without acupuncture treatment for follow-up to the end of 2009.

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