

## Clinical Observation

## Mortality and recurrence of vascular disease among stroke patients treated with combined TCM therapy

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### Abstract

**OBJECTIVE:** To confirm the long-term outcomes of stroke patients and determine predicting factors for death, recurrence of vascular events and poor outcome (either recurrence or death) after the use of combined TCM therapy.

**METHODS:** This was a retrospective hospital-based cohort study and was performed in the First Affiliated Hospital of Tianjin University of Traditional Chinese Medicine in Tianjin. All subjects with stroke consecutively admitted to an inpatient ward of the Acupuncture Department from January 1, 2008, to December 31, 2008 were retrospectively followed through one year. The main outcomes were either

a recurrence of vascular events,, mortality or both. Risk factors were recorded from medical records. Multivariate regression models were used to analyze predictors. The following independent variables were used: age, gender, hypertension, ischemic heart disease, atrial fibrillation, diabetes mellitus, carotid arterial lesions and history of stroke.

**RESULTS:** Four-hundred and five patients were included. The 1-year mortality rate was 11.11% . 23.70% of the patients had a recurrent vascular event, and 30.86% suffered a poor outcome. Multiple logistic regression analysis found that previous stroke, and advanced age were predictors of death within one year, Recurrence of vascular events was associated with carotid arterial lesions, history of diabetes and previous stroke. Long-term poor outcome was predicted by advanced age, history of diabetes, and previous stroke.

**CONCLUSION:** Age, previous stroke, carotid arterial lesions and diabetes history seem to have different impacts on the three outcomes within one year. Our findings provide important data for planning future hospital register studies of stroke patients in TCM hospitals.

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**Key words:** Stroke; Acupuncture; Traditional Chinese medicine; Mortality; Recurrence; Risk factors

### INTRODUCTION

Stroke is the leading cause of death and a major cause of disability in adults in China, which contributes sub-

stantial economic burden to the health care system. Stroke mortality has declined during the past decades in the United States and in most western and northern European countries<sup>[1-2]</sup>. In contrast, in China the stroke mortality rate has remained stable or even increased as the population has aged<sup>[3]</sup>. Among survivors, recurrence is common with cumulative disability among those affected. A survey conducted in 19 urban neurological clinics in China<sup>[4]</sup> showed that patients with recurrent strokes accounted for 47% of stroke cases in outpatient clinics. But hospitals of Traditional Chinese Medicine (TCM) were not included in the survey. In China, acupuncture combined with the use of herbal medicines and conventional medical care (combined TCM therapy) is used for stroke treatment in most TCM hospitals. But little is known about whether combined TCM therapy could reduce the long-term mortality and recurrence of cerebral vascular diseases. We designed the present study to compare three different domains of poor stroke outcome, with special attention given to the factors that predict poor outcomes after stroke onset in patients referred from the inpatient ward of a TCM hospital.

## METHODS

### *Study design and setting*

This was a retrospective hospital-based study performed in the First Affiliated Hospital of Tianjin University of Traditional Chinese Medicine in Tianjin, China. The protocol followed the ethical guidelines of the Clinical Research Ethics Committee of Tianjin University of Traditional Chinese Medicine.

### *Inclusion criteria*

All subjects with stroke consecutively admitted to inpatient ward of the Acupuncture Department during a 12-month period, from January 1, 2008, to December 31, 2008, were followed retrospectively for one year. Stroke was defined according to western medicine diagnosis standards in China<sup>[5]</sup> and confirmed by computerized tomography (CT) or magnetic resonance imaging (MRI). Briefly, we recruited patients admitted with transient ischemic attack (TIA), cerebral infarct and intra-cerebral hemorrhage. Patients with subarachnoid hemorrhage were not included in the present study because of the differences in their etiology and prognosis. Patients that underwent less than 12 sessions of acupuncture were excluded.

### *Interventions*

All patients accepted "Xing Nao Kai Qiao" acupuncture, combined with traditional Chinese medicine and conventional medicine care. "Xing Nao Kai Qiao" is a specific acupuncture method. Points primarily on the Yin and Du meridians are

selected and standard quantitative manipulations are applied, which are quite different from traditional point selection and acupuncture manipulations. It has been used for stroke rehabilitation nearly 40 years. The main points were Shuigou (GV 26), Neiguan (PC 6), Sanyinjiao (SP 6), Jiquan (HT 1), Chize (LU 5), and Weizhong (BL 40).

Chinese doctors trained and accredited at the First Affiliated Hospital of Tianjin University of Traditional Chinese Medicine administered acupuncture. All doctors had at least five years of training in traditional Chinese medicine, combined with additional practice of acupuncture for several years. Five to six sessions were administered weekly. Each session lasted 30 min.

Traditional Chinese medicine Danqi Piantan Jiaonang (DJ) and individualized herbal medicine prescriptions were given to the patients. DJ was taken four capsules after each meal, three times per day. Herbal medicines were prescribed by attending physicians according to the theory of TCM and condition of each patient. Conventional medical care, meaning skilled medical and nursing care was provided.

### *Data collection*

Baseline data on the participants' demographic characteristics, lifestyle-related risk factors and vascular risk factors (history of hypertension, diabetes mellitus, ischemic heart disease, atrial fibrillation and previous TIA or stroke) were collected from medical records. All survivors were followed up over the telephone by a single doctor using a standardized questionnaire.

### *Outcomes*

The specified outcomes were defined as death and occurrence of a further vascular event (including TIA, stroke or acute coronary syndrome). The long-term combined poor outcome was regarded as occurrence of either death or a further vascular event. If death and a further vascular event (supposed cause of death) were recorded as occurring simultaneously, one event was categorized in the analysis. For example, if a patient died of acute myocardial infarction, we regarded the event as death in the mortality analysis and as a further vascular event in the further-vascular-event analysis. The nature of the vascular event and the cause of death were based on medical records and death certificates when possible. A definite and detailed description of the cause of death by the patient's relative was used if the cause could not be obtained by other means. Obscure or indefinite information about cause of death was classified as unknown cause.

### *Statistical analysis*

All data were stored and analyzed using SPSS software (version 13.0 for Windows). Statistical significance was considered at  $P < 0.05$  and was two-sided.

In the present study, age, sex, vascular risk factors and

end point outcomes were used as categorical variables. Age was categorized into two groups:  $\geq 65$  years and  $< 65$  years. In univariate analyses, independent-samples  $t$  test and  $\chi^2$  test or Fisher's exact tests were used. We also applied the  $\chi^2$  test for trends to explore the relationship between vascular risk factors and occurrence of a further vascular event or death. Multivariate logistic regression was used to calculate which factors contributed to the poor outcomes. Odds ratio (OR), 95% confidence interval (CI) and probability values were observed.

## RESULTS

### Study population

Eight hundred and nineteen stroke patients were consecutively admitted to the inpatient wards of the Acupuncture Department between January 1, 2008 and December 31, 2008. Five hundred and twenty-four patients met the inclusion criteria. Sixty-one patients denied consent to answer questions during the telephone interview. Fifty-eight patients were lost to follow-up and 405 patients responded to the telephone interview. The follow-up rate was 77.29 percent. Among the 405 patients, 239 (59%) were male. The age of the patients ranged from 35 to 89 years (median, 61.6 years), with 220 patients (54.3%) younger than 65 years. Two hundred and thirteen (52.59%) of them were admitted for their first stroke. Most (374, 92.3%) were diagnosed with cerebral infarction. Average days admitted to the inpatient wards were 28.5, ranging from 14 to 82 days. Vascular risk factors were common among these patients and hypertension (83.95%), history of cardiovascular disease (80.49%) and previous stroke (47.41%) were the three most common vascular risk factors. Atrial fibrillation was found in 23 patients (5.7%). Of 405 patients, 339 (83.70%) had carotid arterial lesions on ultrasonography in the initial TCD examination. The patients received a mean of  $24.16 \pm 8.23$  acupuncture treatments. Among the total of 405 patients, 239 received equal to or more than 24 acupuncture treatments. The clinical characteristics of patients are reported in table 1.

### Occurrence of death

We followed patients for one year after discharge. After one year, 45 patients (11.11%) died of any cause (including vascular and nonvascular). Three hundred and sixty patients (88.89%) survived, with 280 patients alive free of a further vascular event and 142 patients (35.06%) were independent in activities of daily living. Among the 45 deaths, 18 (40%) died of vascular causes, 10 patients (22.22%) died of nonvascular causes and 17 patients (37.78%) died of unknown causes. Cerebrovascular events were a more common cause of death than cardiac events (15 vs. 3, respectively).

Of the 405 patients, the one-year cumulative mortality rate was 11.1% (95% CI, 10.21 to 11.53). The cumulative mortality rate was 4.20% (95% CI, 3.78 to 4.65) at six months and 2.22% (95% CI, 1.76 to 2.68) at three months. Table 2 shows the detailed underlying causes of death.

Table 1 Baseline characteristics of the study population

No. of subjects	405
Age, median (range)	61.5 (35-89)
Male gender, $n$ (%)	159 (39.26)
Arterial hypertension, $n$ ,% (95% CI)	340, 83.95 (79.86, 87.65)
Ischemic heart disease, $n$ ,% (95% CI)	326, 80.51 (76.04, 84.62)
Whereof myocardial infarction	3, 0.74 (20.50, 99.91)
Atrial fibrillation, $n$ ,% (95% CI)	23, 5.68 (0.13, 18.53)
History of stroke, $n$ ,% (95% CI)	192, 47.41 (40.35, 54.47)
Carotid arterial lesions, $n$ ,% (95% CI)	339, 83.70 (79.58, 87.43)

Table 2 Underlying causes of death

Cause of Death*	Total, $n$ (%)
Recurrent stroke	
Hemorrhage	1(2.22)
Ischemia	12(26.67)
Index stroke	2( 4.44)
Acute coronary syndrome	3(6.67)
Pulmonary carcinosis ,	1(2.22)
Gastric carcinoma,	1(2.22)
Congestive heart failure	8(17.78)
Nonvascular	10(22.22)
Unknown	17(37.78)
Total, $n$ (%)	45(100%)

Note: \* $P < 0.05$ .

To analyze the effect of acupuncture treatments, sessions of acupuncture were divided into two categories: less than 24 times and more than or equal to 24 times. We found a higher cumulative mortality rate at three and six months in the previous group than that in the latter (4.84% vs. 0.04%; relative risk [RR] =11.52; 95% CI, 1.454 to 91.228; 7.83% vs. 2.09%; RR=3.74; 95% CI, 1.360 to 10.301), but not different between the two groups at one year follow-up (12.65% vs. 10.04%; RR=1.26; 95% CI, 0.726 to 2.186,  $P=0.41$  by  $\chi^2$  test).

Univariate analysis showed that more deaths occurred in male and elderly patients ( $\geq 65$  years of age). Patients with history of diabetes or previous history of stroke also had a greater risk of death (Table 3).

To evaluate which risk factors were independent predictors of death within one year, multiple logistic regression analysis was used. The following explanatory variables were included: 1) age, 2) sex, 3) ischemic heart disease, 4) atrial fibrillation, 5) hypertension, 6) diabetes mellitus, 7) carotid arterial lesions and 8) a previous history of stroke. Age (OR=6.25; 95% CI, 2.49 to 15.69;  $P=0.000$ ) and previous history of stroke (OR=

2.86; 95% CI, 1.32 to 6.23;  $P=0.008$ ) were identified as predictors of death within one year.

**Recurrence of Vascular event**

Of the 405 patients, a first major vascular event occurred in 96 patients (23.70%) within one year. These major vascular events included three acute coronary syndromes and 93 strokes. Of the 96 vascular events, 16 were fatal, including 13 cerebrovascular events and three acute coronary syndromes.

Overall, the one-year cumulative recurrence rate of vascular events was 23.70% (95% CI, 23.28 to 24.02), 7.9% (95% CI, 7.68 to 8.32) at six months and 2.96% (95% CI, 2.51 to 3.44) by three months. No significant differences were observed for recurrence of vascular events between patients receiving acupuncture less than or more than and equal to 24 sessions at three months (3.01% vs. 2.93%; RR=1.03; 95% CI, 0.896 to 5.716), six months (9.04% vs. 7.11%; RR=1.27; 95% CI, 0.653 to 2.471) or one year (25.9% vs. 22.18%; RR = 1.17; 95% CI, 0.823 to 1.658).

Univariate analysis showed that the recurrence rate of vascular events was significantly higher in elderly patients ( $\geq 65$  age of years) than in younger patients ( $P=$

0.000 by  $\chi^2$  test). In addition, patients with ischemic heart disease, carotid arterial lesions, diabetes history and previous stroke history also showed a significantly higher recurrence rate for vascular events (Table 3).

Multiple logistic regressions were used to evaluate which risk factors could predict a recurrent vascular event within a year after acupuncture treatment. Carotid arterial lesions (OR=5.76; 95% CI, 1.93 to 17.19;  $P=0.002$ ), history of diabetes (OR=2.57; 95% CI, 1.51 to 4.39;  $P=0.001$ ) and a previous history of stroke (OR=5.77; 95% CI, 3.23 to 11.33;  $P=0.000$ ) were predictors of long-term recurrence of vascular events in stroke patients treated with acupuncture.

**Predictors of poor outcome**

Both vascular events and subsequent death represent poor outcomes after stroke. A total of 125 patients (30.86%) suffered a poor outcome. Total deaths included 10 deaths resulting from nonvascular causes (2.47%), 13 (3.21%) deaths resulting from recurrent stroke, 2 deaths of index stroke (0.49%), 3 deaths resulting from acute coronary syndrome (0.74%) and 17 deaths of unknown causes (4.20%), with 80 subjects alive with subsequent vascular events (19.75%).

Table 3 Mortality and recurrence of vascular events within one year

Factors (n)	Mortality, n(%)	P	RR, (95%CI)	Recurrence, n(%)	P	RR, (95%CI)
Gender			1.77, (1.019-3.067)			1.26, (0.885-1.780)
Male (159)	24 (15.09)	0.040*		43 (27.04)	0.204	
Female (246)	21 (8.53)			53 (21.54)		
Age			7.75, (3.347-17.851)			4.82, (3.034-7.649)
$\geq 65$ (185)	39 (21.08)	0.000*		77 (41.62)	0.000*	
<65 (220)	6 (2.72)			19 (8.64)		
Hypertension			0.88, (0.432-1.810)			1.64, (0.904- 2.992)
Yes (340)	37 (10.88)	0.738		86 (25.29)	0.085	
No (65)	8 (12.31)			10 (15.38)		
Ischemic heart disease			1.94, (0.791-4.752)			1.70, (0.976-2.948)
Yes (326)	40 (12.27)	0.132		84 (25.77)	0.047*	
No (79)	5 (6.33)			12 (15.19)		
Carotid arterial lesions			0.69, (0.355-1.307)			4.48,(1.705-11.764)
Yes (339)	35 (10.32)	0.254		92 (27.14)	0.000*	
No (66)	10 (15.15)			4 (6.06)		
Atrial fibrillation			1.62, (0.635-4.134)			1.11, (0.544-2.254)
Yes (23)	4 (17.39)	0.519		6 (26.08)	0.782	
No (382)	41 (10.73)			90 (23.56)		
Diabetes mellitus			4.63, (2.552-8.404)			1.92, (1.298-2.539)
Yes (131)	31(23.66)	0.000*		46 (35.11)	0.001*	
No (274)	14(5.11)			50 (18.25)		
History of previous stroke			3.89, (1.979-7.636)			3.96, (2.544-6.169)
Yes (192)	35 (18.23)	0.000*		75 (39.06)	0.000*	
No (213)	10 (4.69)			21 (9.86)		

Note: \* $P<0.05$ .

There was a trend for fewer poor outcomes in patients treated with more acupuncture sessions than those receiving fewer sessions at three months (2.93% vs. 6.63%), six months (7.95% vs. 13.86%) and one year (28.03% vs. 34.94%). But the differences did not reach statistical significance. Multiple logistic regression analysis showed that the occurrence of long-term poor outcomes was associated with age (OR=2.42; 95% CI, 1.44 to 4.05;  $P=0.001$ ), history of diabetes (OR=2.06; 95% CI, 1.22 to 3.47;  $P=0.007$ ) and history of previous stroke (OR=6.80; 95% CI, 4.01 to 11.75;  $P=0.000$ ). No association was found between long-term poor outcomes and gender, hypertension, ischemic heart disease, carotid arterial lesions or atrial fibrillation. The results are shown in Table 4 with 95% CI and probability values.

Table 4 Risk factors for poor outcomes within one year

Risk Factors	Univariate model OR (95% CI)	Multivariate model OR (95% CI)
Age	3.85 (2.44-6.05)*	2.42 (1.44-4.05)*
Male gender	0.62 (0.41-0.95)*	0.65 (0.39- 1.08)
Hypertension	1.31 ( 0.72-2.39)	1.73 (0.86-3.47)
Ischemic heart disease	2.17 (1.18-3.99)*	1.61 (0.58-4.47)
Carotid arterial lesions	2.01 (1.05-3.84)*	1.95 (0.93-4.09)
Atrial fibrillation	1.79 (0.76-4.19)	0.535 (0.25-1.16)
Diabetes mellitus	1.81 (1.17-2.82)*	2.06 (1.22-3.47)*
History of stroke	7.66 (4.65-12.60)*	6.86(4.01-11.75)*

Note: \* $P<0.05$ .

## DISCUSSION

No previous study has reported mortality and recurrence of vascular events in stroke inpatients seen in a TCM hospital after treatment with combined TCM therapy. To the best of our knowledge, this was the first retrospective hospital-based study to demonstrate the long-term outcomes after stroke onset in a TCM hospital. Although our study is small compared with some longitudinal or multicenter studies, it has the advantage of a complete case assessment performed by a single investigator who evaluated patients at both baseline and the one-year follow-up.

We found that hypertension, history of cardiovascular diseases and carotid arterial lesions were the main vascular risk factors among stroke patients. Recurrent stroke account for nearly half of the stroke patients, which is consistent with a previous survey conducted in 19 urban neurological clinics in China<sup>[4]</sup>.

The present study showed that the cumulative mortality rate was 2.22% by three months, 4.20% at six months and 11.1% within the first year. The cumulative recurrence rate of vascular events was 2.96% by three months, 7.9% at six months and 23.70% within

the first year. Patients seem to have the greatest risk of death or recurrence after the first six months of a stroke.

This study showed that history of previous stroke had an impact on long-term outcome in terms of mortality, recurrence of vascular events and poor outcomes. Interestingly, carotid arterial lesions were a predictor of recurrence of vascular events within one year but not mortality. Age was associated with both death and poor outcome. Diabetes contributed to vascular events and poor outcomes, but not to deaths. Patients in their first stroke onset had a lower proportion of deaths, recurrence of vascular events and poor outcomes than those with a history of previous stroke. Sessions of combined acupuncture therapy after stroke onset improved short-term, but not long-term survival, vascular events and poor outcomes. Moreover, the mean age of the patients in our study was younger (61.5 years) than many other cohorts, which may indicate that an age bias exists in TCM hospital inpatients.

Our survey found that 83.7% of stroke patients had carotid arterial vascular lesions (339 of 405). Carotid arterial lesions had an impact on the recurrence of vascular event, but were not associated with mortality within one year in univariate and multivariate analyses. This differs from a previously reported meta-analysis, which reported that patients with intracranial carotid stenosis or occlusion had a higher rate of recurrent stroke (rate ratio=1.09; 95% CI, 1.05 to 1.14) and vascular mortality (rate ratio=1.10; 95% CI, 1.06 to 1.14)<sup>[6]</sup>. It is also not consistent with another study conducted in China<sup>[7]</sup>.

Atrial fibrillation is perhaps the most well recognized cardiac risk factor. Atrial fibrillation was a predictor of death<sup>[8,9]</sup> as well as functional independence after stroke onset<sup>[10]</sup>. However, this was not shown in the present study. The number of patients with atrial fibrillation in this study was small, which negatively affects power.

Age and ischemic heart disease are risk factors for mortality and dependency within the first year after a first stroke. It has been reported that advanced age and ischemic heart disease are predicting factors of poor outcome after stroke<sup>[10,11]</sup>. Our data confirmed that age has an adverse influence on long-term prognosis. However, the impact of ischemic heart disease on one-year recurrence in the present study was significant in only the univariate regression model.

Hypertension and diabetes mellitus were previously reported to be the main risk factors in stroke patients<sup>[12]</sup>. Many studies also confirmed the negative impact of hypertension on the long-term mortality and recurrence of stroke. The effect of hypertension is not shown in the present study. This study shows that the best predictor for both recurrence vascular events and poor outcome was diabetes mellitus.

Several studies have demonstrated that acupuncture changed the level of blood pressure modulators such as

endothelin-1<sup>[13]</sup>, rennin<sup>[14]</sup>, and angiotensin II<sup>[15]</sup> in hypertensive patients. Clinical trials also found positive effects of acupuncture on hypertension, lowering blood pressure<sup>[16]</sup>. This study did not take the patients' blood pressure into account during the period of follow-up. We also did not take secondary prevention or stroke severity into account. These are the limitations of our study.

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