Association of dementia with death after ischemic stroke: A two-year prospective study

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Abstract. The association between dementia and the risk of death after ischemic stroke was investigated. Neurological, neuropsychological and functional assessments were evaluated in 619 patients with acute ischemic stroke. Dementia was diagnosed at admission and at three months after stroke onset. The patients were scheduled for a two-year follow-up after the index stroke. The Kaplan-Meier survival and Cox proportional hazards regression analyses were used to estimate the cumulative proportion of survival, and the association between dementia and risk of death after stroke. In total, 146 patients (23.6%) were diagnosed with dementia after stroke. The cumulative proportion of surviving cases was 49.3% in patients with dementia after a median follow-up of 21.2±5.6 months, and 92.5% in patients without dementia. Multivariate analysis revealed that dementia (HR, 7.21; 95% CI, 3.85-13.49) was associated with death, independent of age, atrial fibrillation, previous stroke and NIH stroke scale. In conclusion, the mortality rate is increased in stroke patients with dementia. Dementia is an important risk factor for death after stroke, independent of age, atrial fibrillation, previous stroke, and the severity of the stroke.

Introduction

Epidemiological studies have consistently demonstrated that there is a high incidence rate of stroke and mortality (11,663/100,000 per year) in China (1). Poor outcomes after stroke have been reported in numerous countries worldwide (2-5). The risk factors of death after stroke include age, stroke severity, history, previous stroke and atrial fibrillation. Previous studies have focused on the association between death after stroke and the decline of cognitive function or dementia caused by stroke (6-8). The results suggested that dementia is a potentially important factor influencing survival after stroke (7,9-12).

With a population of 1.3 billion in China, the prevalence of patients with ischemic stroke is extremely high (1). Owing to racial differences and economic lifestyle, the mortality rate and its risk factors in Chinese patients after ischemic stroke may differ from that in western countries (13). At present, few studies have focused on the relationship between dementia and survival after stroke in China.

In the present study, we studied a large cohort of patients in Chongqing, China with acute ischemic stroke, to investigate the association of mortality with dementia post-stroke.

Subjects and methods

Subjects. From January 2005 to July 2008, patients with ischemic stroke who were admitted to Daping Hospital (Chongqing, China) were registered. Eligibility requirements included: i) acute onset of ischemic stroke within 48 h; and ii) aged ≥55 years. The diagnosis of ischemic stroke was confirmed when there were focal signs of cerebral dysfunction of acute onset lasting for >24 h, brain CT scan or MRI.

In total, 727 patients were admitted during the study period, and 95 declined to participate. Thus, 619 patients were enrolled into the present study.

Clinical assessment. During admission, the patients underwent structured demographic data, medical history, neurological and head imaging examinations. The data collected were: age, gender, educational level (<6 or ≥6 years), cigarette smoking (current, past and non-smoking) and alcohol intake (daily, weekly, monthly and non-alcohol intake), heart diseases (myocardial infarction, atrial fibrillation, and heart failure, diagnosed and treated previously or during admission), hypertension (previously diagnosed and treated or systolic pressure >160 mmHg and/or diastolic pressure >90 mmHg persistently observed during admission after the acute phase), diabetes mellitus (previously diagnosed and

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treated or fasting glucose >7 mmol/l in two blood samples after the acute phase), stroke severity (NIH stroke scale), neurological sign, and stroke features (location, type of lesion, and stroke mechanism).

Neuropsychological evaluation. During admission, the dementia before index stroke was assessed by inquiring close relatives of the patients using a Chinese version of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), previously validated in the Chinese population (14). Functional status prior to stroke was assessed with the activity of daily living (ADL) (15).

At three months after the index stroke, the subjects were administered with a battery of neuropsychological tests developed for use in epidemiologic studies of dementia (16,17). This neuropsychological battery of tests included: the Chinese Mini-Mental State Examination (CMMS) (18), ADL (19,20), instrumental ADL (15), Pfeiffer's Outpatient Disability Questionnaire (POD) (21), the Fuld Object-Memory Evaluation (FOM) (22), rapid verbal retrieval (RVR) (23), revised Wechsler Adult Intelligence Scale (DS and BD subtests) (24), and the Hamilton Rating Scale for Depression. The normative data for these tests were previously established in a control group of healthy elderly volunteers living in the same urban area and with the same age, gender distribution, and cultural background (16). The score ≤1 SD of normative value was judged as unnormative.

The diagnosis of dementia was performed by a group of senior neurologists and psychiatrists based on criteria modified from the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) (25).

Statistical analyses. Participants who were lost or declined for follow-up were considered as censored data. As the onset time of dementia was not exactly observed, we defined the time to an event as the time of a diagnosis of dementia.

The univariate analyses were taken to compare the data of the death and survival groups, including demographic data, smoking, drinking, comorbidities, stroke severity and characteristics. Categorical variables were compared using the Pearson Chi-square test, and quantitative variables were compared using an independent samples t-test or the Mann-Whitney U test in appreciation.

The cumulative proportion of patients surviving in the groups with and without dementia was determined using the Kaplan-Meier survival analyses (26). In the multivariate analysis, we studied the association between dementia and risk of death using the Cox proportional hazards regression analysis with a backward procedure and with p>0.05 as the criterion for exclusion to estimate hazard ratios (HRs), with 95% confidence intervals (CIs). These analyses were performed using SPSS for Windows, version 10.0 (SPSS Inc., Chicago, IL, USA).

Results

Follow-up, prevalence and incidence of dementia and mortality. Of the 619 patients, 39 (6.3%) were diagnosed with dementia during admission and 107 (17.3%) three months after index stroke. Thus, 146 (23.6%) patients were diagnosed with dementia.
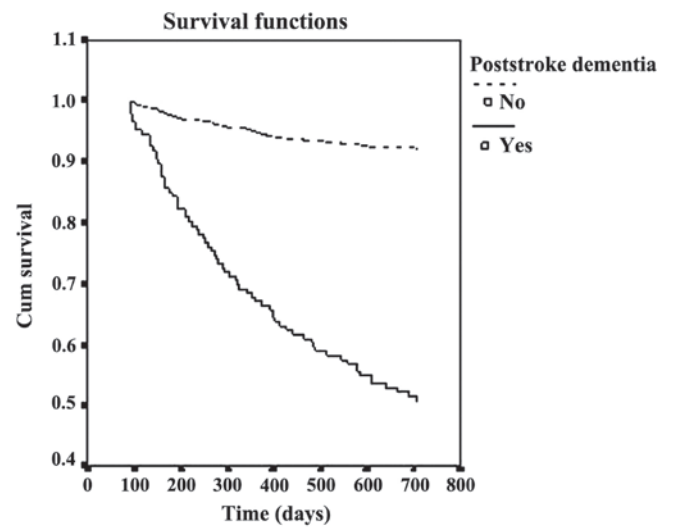

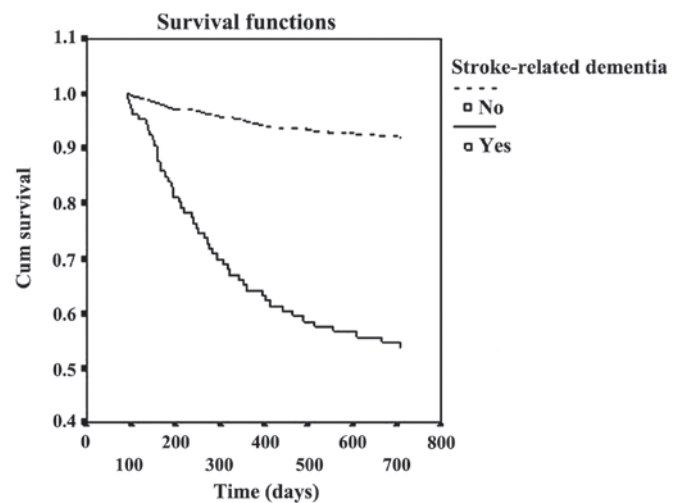Figure 1. Relationship between probability of survival and time.

Figure 2. Relationship between probability of survival and time.

After a median follow-up of 10.3±5.7 months, 112 patients (16.5%) succumbed during the study. A total of 29 patients (4.7%) were lost during follow-up. The median follow-up time was 9.1±5.3 months and four of 29 patients were diagnosed as having dementia.

After a median follow-up of 21.2±5.6 months, the cumulative proportion of case survival was 49.3 and 92.5% in patients with and without dementia, respectively. The survival curves were significantly different (p<0.001) between the two groups (Figs. 1 and 2).

Demographic characteristics, smoking, drinking, comorbidities, dementia and stroke features of patients according to death. Table I indicates the demographic characteristics, smoking and drinking status, and comorbidities of deceased and surviving patients. Deceased patients were older (74.6±11.2 vs. 65.2±9.3, p<0.001), less frequent with diabetes mellitus [odds ratio (OR), 0.93; 95% CI, 0.63-1.40], and more frequent in female (OR, 1.04; 95% CI, 0.72-1.48), hypertension (OR, 1.13; 95% CI, 0.75-1.70), myocardial infarction (OR, 1.26; 95% CI, 0.67-2.39), heart failure (OR, 1.22; 95% CI, 0.61-2.43),

Table I. Demographic characteristics, smoking, drinking and comorbidities according to death after stroke.

Variable	Death (n=112)	Survival (n=507)	P-value or OR (95% CI)[a]
Age (years), mean ± SD	74.6±11.2	65.2±9.3	p<0.001
Lower education (≤6 y), n (%)	38 (33.9)	187 (36.9)	0.881 (0.543-1.429)
Female, n (%)	57 (50.9)	249 (49.1)	1.04 (0.72-1.48)
Hypertension, n (%)	63 (56.3)	271 (53.5)	1.13 (0.75-1.70)
Diabetes mellitus, n (%)	34 (30.3)	158 (31.1)	0.93 (0.63-1.40)
Myocardial infarction	12 (10.7)	43 (8.5)	1.26 (0.67-2.39)
Heart failure, n (%)	15 (13.4)	59 (11.6)	1.22 (0.61-2.43)
Atrial fibrillation, n (%)	39 (34.8)	97 (19.1)	2.24 (1.41-3.53)
Prior stroke, n (%)	28 (25.0)	65 (12.8)	2.28 (1.40-3.70)
Current smoking, n (%)	47 (41.9)	192 (37.1)	1.16 (0.76-1.79)
Daily alcohol intake, n (%)	39 (34.8)	149 (28.8)	1.36 (0.83-2.21)
Post-stroke dementia, n (%)	74 (66.1)	72 (14.2)	12.01 (7.35-19.64)

[a]OR was adjusted for age, educational level and gender. OR, odds ratio; CI, confidence interval; SD, standard deviation.

Table II. Stroke features according to death after stroke.

Variable	Death) (n=112)	Survival (n=507)	P-value or OR (95% CI)
Location, n (%)			
Left hemisphere	47 (41.9)	206 (40.1)	1.48 (0.95-2.28)[a]
Right hemisphere	49 (43.8)	145 (28.6)	
Vertebrobasilar	16 (14.3)	156 (30.8)	
Type of lesion, n (%)			2.15 (1.49-3.11)[b]
Single	66 (58.9)	386 (76.9)	
Multiple	46 (41.1)	116 (23.1)	
Stroke mechanism, n (%)			4.21 (2.36-7.53)[c]
Thrombotic	86 (76.8)	461 (90.9)	
Embolic	23 (20.5)	30 (5.9)	
Others	3 (2.7)	16 (3.2)	
NIH stroke scale (SD)	9.34 (6.7)	6.81 (4.7)	p<0.001

OR was adjusted for age, educational level and gender. [a]Right vs. left; [b]multiple vs. single; [c]embolic vs. thrombotic; OR, odds ratio; CI, confidence interval.

Table III. Cox proportional hazards regression analysis according to dementia.

Variable	SE OR (95% CI)
Age (years)	1.06 (1.02-1.10)
Atrial fibrillation	1.78 (1.32-2.40)
Previous stroke	2.14 (1.49-3.08)
NIH stroke scale	1.15 (1.04-1.27)
Dementia	7.21 (3.85-13.49)

Values are expressed as HR (95% CI). HR, hazard ratio; CI, confidence interval.

with ischemic stroke were age (HR, 1.06; 95% CI, 1.02-1.10), atrial fibrillation (HR, 1.78; 95% CI, 1.32-2.40), previous stroke (HR, 2.14; 95% CI, 1.49-3.08), NIH stroke scale score (HR, 1.95; 95% CI, 1.04-1.27), and dementia (HR, 7.21; 95% CI, 3.85-13.49) in the Cox's regression model (Table III).

Discussion

Chongqing, the largest city in southwest China, has an urban population of five million individuals, of whom 93.6% are Han, and have similar lifestyles (27). Furthermore, the social and economic characteristics of the city is a miniature version of China today, and can be a good sample to study disease features. In the present study, the Kaplan-Meier analysis revealed that the cumulative proportion of survival cases was 49.3 and 92.5% in patients with and without dementia, after median follow-up of 21.2±5.6 months. The mortality rate of patients with dementia was >4-fold that of patients without dementia.

The results of the present study with regard to the cumulative proportion of survival of dementia after stroke str consistent with other studies in western countries. Previous findings on vascular dementia suggested that patients with vascular dementia had a higher risk for

atrial fibrillation (OR, 2.24; 95% CI, 1.41-3.53), prior stroke (OR, 2.28, 95% CI, 1.40-3.70), current smoking (OR, 1.16; 95% CI, 0.76-1.79), daily alcohol intake (OR, 1.36; 95% CI, 0.83-2.21), and dementia (OR, 12.01; 95% CI, 7.35-19.64). Only differences in age (p<0.001), atrial fibrillation (p<0.001), prior stroke (p=0.001) and dementia (p<0.001) reached statistical significance.

Table II shows the stroke features according to death. Stroke features associated with death included multiple stroke lesions (OR, 2.15; 95% CI, 1.49-3.11), and embolism (OR, 4.21; 95% CI, 2.36-7.53), and NIH stroke scale score (p<0.001).

Multivariate analysis of death after ischemic stroke in patients with dementia. Independent predictors for death in patients

mortality compared to the control subjects (28,29). A study in Finland showed dementia is a significant predictor of poor long-term survival and death from brain-associated causes in patients with acute stroke (30). Barba *et al* (31) also found that dementia increased the risk for mortality in stroke patients. A study demonstrated that the mortality rate was 15.90 deaths/100 person-years in dementia patients with ischemic stroke and 5.37 deaths/100 person-years in non-dementia patients with ischemic stroke during a period of up to 10 years of follow-up (32). Another study suggested that the cumulative proportion surviving after a median follow-up of 58.6 months was 38.9±0.08% for those with dementia and 74.5±0.04% for those without dementia (12). There are discrepancies between our findings and those of the abovementioned studies. The reason may be because the duration gap and outpatient treatment is different.

Consistent with other studies (9,23-38), age, atrial fibrillation, NIH stroke scale, and prior stroke were found to be associated with death after stroke in the present study. We also found that dementia was associated with long-term survival of stroke patients. This association was independent of other predictors of post-stroke death such as older age, higher stroke severity, presence of atrial fibrillation and previous stroke. In a prospective study on the association between mortality and dementia after stroke, dementia was demonstrated to adversely influence long-term survival after stroke, even after adjusting for other commonly accepted predictors of stroke mortality (12). In studies of cognitive decline and death after first-ever stroke, dementia was also proven to be an important predictor (9,39). Dementia was considered to have prognostic implications in stroke patients, i.e., stroke prior to the index stroke and dementia developed after stroke may determine a significant reduction in survival and were among the most important risk factors of mortality in these patients (31). Dementia was identified to be a significant independent risk factor for reduced survival after ischemic stroke, after adjusting for other recognized predictors of mortality in a 10-year follow-up study (32).

Four explanations may be proposed for the mechanism of the elevated risk of death among patients with dementia after ischemic stroke (6,10,12,32,40,41). First, patients with dementia after stroke have an increased burden of cerebrovascular disease, which later may in return increase their risk of death. Second, patients with dementia tend to be treated less aggressively for stroke prophylaxis as well as other medical conditions for their weakened social abilities. Third, patients with dementia may be less compliant with prescribed treatment regiments. Fourth, dementia, either degenerative or vascular, tends to appear in an already weak individual and constitutes by itself a general deleterious condition.

In conclusion, mortality is increased in Chinese stroke patients with dementia. Dementia is a risk factor for death after stroke, independent of other factors including age, stroke severity, atrial fibrillation and previous stroke. Prevention and management of the dementia after stroke is critical to reduce the mortality after stroke.

Acknowledgements

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