Effects of Sex Difference on Clinical Features of Acute Ischemic Stroke in Japan

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Background: Sex differences in stroke characteristics and outcomes have been inconsistent. The goal of this study was to determine the influence of sex on underlying patient characteristics, stroke subtypes and conditions, and outcomes after ischemic stroke from a nationwide registration study. *Methods:* A total of 33,953 patients with acute ischemic stroke, including 13,323 women, were registered in a multicenter, hospital-based registration study based on a computerized database from 162 Japanese institutes (the Japan Standard Stroke Registry Study) between January 2000 and November 2007. *Results:* Women were significantly older than men at stroke onset (75.0 ± 11.7 v 69.3 ± 11.4 years; $P < .0001$). After age adjustment, women more frequently had cardioembolic events (odds ratio [OR] 1.090; 95% confidence interval [95% CI] 1.036-1.146; $P = .0009$) and other strokes (OR 1.177; 95% CI 1.079-1.284; $P = .0003$) and were more hypertensive (OR 1.056; 95% CI 1.006-1.108; $P = .0267$) and more dyslipidemic (OR 1.301; 95% CI 1.234-1.373; $P < .0001$) than men. After multivariate adjustment, onset-to-arrival time was longer (β = 0.0554; $P = .026$), the initial National Institutes of Health Stroke Scale score was higher (β = 0.1565; $P < .001$), and the duration of hospitalization was longer (β = 0.035; $P = .010$) in women than in men. At hospital discharge, women less commonly had a modified Rankin Scale (mRS) score of 0 to 1 (OR 0.802; 95% CI 0.741-0.868; $P < .0001$) and more commonly had a mRS score of 4 to 6 (OR 1.410; 95% CI 1.293-1.537; $P < .0001$) than men. *Conclusions:* Women developed more severe strokes than men in Japan. After multivariate adjustment for initial severity and other characteristics, acute care hospital stays were longer and stroke outcomes at discharge were worse in women than in men. **Key Words:** Asian ethnic—brain infarction—gender—sex difference—stroke.
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Patient sex may be an important determinant for stroke conditions and outcomes. Several studies have shown an advanced age distribution,[1-7] a predominance of cardioembolic mechanisms,[2,8,9] the frequent coexistence of atrial fibrillation,[1,3-5,10,11] and hypertension[1-5,10,11] in female stroke patients compared to male stroke patients. In contrast, the influence of sex on stroke severity and outcomes seems to be inconsistent,[2-5,7,10-14] especially in patients of Asian ethnicity. Stroke is the third most common cause of death and the leading cause of dependency in Japan; among stroke types, subarachnoid hemorrhage is known to predominantly occur in women.[15] However, little evidence of sex differences in subtype, severity, and outcome has been reported for ischemic stroke patients.

A multicenter stroke registration study (the Japan Standard Stroke Registry Study [JSSRS]) was conducted to clarify characteristics of Japanese stroke patients.[16,17] Using data from the JSSRS, the present study aimed to clarify the contribution of sex to stroke subtypes, underlying risk factors, initial conditions at onset, and outcomes of ischemic stroke patients. As another essential demographic factor, contribution of age to these issues was also sought.

Methods

JSSRS is a multicenter stroke registration study based on a computerized database from 162 Japanese institutes. Between January 2000 and November 2007, a total of 47,782 acute stroke patients who were hospitalized within 7 days after stroke onset were registered. Among them, 33,953 patients with ischemic stroke were enrolled in the present study.

The subtype of the initial stroke was determined based on the patient's neurologic, radiologic, hematologic, and cardiologic profiles, principally according to the National Institute for Neurologic Disorders and Stroke (NINDS) Classification of Cerebrovascular Diseases III system: atherothrombotic, cardioembolic, lacunar, and stroke of other etiology. Underlying risk factors (listed in Table 1) were also assessed. As the initial condition, the time interval between symptom onset and hospital arrival and National Institutes of Health Stroke Scale (NIHSS) score on admission were evaluated. As stroke outcomes, length of hospital stay in days, the modified Rankin Scale (mRS) score at hospital discharge and in-hospital death were assessed. Favorable outcome was defined as a mRS score of 0 to 1, corresponding to minimal or no disability. Poor outcome was defined as a mRS score of 4 to 6, corresponding to severe disability or death.

Statistical Analysis

Univariate comparisons of characteristics between women and men and among different age distributions were performed with the Chi-square test for dichotomous variables and the *t* or Mann–Whitney tests for continuous variables. Multivariate logistic regression analyses or multiple linear regression analyses were performed to identify the independent influence of sex and age distribution on stroke conditions and outcome. For each condition and outcome, underlying characteristics which were appropriate for each analysis were entered for adjustment by a forced entry method. *P* < .05 was considered statistically significant. All statistical analyses were performed with the JMP package 8 (SAS Institute Inc, Cary, NC) for Windows.

Results

Of the 33,953 patients who were enrolled in the study, 13,323 (39.2%) were women. The age distribution of stroke patients registered in the study is shown in Figure 1. Women were older than men at stroke onset (75.0 ± 11.7 *v* 69.3 ± 11.4 years; *P* < .0001). Men were more common than women in the septuagenarians or younger, and women were more common in the octogenarians or older.

Stroke Subtypes and Risk Factors

Prevalence of stroke subtypes and risk factors for each sex are shown in Table 1. In both women and men,

Table 1. *Stroke subtypes and risk factors*

	Women (n = 13,323)	Men (n = 20,630)	OR for women	95% CI	OR by 10-year increase	95% CI
Stroke subtype, %						
Atherothrombotic	31.8	35.3	0.831	0.793-0.872*	1.048	1.027-1.068*
Cardioembolic	30.3	24.9	1.090	1.036-1.146*	1.390	1.358-1.422*
Lacunar	30.9	32.5	1.035	0.986-1.086	0.827	0.811-0.844*
Other/unknown	7.0	7.3	1.177	1.079-1.284*	0.687	0.665-0.710*
Risk factor, %						
Previous stroke (n = 32,418)	27.8	30.6	0.687	0.628-0.751*	1.232	1.186-1.280*
Hypertension (n = 32,698)	66.7	64.3	1.056	1.006-1.108†	1.093	1.071-1.114*
Diabetes mellitus (n = 32,891)	24.2	29.5	0.824	0.783-0.868*	0.866	0.848-0.884*
Dyslipidemia (n = 29,873)	29.7	27.0	1.301	1.234-1.373*	0.801	0.784-0.819*
Atrial fibrillation (n = 32,799)	26.1	22.3	0.947	0.897-1.001	1.592	1.552-1.634*
Heavy drinking‡ (n = 26,278)	0.9	14.2	0.066	0.053-0.080*	0.678	0.654-0.703*
Current smoking (n = 26,288)	7.7	40.6	0.142	0.131-0.154*	0.568	0.553-0.584*

Abbreviations: CI, confidence interval; OR, odds ratio.

OR for women is adjusted for age. OR by 10-year increase is adjusted for sex.

*P < .001.

†P < .05.

‡>46 g of alcohol/day.