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Gender Differences in Long-term Functional Outcome after First-ever Ischemic Stroke

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Abstract

Objective Recent studies have demonstrated gender differences in functional outcome after stroke. However, the underlying reasons for differences have been inconsistent. The present study examined whether gender differences in long-term functional outcomes exist among surviving patients with first-ever ischemic stroke and with individual subtypes of stroke.

Methods A total of 997 patients (654 men, 343 women) were followed for 5 years after discharge. Patients were assigned to 4 subtypes of ischemic stroke (atherothrombotic, lacunar, cardioembolic and unclassified infarction). Functional outcomes were expressed as locomotor activity, assessed using a questionnaire delivered by mail 1 and 5 years after stroke. Locomotor function was classified into 5 categories according to the grade of disability.

Results Women showed significantly worse locomotor function than men at both 1 and 5 years ($p < 0.001$ and $p < 0.01$, respectively). Furthermore, significant gender differences in functional outcome were observed in all subtypes of ischemic stroke at 1 and 5 years after stroke. Logistic regression analysis revealed that gender was a significant determinant for functional outcome at 1 and 5 years after stroke ($p < 0.01$ and $p < 0.001$, respectively). No significant gender difference was seen in the rate of stroke recurrence. Women also showed a worse survival ratio after stroke than men ($p < 0.01$).

Conclusion The present study demonstrated significantly worse functional outcomes for women than for men at 1 and 5 years after stroke. Gender differences in long-term functional outcomes by subtypes of ischemic stroke were also significant.

Key words: gender differences, long-term functional outcomes, ischemic stroke

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Introduction

Gender differences are known to exist in the management and outcome of patients with ischemic heart disease in epidemiological studies (1-3). Recent studies have demonstrated the existence of differing functional outcomes between men and women after stroke (4-11). However, the results of these studies have been inconsistent and the reasons underlying any gender difference in stroke outcome remain contentious. In addition, the follow-up period for patients in the previous studies has seemed insufficient to evaluate long-term functional outcomes and the gender differences in outcome by stroke subtypes have remained uncertain.

We have previously reported that locomotor activity at the time of discharge is significantly worse among female stroke patients than among male patients (12). Since gender differences in functional status are thought to be important when treating or following stroke patients, we investigated whether these differences exist for a longer term and for subtypes of ischemic stroke.

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Materials and Methods

Subjects

A total of 1,305 patients (835 men, 470 women) with first-ever ischemic stroke were consecutively admitted to the Department of Neurology at Kitasato University Hospital between January 1986 and December 2000. All patients were hospitalized within 3 days after stroke onset and underwent computed tomography and/or magnetic resonance imaging of the brain. All subjects were registered on admission, and characteristics of each patient (past history, age at onset, sex, risk factors for stroke and clinical categories of stroke subtypes) were recorded. Hypertension, diabetes mellitus and atrial fibrillation were regarded as risk factors for stroke. Patients who had been treated with antihypertensive agents or whose blood pressure was > 140/90 mmHg at the time of discharge (more than 2 weeks after stroke onset) were defined as hypertensive. Patients treated with insulin or oral antidiabetic agents were defined as diabetics. Patients who had a history of diabetes or treated with diet for diabetes were also defined as diabetics. Atrial fibrillation was confirmed by electrocardiogram on admission or during hospital stay. Ischemic stroke was classified as atherothrombotic infarction, lacunar infarction, cardioembolic infarction or unclassified infarction according to clinical categories (13).

A total of 135 patients (72 men, 63 women) died during hospitalization. As a result, the 1,170 surviving patients (763 men, 407 women) were prospectively followed for 5 years after discharge or until death. Long-term functional outcomes were assessed at 1 year (first survey) and 5 years (second survey) using a questionnaire that was delivered by mail with a postage-paid reply envelope. A letter mailed with the questionnaire provided all patients with a detailed explanation of the purposes of the research. Informed consent was obtained from all patients who answered the questionnaire. A reminder letter was mailed to patients who had not responded within 3 months.

Variables

Functional outcomes of surviving patients were assessed at the time of discharge. Functional status was expressed as locomotor activity, classified into 5 categories: 1) no significant disability in walking; 2) slight disability (walking without the aid of a cane or braces); 3) moderate disability (walking with a cane and/or braces); 4) moderately severe disability (using a wheelchair); and 5) severe disability (bedridden). Locomotor function of discharged patients was assessed using the same disability score in the surveys conducted 1 and 5 years after stroke. If a patient was unable to complete the questionnaire, a primary caregiver of the patient provided assistance. If the patient had died or experienced stroke recurrence during follow-up, the date was entered into the form.

Statistical analysis

Values are expressed as means and standard deviations. The unpaired t-test or χ^2 test was used to analyze gender differences in each item of baseline characteristics. The Mann-Whitney U test was used to examine gender differences in functional outcomes. Locomotor status of patients was given a score from 1 to 5 according to the grade of disability. The χ^2 test was performed to evaluate differences in stroke recurrence between genders. To investigate factors influencing functional outcomes at 1 and 5 years after stroke, logistic regression analysis was performed. Long-term survival ratios for male and female patients were estimated using Kaplan-Meier methods, and the log-rank test was used to assess gender differences.

Values of $p < 0.05$ were considered statistically significant. All analyses were performed using SPSS for Windows statistical software (version 11.0; SPSS, Chicago, IL, USA).

Results

Table 1 shows baseline characteristics in male and female patients at the time of discharge and at the time of surveys 1 and 5 years after stroke. In the first survey by mailed questionnaire conducted 1 year after stroke, 997 patients or caregivers (85.2%; 654 men, 343 women) responded to the questionnaire. A total of 118 patients (69 men, 49 women) were found to have died after discharge. Functional outcomes were thus assessed in the remaining 879 patients (585 men, 294 women). These patients were followed for a further 4 years and the second survey was conducted using the same questionnaire 5 years after stroke. A total of 618 patients or caregivers (70.3%; 415 men, 203 women) responded to the questionnaire. A total of 71 patients (48 men, 23 women) were found to have died between the first and second surveys. A total of 547 patients (367 men, 180 women) were thus considered eligible for final analysis of functional outcomes at the time of the second survey 5 years after stroke.

Significant gender differences in mean patient age were observed at the time of discharge ($p < 0.05$). However, gender differences in mean age were not significant at 1 and 5 years after stroke. Differences in other characteristics, including risk factors for stroke and clinical categories of stroke subtypes, were not significant.

Functional status by gender assessed in the first and the second surveys is shown in Fig. 1. The results of the first survey conducted 1 year after stroke, with 75% of male patients able to walk without difficulty or with only slight difficulty, compared to 66.3% of female patients. The difference in functional outcome between genders was significant ($p < 0.001$). In the second survey women again displayed significantly poorer functional outcomes than men ($p < 0.01$).

Table 2 indicates functional outcomes by subtype of ischemic stroke at discharge and at the time of the first and

Table 1. Baseline Characteristics of Patients by Gender

	At discharge (n = 1,170)		p	At 1 year (n = 879)		p	At 5 years (n = 547)		p
	Men	Women		Men	Women		Men	Women	
Total cases, n	763	407		585	294		367	180	
Mean age ± SD, years	64.1 ± 12.0	65.8 ± 13.9	<0.05	65.1 ± 11.3	66.5 ± 14.4	NS	67.2 ± 11.0	66.7 ± 13.4	NS
Risk factors									
Hypertension	431 (59.0)	237 (60.6)	NS	329 (58.9)	176 (62.6)	NS	206 (56.1)	100 (55.6)	NS
Diabetes mellitus	219 (30.4)	105 (27.8)	NS	164 (29.7)	79 (29.2)	NS	91 (24.8)	45 (25.0)	NS
Atrial fibrillation	168 (23.4)	93 (24.5)	NS	122 (22.1)	53 (19.4)	NS	80 (21.8)	28 (15.6)	NS
Clinical categories			NS			NS			NS
Atherothrombotic infarction	260	131		195	98		128	56	
Lacunar infarction	287	145		232	119		144	80	
Cardioembolic infarction	180	106		130	59		79	33	
Unclassified infarction	36	25		28	18		16	11	

Value: n (%). SD, standard deviation. Differences in mean age were estimated by unpaired *t* test. NS, not significant by χ^2 test.

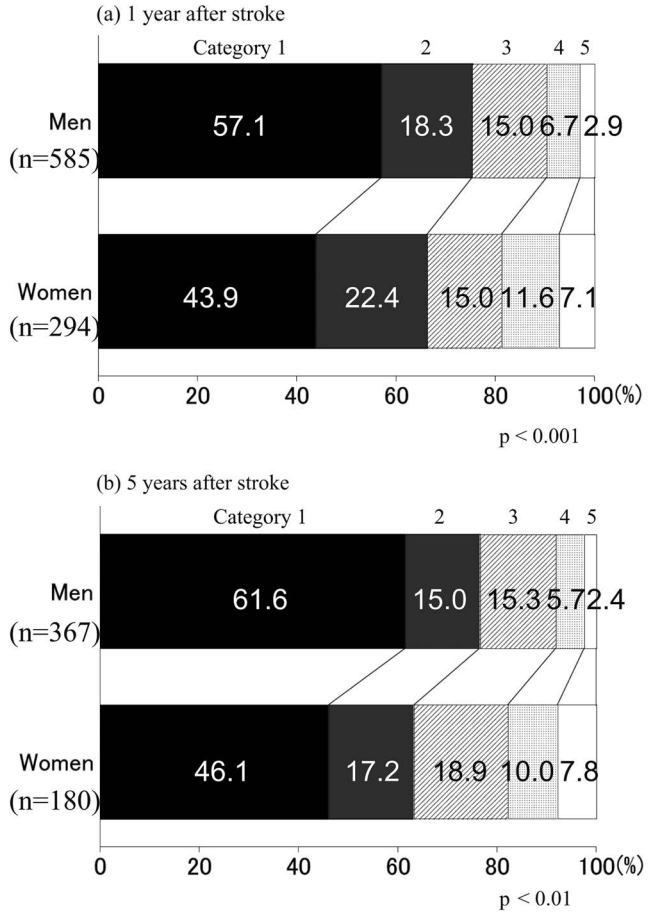

Figure 1. Functional outcome in male and female patients with first-ever ischemic stroke at 1 year (a) and 5 years (b) after onset. (a) Significant gender differences in functional outcomes were observed between men and women (p<0.001) (Mann-Whitney U test). (b) Functional outcome with first-ever stroke was significantly better for male patients than for female patients (p<0.01) (Mann-Whitney U test). Black: 1) no significant disability in walking; Gray: 2) slight disability (walking without the aid of a cane or braces); Diagonal lines: 3) moderate disability (walking with a cane and/or braces); Dotted lines: 4) moderately severe disability (using a wheelchair); White: 5) severe disability (bedridden).

second surveys. Significant gender differences were observed in all subtypes of ischemic stroke except in lacunar infarction at discharge. In the survey made 1 year after stroke, 73.8% of male patients with atherothrombotic infarction could walk unaided, compared to 61.2% of female patients. This difference was significant ($p < 0.05$). Locomotor function following lacunar infarction or cardioembolic stroke was again better among male patients than among female patients ($p < 0.05$ and $p < 0.001$, respectively). Similarly, functional outcome of male patients at 5 years after stroke was significantly better for male patients than for female patients in all subtypes of infarction (atherothrombotic infarction, $p < 0.01$; lacunar infarction, $p < 0.05$; cardioembolic infarction, $p < 0.05$).

Logistic regression analysis

Factors influencing functional outcome were assessed using logistic regression analyses. For analysis of functional outcome (dependent variable) at the time of the first survey, patients were divided into 2 groups; patients belonging to category of locomotion activity from 1 to 3 and patients belonging to category 4 and 5. Age at which the survey was conducted, gender (men and women) and risk factors for stroke (hypertension, diabetes mellitus and atrial fibrillation) were selected as independent variables. As a result of analysis, the following 2 factors showed significant associations with locomotor function 1 year after stroke: age ($p < 0.001$) and gender ($p < 0.01$). Advancing age or female gender had an adverse influence on locomotor function (Table 3). Similarly, in the second survey, age at which the survey was made, gender and risk factors for stroke were selected as independent variables. Consequently, age ($p < 0.001$) and gender ($p < 0.001$) were significantly associated with locomotor function at 5 years. Advancing age or female gender also showed deteriorated locomotor function (Table 4).

Recurrence of stroke

Of the 997 patients (654 men 343 women), 65 patients (42 men 23 women) experienced stroke recurrence within 1

Table 2. Functional Outcome according to Clinical Categories of Two Subgroups (Men and Women)

	At discharge		p	At 1 year		p	At 5 years		p
	Men	Women		Men	Women		Men	Women	
Atherothrombotic infarction	260	131	<0.05	195	98	<0.05	128	56	<0.01
No significant disability	28 (10.8)	19 (14.5)		96 (49.2)	39 (39.8)		71 (55.5)	20 (35.7)	
Slight disability	139 (53.5)	47 (35.9)		48 (24.6)	21 (21.4)		24 (18.8)	10 (17.9)	
Moderate disability	36 (13.8)	22 (16.8)		35 (17.9)	15 (15.3)		22 (17.2)	14 (25.0)	
Moderately severe disability	34 (13.1)	29 (22.1)		11 (5.6)	12 (12.2)		8 (6.3)	6 (10.7)	
Severe disability	23 (8.8)	14 (10.7)		5 (2.6)	11 (11.2)		3 (2.3)	6 (10.7)	
Lacunar infarction	287	145	NS	232	119	<0.05	144	80	<0.05
No significant disability	84 (29.3)	35 (24.1)		141 (60.8)	59 (49.6)		96 (66.7)	43 (53.8)	
Slight disability	151 (52.6)	64 (44.1)		41 (17.7)	21 (17.6)		19 (13.2)	12 (15.0)	
Moderate disability	40 (13.9)	35 (24.1)		38 (16.4)	23 (19.3)		22 (15.3)	15 (18.8)	
Moderately severe disability	11 (3.8)	10 (6.9)		9 (3.9)	12 (10.1)		6 (4.2)	5 (6.3)	
Severe disability	1 (0.3)	1 (0.7)		3 (1.3)	4 (3.4)		1 (0.7)	5 (6.3)	
Cardioembolic infarction	180	106	<0.001	130	59	<0.001	79	33	<0.05
No significant disability	32 (17.8)	9 (8.5)		81 (62.3)	19 (32.2)		50 (63.3)	13 (39.4)	
Slight disability	78 (43.3)	39 (36.8)		14 (10.8)	18 (30.5)		9 (11.4)	7 (21.2)	
Moderate disability	13 (7.2)	7 (6.6)		13 (10.0)	6 (10.2)		10 (12.7)	4 (12.1)	
Moderately severe disability	32 (17.8)	27 (25.5)		16 (12.3)	10 (16.9)		5 (6.3)	6 (18.2)	
Severe disability	25 (13.9)	24 (22.6)		6 (4.6)	6 (10.2)		5 (6.3)	3 (9.1)	

Value: n (%), Mann-Whitney U test

Table 3. Multivariate Predictors of Locomotor Function at 1 Year after Stroke

	OR	95% CI	p
Age per 1-year increase	1.078	1.054-1.103	<0.001
Female gender	1.832	1.185-2.832	<0.01
Risk factors			
Hypertension	0.915	0.579-1.447	0.704
Diabetes mellitus	1.437	0.907-2.276	0.123
Atrial fibrillation	1.486	0.894-2.468	0.126

OR, odds ratio; Higher values predict worse functional outcome.

95% CI, 95% confidence interval

Table 4. Multivariate Predictors of Locomotor Function at 5 Years after Stroke

	OR	95% CI	p
Age per 1-year increase	1.078	1.045-1.112	<0.001
Female gender	2.929	1.636-5.244	<0.001
Risk factors			
Hypertension	1.003	0.537-1.875	0.992
Diabetes mellitus	1.476	0.784-2.782	0.228
Atrial fibrillation	1.785	0.880-3.619	0.108

OR, odds ratio; Higher values predict worse functional outcome.

95% CI, 95% confidence interval

year after initial stroke. In addition, another 79 patients (47 men 32 women) suffered stroke recurrence by 5 years after initial stroke. Gender differences in recurrence ratio for stroke were not significant.

Mortality rate (Kaplan-Meier method)

Cumulative mortality rate for male patients after onset of stroke was 19.3% at 1 year and 35.9% at 5 years, compared to 28.4% and 46.4%, respectively, for female patients. Figure 2 shows cumulative long-term survival ratios by gender for hospitalized patients as estimated by the Kaplan-Meier method. The survival ratio was higher for men than that for women throughout the follow-up period and gender differences examined by the log-rank test reached the significant level ($p < 0.01$).

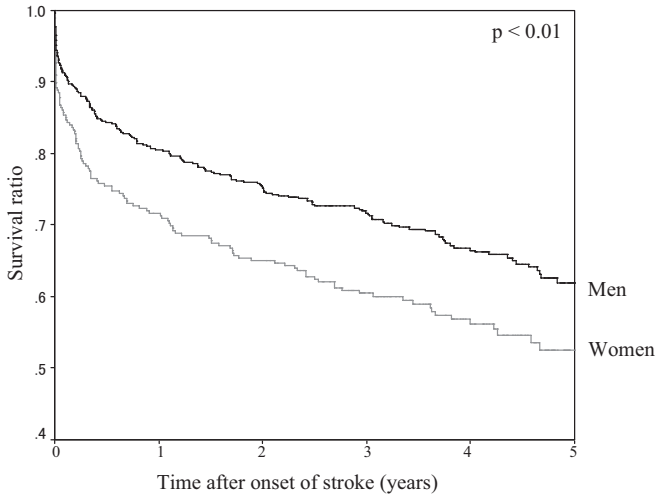

Figure 2. Survival ratio by gender for patients after first-ever ischemic stroke (Kaplan-Meier method). Gender differences as estimated by the log-rank test were significant (p<0.01).

Discussion

The present study was based on a large sample of hospitalized patients with first-ever ischemic stroke, and patients were followed for 5 years to assess long-term functional outcomes. We have previously reported that female patients display worse locomotor activity than male patients at the time of discharge (12). The present results indicate that female patients have significantly worse ability to walk than male patients and gender differences in locomotor function still exist 5 years after stroke onset, as well as at the time of discharge. Logistic regression analysis revealed that gender was a determinant for long-term functional outcomes at 1 and 5 years after stroke. Interestingly, gender differences in long-term functional outcomes by subtype of ischemic stroke were also significant.

Little attention had been paid to gender differences in functional outcomes after stroke. Some studies before 2000 reported that state of motor function after stroke was unrelated to gender (14) or that male stroke patients received more support from family members in activities of daily living (ADL) (4). However, most subsequent studies have revealed that women experience greater disability than men after stroke. Table 5 demonstrates the results of recent studies for gender differences in functional outcome among stroke patients (5-12). Common findings of these studies,

Table 5. Summary of Studies on Gender Differences in Functional Outcome after Stroke

Author (Published year)	Subjects	Follow-up period	Worse outcome by sex	Results
Appelros[5] (2003)	377 first-ever stroke (169 men, 208 women)	1 year	(No difference)	mRS ≥ 3 in men: OR 1.1; 95% CI, 0.7-1.8
Di Carlo[6] (2003)	4,499 first-ever acute stroke (2,239 men, 2,260 women)	3 months	Women	BI: 16.6 in men, 14.7 in women ($p < 0.001$) mRS: 2.2 in men, 2.6 in women ($p < 0.001$)
Roquer[7] (2003)	1,581 first-ever acute stroke (809 men, 772 women)	at discharge	Women	mRS ≥ 3: 24.2% in men, 36.1% in women ($p < 0.001$)
Glader[8] (2003)	19,547 acute stroke (9,881 men, 9,666 women)	3 months	Women	Independent ADL: 67.0% in men, 53.8% in women (OR 0.71; 95% CI, 0.66-0.76)
Kapral[9] (2005)	3,323 first-ever acute stroke (1,796 men, 1,527 women)	at discharge	(No difference)	mRS ≥4: 26% in men, 30% in women ($p < 0.1$)
		6 months	Women	SIS-16 score, median: 92.2 in men, 85.9 in women ($p < 0.001$)
Paolucci[10] (2006)	440 first-ever acute ischemic stroke (220 men, 220 women)	at discharge	Women	ADL autonomy: 27.60% in men, 14.87% in women ($p < 0.01$) Stair climbing: 20.83% in men, 8.21% in women ($p <0.001$)
Gray[11] (2007)	1,268 acute ischemic stroke (694 men, 574 women)	6 months	Women	mRS (median): 2 in males, 3 in females ($p < 0.01$) BI: 95 in men, 90 in women ($p < 0.0001$)
Fukuda[12] (2008)	1,291 acute first-ever ischemic stroke (846 men, 445 women)	at discharge	Women	Unaided walk: 70.4% in men, 56.4% in women ($p < 0.001$)

mRS, modified Rankin Scale; OR, odds ratio; 95% CI, 95% confidence interval; BI, Barthel Index; ADL, activity of daily living; SIS-16, Stroke Impact Scale-16

with the exception of 2 studies (5, 9), have been poor functional outcome among female patients compared with those among male patients. In another study, men were more likely to be discharged home and less likely to be discharged to chronic care facilities after stroke than women (15), suggesting worse functional status among female patients. As shown in Table 5, duration of follow-up in previous reports has been less than 1 year after stroke (5-12) and gender differences were not investigated by subtypes of ischemic stroke.

The precise reasons for gender differences in poststroke functional status remain unclear. However, the following factors have been discussed in relation to poorer outcomes for female patients: differences in mean age between genders (6-8); risk factors for stroke (6, 7, 11); distribution of stroke subtypes (7, 11); stroke severity on admission (7); poststroke depression (PSD) (16); muscular strength (greater in men at all ages) (10); prestroke conditions including functional status (6, 8); and musculoskeletal comorbidities, such as osteoarthritis of the knee and osteoporosis (10).

Previous studies have demonstrated that advanced age adversely influences ADL after stroke (17). In other studies, in which women were significantly older than men, women displayed worse prestroke Rankin scores, and were more often disabled, living at home with community support, or in institutions before stroke. These factors might thus significantly influence worse outcome (6, 8). The results of these studies have implied that prestroke conditions offer important predicting factors for poststroke outcomes in the elderly. Moreover, some studies have detected differences in risk factors for cerebrovascular diseases between men and women, with a history of diabetes mellitus more frequent in male stroke patients, and a history of hypertension and atrial fibrillation more frequent in female patients (6, 7, 11), and women suffering more cardioembolic strokes and less atherothrombotic and lacunar strokes (7). These findings suggest that differing distributions of stroke subtypes may influence gender differences in functional outcomes. However, on the basis of our results, these factors seem unlikely to adequately explain the existence of gender differences, since patients in our study had no history of stroke and mostly stayed at home before admission. In addition, in our investigation, no significant gender differences in age at which the survey was conducted, risk factors for stroke, or sex-related features of stroke subtype were present. Furthermore, differences in long-term functional outcome were identified by all subtypes of ischemic stroke.

Previous reports have shown that women have more severe strokes on admission measured by stroke scales such as Canadian Score Scale or Scandinavian Stroke Scale (7, 18) suggesting that stroke severity at onset might be a predictor of disability or survival.

As has already been reported, PSD is the most frequent mental complication of cerebrovascular diseases (19). An Italian study indicated female sex as a reliable risk factor for developing PSD and prevalence of depression as a basal variable that was potentially relevant to functional outcomes (16). In fact, our previous study demonstrated that health-related quality of life and ADL was significantly better among male stroke patients than among female patients and the higher proportion of poststroke anxiety and depression among women might be related to gender differences (20).

A recent report emphasized that gender-related differences in muscular strength, which is greater in men at all ages, influences the functional status of stroke patients (10). The report also suggested that musculoskeletal comorbidities, such as osteoarthritis of the knee, osteoporosis and lumbar degenerative diseases, might represent important determinants for gender differences in locomotor function, since decreased estrogen levels after menopause exacerbate osteoporosis (21). Long-term functional outcomes might be influenced by various factors, particularly by the period of time for physical rehabilitation patients underwent after discharge. However, we have no information on rehabilitation to discuss the matter.

In addition to functional outcome, the impact of stroke recurrence and mortality are important for discussing long-term prognosis of patients. Regarding gender differences in stroke mortality, the Danish MONICA study group reported that excess risk for death was significantly higher for women than for men during the first year after stroke but did not differ significantly between sexes after that first year (22). Another study identified that male gender was an important predictor of 6-month mortality in ischemic stroke patients (23). In the present study, survival rate was also significantly higher for men than for women throughout follow-up. Worse functional outcome among female patients might be related to the lower survival ratio for women. However, the reason for worse functional outcome among women was not clarified in the present study.

In conclusion, our data show that female patients with first-ever ischemic stroke displayed significantly worse functional outcome than male patients even 5 years after stroke, as well as at the time of discharge. In addition, gender differences in functional outcome by stroke subtype were also significant. On the basis of our findings, factors such as risk factors for stroke, distribution of stroke subtypes or prestroke conditions appear relatively unimportant in terms of gender differences in long-term stroke outcomes.

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