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# Gender Differences in Outcomes after Ischemic Stroke: Role of Ischemic Lesion Volume and Intracranial Large-Artery Occlusion

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**Key Words**

Sex differences · Ischemic stroke · CT angiography

**Abstract**

***Background:*** The reasons for gender disparities in stroke outcome remain unclear, and little is known about the value of acute neuroimaging characteristics in elucidating differential stroke outcomes between the sexes. ***Methods:*** We prospectively evaluated consecutive patients with acute ischemic stroke. CT angiography (CTA) was performed in all patients within 24 h of symptom onset. CTA source images were used to evaluate lesion volume. The primary outcome measure was a modified Rankin scale (mRS) score ≥3 at 6 months. ***Results:*** We evaluated 676 consecutive patients (322 women). Women were older than men ($p < 0.01$), more frequently had a prestroke mRS >0 ($p < 0.01$), and had higher admission National Institutes of Health Stroke scale scores ($p = 0.01$). More women had intracranial artery occlusions than men (46 vs. 33.1%, $p = 0.01$), but there was no significant difference between ischemic lesion volumes ($p = 0.21$). Using multiple regression, female gender remained an independent predictor of poor mRS scores at 6 months (odds ratio 1.57; 95% confidence interval 1.02–2.36) after adjustment for clinical and imaging covariates. ***Conclusion:*** Compared with men, women are less likely to achieve independence after acute ischemic stroke. The disparity in stroke outcome is not explained by differences in ischemic lesion volume or the presence of intracranial artery occlusions.



## Introduction

Because women have, on average, a longer life expectancy than men, and stroke incidence increases with age, older female patients are likely to bear the major burden of stroke-related mortality and disability [1, 2]. Indeed, after controlling for variables such as age, comorbidities, prestroke functional status and stroke severity, more women than men require institutional care after a stroke [3–6]. The reasons for the disparities in stroke outcome related to gender are still unclear [4, 7–9].

Many of the studies that have evaluated sex differences in acute stroke presentation, treatment and outcomes have combined patients with hemorrhagic and ischemic strokes [3, 8–10]. The determinants of prognosis in hemorrhagic and ischemic strokes are different, and analyz-

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ing them together may lead to erroneous conclusions. In ischemic stroke, age, treatment with intravenous recombinant tissue plasminogen activator (rt-PA), admission National Institute of Health Stroke scale (NIHSS) score, ischemic lesion volume, and the presence of an intracranial large-artery occlusion are independent predictors of long-term functional outcomes [11–15].

The extent to which neuroimaging characteristics such as ischemic lesion volume and intracranial large-artery occlusion add to known determinants of prognosis after ischemic stroke in explaining gender disparity in outcome has not been previously investigated. We hypothesized that women were more likely to have larger infarct volumes and a higher prevalence of intracranial large-vessel occlusions, which might be independent neuroimaging prognostic markers.

## Patients and Methods

We evaluated consecutive patients enrolled in a prospective cohort study at two university-based hospitals from March 2003 to December 2005. Noncontrast CT scans (NCCT) and CT angiograms (CTA) were performed for acute ischemic stroke within 24 h from symptom onset or from last seen well. Patients with primary intracranial hemorrhage and those in whom iodinated contrast agent administration was contraindicated were excluded. Data collected included demographics, presence of stroke risk factors, circumstances of stroke onset, NIHSS scores, modified Rankin scale scores (mRS; before stroke and at 6 months), Stop Stroke Study-TOAST (SSS-TOAST) classification, neuroimaging characteristics and thrombolysis status [16]. The prospective study received institutional review board approval. All participants gave written informed consent.

*Neuroimaging Protocol*

NCCT and CTA acquisitions were performed with 16- or 64-section multidetector CT scanners (LightSpeed; GE Healthcare, Milwaukee, Wisc., USA). Representative sample parameters were: 120–140 kVp, 170 mA, 2 s scan time, and 5 mm section thickness for NCCT and 2.5 mm section thickness for CTA source images (CTA-SIs). NCCT imaging was immediately followed by biphasic helical scanning. CTA was performed after a 25-second delay (40 s for patients in atrial fibrillation) and intravenous administration of 100–140 ml of a nonionic contrast agent (Isovue; Bracco Diagnostics, Princeton, N.J., USA) at a rate of 3 ml/s by power injector (Medrad Power Injector; Medrad, Indianola, Pa., USA). Parameters were 140 kVp, 220–250 mA, 0.8–1.0 s rotation time, 2.5 mm section thickness, 1.25 mm reconstruction interval, 3.75 mm per rotation table speed, and 0.75:1 pitch. CTA-SIs were reconstructed into standardized maximum-intensity projection views of the intracranial and extracranial vasculature. CT and CTA images were analyzed in consensus by a neuroradiologist and two neurologists experienced in stroke neuroimaging. CTA-SIs were evaluated for the presence of ischemic regions by identifying areas of relative hypoattenuation. Using a semiautomated software package (Alice; Parexel, Waltham, Mass., USA), these ischemic regions of interest were visually segmented to determine total lesion volume [17]. CTA was used to assess for intracranial arterial occlusions. Large-vessel intracranial occlusions amenable to intra-arterial neurointerventional approaches were defined as middle cerebral artery (M1 or proximal M2), internal carotid artery, or basilar occlusions when those arteries were the culprits for the acute stroke [18].

*Statistical Analysis*

Means and standard deviations or medians and interquartile intervals were used to describe patients' characteristics. The independent samples t test was used to compare means between men and women. Nonparametric data were compared using the Mann-Whitney test. Categorical variables were compared with the $\chi^2$ test or Fisher's exact test. We used multiple logistic regression to investigate the influence of gender upon 6-month mRS scores dichotomized at 2 (mRS $\leq 2$ vs. $\geq 3$). All variables that showed an association in the univariate analysis with a $p \leq 0.1$ were included in the multivariate analysis. A 2-tailed $p < 0.05$ was considered statistically significant. Statistical analysis was performed with SPSS 15.0 software (Chicago, Ill., USA).

## Results

We evaluated 676 consecutive patients with acute ischemic stroke, of whom 322 (48%) were women. Women were older ($p < 0.01$), more often had a prestroke mRS greater than 0 ($p < 0.01$), were more likely to have an unknown time of symptom onset ($p = 0.03$) and had a higher prevalence of atrial fibrillation ($p < 0.01$) and hypertension ($p < 0.01$). Stroke mechanisms varied by sex, with more women having cryptogenic embolic events ($p < 0.01$). Baseline characteristics stratified by sex are presented in table 1.

NIHSS scores at admission were higher in women (median 6 [2–13] vs. 4 [2–11], $p = 0.01$). There were no differences between genders in time to first neuroimaging, lesion volumes on CTA-SI or rates of treatment with intravenous or intra-arterial thrombolysis. Large-artery intracranial occlusions were more prevalent in women (46 vs. 33.1%, $p = 0.01$) (table 2). The rates of intensive care unit admission, pneumonia, and deep-venous thrombosis during admission were similar in men and women. Urinary tract infections were more common in women ($p < 0.01$; table 3).

We obtained follow-up data in 597 patients (88.3%) at 6 months. Mortality rates were not different between men and women. Two-hundred and twenty patients (32.5%) had a poor outcome (mRS 3–6), 133 (41.3%) were women and 87 (24.6%) were men ($p < 0.01$). Age, prestroke mRS, gender, marital status, history of hypertension, atrial fibrillation, diabetes, ischemic lesion volume, presence of

**Table 1.** Baseline characteristics of patients by gender

| | Female (n = 322) | Male (n = 354) | p |
|---|---|---|---|
| Age (means ± SD), years | 72.2 ± 15.8 | 65 ± 13.9 | <0.01 |
| mRS >0 at baseline, % | 35.2 | 24 | <0.01 |
| Marital status | | | |
| Widowed, % | 37.5 | 5.1 | <0.01 |
| Married, % | 38.4 | 75.5 | <0.01 |
| Single, % | 10.6 | 9.1 | 0.51 |
| Divorced, % | 11.7 | 7.7 | 0.16 |
| Unknown, % | 2.2 | 2.6 | 0.75 |
| Unknown time of symptom onset[1], % | 42 | 34.2 | 0.04 |
| Hypertension, % | 66.8 | 56.8 | <0.01 |
| Diabetes, % | 18.3 | 18.1 | 0.93 |
| Dyslipidemia, % | 27.6 | 29.4 | 0.61 |
| Atrial fibrillation, % | 25.2 | 18.6 | 0.04 |
| Previous stroke, % | 7.5 | 4.8 | 0.14 |
| Coronary artery disease, % | 15.5 | 29.9 | <0.01 |
| Current smoker, % | 11.2 | 21.5 | <0.01 |
| SSS-TOAST | | | |
| Cardioembolic, % | 39.2 | 39.1 | 0.96 |
| Small vessel, % | 9.8 | 9.2 | 0.79 |
| Large artery, % | 12 | 19.8 | <0.01 |
| Undetermined: cryptogenic emboli, % | 12.7 | 4.3 | <0.01 |
| Undetermined: no embolus, % | 8.2 | 12.1 | 0.1 |
| Undetermined: incomplete investigation, % | 3.2 | 3.4 | 0.84 |
| More than one mechanism, % | 7.3 | 4.6 | 0.14 |
| Other, % | 6.6 | 7.2 | 0.14 |

mRS = Modified rankin scale; SSS-TOAST = Stop Stroke Study-TOAST.

[1] Stroke symptoms on awake or unknown onset time due to lack of a witness when the patient was unable to determine time from symptom onset.

**Table 2.** Intracranial occlusions on CTA according to gender

| | Female (n = 322) | Male (n = 354) | p |
|---|---|---|---|
| Any intracranial occlusion[1] | 46% | 33.1% | <0.01 |
| Middle cerebral artery M1 | 24.2% | 16.4% | 0.01 |
| Middle cerebral artery M2 | 23.9% | 17.2% | 0.03 |
| Internal carotid artery | 30.7% | 22.3% | 0.01 |
| T occlusion | 1.9% | 2.0% | 0.91 |
| Basilar | 2.5% | 2.5% | 0.96 |

[1] M1, proximal M2, internal carotid artery (including T lesions) or basilar occlusions. Some patients had occlusions of more than one artery.

intracranial large-artery occlusion, admission NIHSS and treatment with intravenous or intra-arterial thrombolysis were all univariate predictors of mRS scores at 6 months (table 4). Female sex remained an independent predictor of a poor mRS score at 6 months (odds ratio 1.57; 95% confiedence interval 1.03–2.36, p = 0.04) after adjustment for all factors identified in the univariate analyses (fig. 1). Age, prestroke mRS, admission NIHSS scores and ischemic lesion volume on CTA-SI were also predictors of poor outcome (fig. 1).

**Table 3.** Acute stroke characteristics, treatment, complication and outcomes by gender

| | Female | Male | p |
|---|---|---|---|
| NIHSS score (median) | 6 (2–13) | 4 (2–11) | 0.01 |
| CTA-SI volumes (median), $cm^3$ | 23.73 (0–184.19) | 13.21 (0–150.88) | 0.21 |
| Intracranial occlusion, % | 46 | 33.1 | 0.01 |
| Time to first neuroimaging (means ± SD), h | 6.73 ± 7.94 | 7.45 ± 7.96 | 0.27 |
| IV thrombolysis, % | 17.3 | 14.8 | 0.36 |
| IA thrombolysis, % | 6.2 | 4.8 | 0.32 |
| ICU admission, % | 33.5 | 30.2 | 0.35 |
| Pneumonia, % | 5 | 7.1 | 0.26 |
| Deep-vein thrombosis, % | 0.3 | 0.8 | 0.36 |
| Urinary tract infection, % | 10.6 | 2.9 | <0.01 |
| Symptomatic intracranial hemorrhage[1], % | 2.8 | 3.1 | 0.92 |
| Asymptomatic intracranial hemorrhage[1], % | 4.2 | 6.2 | 0.61 |
| Mortality at 6 months, % | 12.28 | 8.54 | 0.13 |
| Living home independent at 6 months, % | 49.4 | 66.9 | <0.01 |
| mRS (3–6) at 6 months, % | 41.3 | 24.6 | <0.01 |

Figures in parentheses represent 25 and 75 interquartile intervals. CTA-SI = CT angiography source image; IV = intravenous; IA intra-arterial; ICU = intensive care unit. [1] Only patients treated with intravenous or intra-arterial thrombolysis.

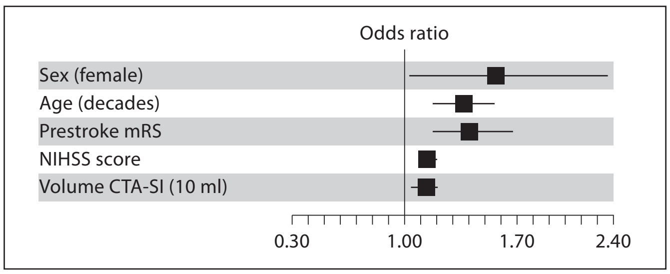


**Fig. 1.** Factors independently associated with functional outcome (mRS scores 3–6 at 6 months) on a multivariate logistic regression model.

**Table 4.** Univariate predictors of poor functional status (mRS scale 3–6) at 6 months

| Variable | OR (95% CI) | p |
|---|---|---|
| Age | 1.47 (1.30–1.67) | <0.01 |
| Pre-stroke mRS | 1.50 (1.29–1.73) | <0.01 |
| Female sex | 2.21 (1.58–3.11) | <0.01 |
| Marital status | | |
| Married-partner | 0.61 (0.43–0.85) | <0.01 |
| Unknown | 0.56 (0.15–2.11) | 0.39 |
| Divorced | 0.54 (0.28–1.04) | 0.07 |
| Widowed | 3.45 (2.29–5.20) | <0.01 |
| Single | 0.67 (0.37–1.20) | 0.17 |
| Diabetes | 1.75 (1.15–2.65) | <0.01 |
| Atrial fibrillation | 2.00 (1.37–2.99) | <0.01 |
| Coronary artery disease | 1.29 (0.8–1.8) | 0.2 |
| Hypertension | 1.56 (1.10–2.22) | 0.01 |
| Dyslipidemia | 0.91 (0.628–1.32) | 0.91 |
| Admission NIHSS | 1.14 (1.11–1.17) | <0.01 |
| Time to first neuroimaging | 0.99 (0.96–1.017) | 0.99 |
| Intracranial occlusion | 2.89 (2.05–4.08) | <0.01 |
| Volumes CTA-SI (10 $cm^3$) | 1.22 (1.15–1.31) | <0.01 |
| IV thrombolysis | 1.7 (1.13–2.6) | 0.01 |
| IA thrombolysis | 4.08 (1.8–9.1) | <0.01 |

mRS = Modified Rankin scale; CTA-SI = CT angiography source image; IV = intravenous; IA = intra-arterial.

## Discussion

We found that women with acute ischemic stroke were older and more commonly widowed than men, had a higher prevalence of prestroke disability, of intracranial arterial occlusions and of uncertain time of stroke onset; they also had higher admission NIHSS scores and a worse functional outcome. After adjusting for other predictors of functional outcome, female sex was still an independent predictor of poor prognosis at 6 months. Our findings are consistent with previous studies, which have shown that compared to men, women with stroke tend to be older, are less likely to emerge independent or be discharged home [3, 4, 10, 19, 20].

Among our patients, women had higher NIHSS scores at presentation, but similar ischemic lesion volumes when compared to men. Their increased neurologic deficits at presentation might have been partly explained by a higher frequency of previous stroke. There were no differences in the time to first neuroimaging, or in the rates of intravenous or intra-arterial thrombolysis between men and women. Our data support previous studies that found no difference in intravenous rt-PA utilization between men and women during the treatment window [21, 22]. However, several other studies have reported that females are less frequently treated with intravenous rt-PA after multivariable adjustment [3, 23, 24].

Our study is the first to report a higher prevalence of intracranial large-artery occlusion at stroke presentation in women. Despite this, ischemic lesion volumes were not different between men and women, raising interesting hypotheses concerning potential differences in collateralization and infarct growth. A recent publication showed that in patients treated with intravenous rt-PA, the frequency of residual arterial occlusion is higher in males and that women had a trend to a higher frequency of large territorial infarcts although neither ischemic lesion volume nor the rates of intracranial large-artery occlusion before thrombolysis were described [25]. A higher recanalization rate after intravenous rt-PA in women, as well as a higher response rate to intra-arterial thrombolysis, was also described [26, 27]. A pooled analysis of randomized controlled trials showed a greater benefit for intravenous thrombolysis in women and nullification of the usual gender difference in outcome [28]. The considerable frequency of intracranial occlusions and the worse prognosis of women after stroke in our patients confer even more importance to the use of recanalization therapies in females.

Our study has some limitations. First, no gold-standard tests (magnetic resonance imaging with diffusion-weighted imaging or follow-up CT scans) were used to verify ischemic lesion volumes. Nevertheless, CTA-SIs correlate with lesion volumes on diffusion-weighted imaging and may have advantages over other techniques because CTA-SIs cover the entire brain and are available at the completion of imaging [17]. Secondly, factors not included in our analysis that could partially explain gender disparity in outcome after acute ischemic stroke include poststroke depression, degree of social support, biological effects of gender as a modulator of ischemic cell death and baseline frequency of silent brain injury (e.g. silent infarcts, white matter disease, atrophy) [29–32].

In conclusion, women less frequently achieve independence after acute ischemic stroke independent of admission NIHSS scores, age, ischemic volume lesion, prestroke mRS, and the presence of intracranial large-vessel occlusion. A better understanding of the causes of gender disparities in ischemic stroke, including risk factors, stroke mechanisms, response to acute stroke therapies, and recovery will hopefully lead to better outcomes in both sexes in the future.


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