Effect of sex differences on prognosis of intravenous thrombolysis: data from the Thrombolysis Implementation and Monitor of Acute Ischemic Stroke in China (TIMS-China)

Hongyu Zhou [ID],[1,2] Weiqi Chen,[1,2] Yuesong Pan [ID],[1,2] Yue Suo [ID],[1,2] Xia Meng,[1,2] Hao Li [ID],[1,2] Yongjun Wang [ID][1,2]

[1]Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China
[2]China National Clinical Research Center for Neurological Diseases, Beijing Tiantan Hospital, Capital Medical University, Beijing, China

Correspondence to
Dr Yongjun Wang;
yongjunwang@ncrcnd.org.cn

ABSTRACT

Background and purpose Previous studies have reported conflicting results as to whether women have poorer functional outcome than men after thrombolytic therapy. This study aims to investigate the relationship between sex differences and the prognosis of intravenous thrombolysis in Chinese patients with acute ischaemic stroke.

Methods The patients enrolled in this study were from the Chinese Acute Ischemic Stroke Thrombolysis Monitoring and Registration study. The primary outcome was poor functional outcome, defined as a 3-month modified Rankin score of 3–6. The safe outcome was symptomatic intracranial haemorrhage (SICH) and mortality within 7 days and 90 days. Multiple Cox regression model was used to correct the potential covariates to evaluate the association between sex disparities and prognosis. Furthermore, the interaction of preonset Rankin scores, baseline National Institute of Health Stroke Scale (NIHSS) scores and Trial of Org 10172 in Acute Stroke Treatment (TOAST) types was statistically analysed.

Results A total of 1440 patients were recruited, including 541 women and 899 men. The baseline information indicated that women were older at the time of onset (66.2±11.2 years vs 61.0±11.3 years, p<0.001), and more likely to have a history of atrial fibrillation (25.3% vs 11.2%, p<0.001), and had a higher NIHSS score on admission (12.3±6.8 vs 11.6±6.7, p=0.04). According to the prognosis analysis of unsatisfactory functional recovery, there was no significant difference between women and men (45.9% vs 37.1%; adjusted OR 1.01, 95% CI 0.75 to 1.37). As for the safe outcome, the proportion of SICH and mortality in women is relatively high but did not reach statistical significance. There was no significant interaction with sex, age, preonset Rankin score, NIHSS score, TOAST classification and the prognosis of intravenous thrombolysis.

Conclusions For Chinese patients with ischaemic stroke, although women are older and more severe at the time of onset, the prognosis after intravenous thrombolysis is not significantly different from men.

INTRODUCTION

Sex differences in biological and gender differences in sociology and culture affect epidemiology, pathophysiology, treatment and prognosis of cardiovascular diseases.[1] It is well known that distinctive expression of sex chromosomes and peculiar sexual hormones leads to different physiology and pathophysiology processes among men and women, such as immunity and coagulation.[2 3] And compared with men, women have some unique or more prevalent stroke risk factors, such as pre-eclampsia, atrial fibrillation and migraine.[4–6] However, multiple evidence from previous studies showed that women have a higher survival rate, but weaker functional recovery, higher disability rate and poorer quality of life compared with men.[7 8] Therefore, the American Heart Association/American Stroke Association have issued guidelines on stroke prevention for women.[9]

The proportion of women among the prevalent cases of stroke globally is higher than men in general.[10 11] Confronting aggravating process of ageing, analysing the influences of sex differences on prevention and treatment of stroke will have a remarkable impact on reducing global health burden.[12]

Intravenous thrombolysis is one of the most effective treatments for patients with acute ischaemic stroke (AIS), accompanying with increased risk of bleeding events disappointedly.[13] Recent work showed that women are more responsive to intravenous tissue plasminogen activator (tPA).[14] However, studies are still controversial about sex-related functional outcomes, symptomatic intracranial haemorrhage (SICH) rate and mortality of patients with AIS after thrombolytic therapy.[15–17] Since most acute stroke studies were not mainly designed to assess sex effection, it is tough to adjust the results by sex-specific risk factors, such as premorbid functional status or door-to-needle times. The analysis of the correlation

between sex and prognosis after thrombolysis is partly not comprehensive. Thus, we collected and analysed the data from the Thrombolysis Implementation and Monitor of Acute Ischemic Stroke in China (TIMS-China) to figure out new evidence on sex differences in prognosis after intravenous thrombolysis in Chinese patients.

METHODS
Study design
TIMS-China was a nationwide prospective stroke registry programme enrolling patients with AIS (18–80 years old; platelet ≥100 000/mm^3) who received intravenous tPA within 4.5 hours after symptom onset in China.[18] Recruitment of patients in TIMS-China opened in May 2007, and closed in April 2012. Sixty-seven major stroke centres participated. Details of the trial design and some results have been reported in the previous literature.[19 20] The ethics committee approved the study protocol of Beijing Tiantan Hospital with the Helsinki Declaration. The registry was regularly monitored by the quality monitoring committee of TIMS-China and the Contract Research Organization independently. Each participant signed informed consent, and was followed up for 3 months. According to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria, all patients were divided into five subtypes: large-artery atherosclerosis (LAA), cardioembolism (CE), small-artery occlusion, stroke of other determined cause and stroke of undetermined cause.[21]

Clinical outcome measurement
The primary outcome was functional recovery assessed with the modified Rankin Scale (mRS) at 3 months. The poor functional outcome was defined as disability/death (mRS score of 3–6), while the good functional outcome was defined as excellent recovery (mRS score of 0–1) and functional independence (mRS score of 0–2).[22]

The secondary outcomes included SICH and mortality after thrombolysis within 7 days and 90 days. Depending on previous trials, SICH was evaluated by the following three definitions: (1) safe implementation of treatments in stroke-monitoring study: local or remote parenchymal haemorrhage type 2 on the 22–36 hours post-treatment imaging scan, combined with a neurological deterioration of ≥4 points on the National Institute of Health Stroke Scale (NIHSS) from baseline, or the lowest NIHSS value between baseline and 24 hours, or leading to death[22]; (2) National Institute of Neurological Disorders and Stroke: a haemorrhage that was not present on previous CT scans, and there had subsequently been either a suspicion of haemorrhage or any decline in neurological status[23]; (3) second European–Australasian acute stroke study: any intracranial bleeding, with ≥4 points clinical worsening on NIHSS score.[24]

Statistical analysis
Continuous variables were presented as mean±SD or medians (IQR) and categorical variables as percentages. The baseline characteristics of different sex were compared by Wilcoxon rank-sum tests for continuous variables and χ^2 test for categorical variables. The ORs with their 95% CIs and the adjusted ORs with their 95% CI were calculated using univariate and multivariate logistic regression. Adjusted variables included age, diastolic blood pressure (BP), current smoking status, NIHSS on admission and the baseline variables significantly differed (p<0.05) between women and men. The different distribution of mRS was tested by multiple linear regression. Wilcoxon rank-sum test was used to compare the improvement of NIHSS score between different sex, and multiple linear regression was used to correct it. The interaction of preonset Rankin scores, baseline NIHSS scores and TOAST types was analysed by the multivariate Cox model. Statistical significance was determined as p<0.05, two sided. SAS 9.4 (SAS Institute) was used for all statistical analyses.

RESULTS
Baseline characteristics
A total of 1440 consecutive patients who received intravenous thrombolysis were enrolled in this study, among which 541 (37.6%) were women. Table 1 shows the demographics and clinical characteristics of the patients by sex. Compared with men, women were older, more likely to have a history of atrial fibrillation, hypertension and diabetes mellitus, but less likely to be current smokers. Meanwhile, women were more severe on admission. However, no matter the stroke-to-needle time or the stroke-to-visit time, men were longer than women. As for TOAST types, the proportion of CE in women was higher than in men (26.6% vs 13.0%). There was no difference in total stay time.

Clinical outcomes
There were 1410 patients (97.9%) who had a 3-month mRS score. The proportion of poor function outcomes is 45.9% for women and 37.1% for men (crude OR 1.44; 95% CI 1.16 to 1.79). After adjustment for age, diastolic BP, current smoking, hypertension, diabetes mellitus, atrial fibrillation, antihypertensive agents before stroke, stroke-to-needle time, stroke-to-visit time, stroke-to-imaging time, NIHSS on admission and TOAST types, there was no statistical difference (adjusted OR 1.01; 95% CI 0.75 to 1.37; table 2). Further analysis of the relationship between sex, age, preonset mRS score, NIHSS on admission and TOAST types, there was no interaction in poor functional outcome after thrombolysis of patients with AIS (table 3). After age 50 years, the rate of poor functional outcomes in women was somewhat higher than that in men, but no significance was found in further age stratification analysis (table 3; online supplementary tables 1-3).

Although there was a numerical difference in the distribution of 3-month mRS among patients of different sex, it did not reach a statistical difference after adjustment (crude p=0.001, adjusted p=0.78; figure 1). Table 4 shows

Table 1 Demographics and clinical characteristics of patients in Thrombolysis Implementation and Monitor of Acute Ischemic Stroke in China (N=1440)

	Women (n=541)	Men (n=899)	P value
Age, years, mean (SD)	66.2±11.2	61.0±11.3	<0.001
Clinical features			
Systolic BP, mm Hg (IQR)	150(135-162)	148(132-162)	0.24
Diastolic BP, mm Hg (IQR)	85 (78–91)	89 (80–97)	<0.001
Glucose, mmol/L (IQR)	6.8 (5.8–8.8)	6.8 (5.8–8.4)	0.06
Current smoking, n (%)	25 (4.6)	490 (54.4)	<0.001
Medical history			
Previous ischaemic stroke, n (%)	96 (17.7)	151 (16.8)	0.64
Previous TIA, n (%)	42 (9.3)	84 (9.3)	0.30
Hypertension, n (%)	337 (62.3)	507 (56.4)	0.03
Hyperlipidaemia, n (%)	35 (6.5)	59 (6.6)	0.94
Diabetes mellitus, n (%)	116 (21.4)	140 (15.6)	0.005
Atrial fibrillation, n (%)	137 (25.3)	101 (11.2)	<0.001
Baseline medication			
Antiplatelets use before stroke, n (%)	79 (14.6)	112 (12.5)	0.25
Anticoagulants use before stroke, n (%)	9 (1.7)	15 (1.7)	0.99
Antihypertensive agents before stroke, n (%)	236 (43.6)	296 (32.9)	<0.001
Prestroke mRS 0–2, n (%)	528 (97.8)	884 (98.7)	0.21
Median NIHSS on admission, mean (SD)	12.3±6.8	11.6±6.7	0.04
Median stroke-to-visit time, min (IQR)	1.2 (0.7–2.0)	1.3 (0.8–2.2)	0.04
Median stroke-to-imaging time, min (IQR)	1.9 (1.3–2.9)	1.8 (1.3–2.6)	0.03
Median stroke-to-needle time, min			0.04
0–3 hours, n (%)	305 (56.5)	449 (50.2)	
3–4.5 hours, n (%)	135 (25.0)	239 (26.7)	
>4.5 hours, n (%)	100 (18.5)	207 (23.1)	
TOAST type			<0.001
LAA, n (%)	272 (50.5)	549 (61.7)	
SAO, n (%)	44 (8.2)	83 (9.3)	
CE, n (%)	143 (26.6)	116 (13.0)	
Other, n (%)	79 (14.7)	142 (16.0)	
Total length of stay (days)	15 (11–21)	14 (11–21)	0.10

BP, blood pressure; CE, cardioembolism; LAA, large-artery atherosclerosis; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; SAO, small-artery occlusion; TIA, transient ischaemic attack; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

the NIHSS scores in different periods after thrombolysis. The NIHSS score of women was higher on admission and 2 hours after thrombolysis (on admission, 12.3±6.8 vs 11.6±6.7, p=0.04; 2 hours, 9.8±7.0 vs 9.0±7.2, p=0.004). But there was no difference in NIHSS scores between women and men in 24 hours and 7 days after thrombolysis (24 hours, 9.1±8.3 vs 8.3±7.9, p=0.07; 7 days, 6.7±7.8 vs 6.2±7.0, p=0.41). Moreover, NIHSS improving scores, that is, using of NIHSS score on admission to minus NIHSS score at different times, were similar between men and women.

In terms of safety outcomes, the proportion of SICH and mortality in women is relatively high but did not reach statistical significance (table 2).

DISCUSSION

In this study, we found that the prognosis of intravenous thrombolysis has no significant correlation with sex differences. The trend in the relatively poor prognosis of women may be related to severity and age at the time of onset, rather than sex disparities.

In fact, it has been long recognised that women are more severe and older at the onset of stroke worldwide than men.[7 8 25] The reasons for these sex disparities are still not clear. Early studies pointed out that women were more likely to live alone, have atypical symptoms and delay in hospital arrival and acute imaging, potentially resulting in exacerbating the illness.[26 27] However, in our study, the functional status before the onset of women and men was

Table 2 Outcomes after intravenous thrombolysis in women versus men

Outcome	No. (%) of patients		Unadjusted OR (95% CI)	P value	Adjusted OR (95% CI)*	P value
	Women (n=529)	Men (n=881)				
Primary outcomes						
mRS 3–6 at 3 months	243 (45.9)	327 (37.1)	1.44 (1.16 to 1.79)	0.001	1.01 (0.75 to 1.37)	0.95
Safety outcomes						
SICH (SITS-MOST)	12 (2.4)	15 (1.7)	1.45 (0.69 to 3.07)	0.33	1.26 (0.50 to 3.21)	0.63
SICH (NINDS)	35 (6.5)	43 (4.8)	1.15 (0.66 to 2.00)	0.62	0.89 (0.51 to 1.55)	0.67
SICH (ECASS II)	22 (4.1)	32 (3.6)	1.38 (0.87 to 2.18)	0.17	0.82 (0.42 to 1.61)	0.56
Mortality at 7 days	32 (5.9)	43 (4.8)	1.25 (0.78 to 2.00)	0.35	0.94 (0.51 to 1.71)	0.83
Mortality at 3 months	60 (11.3)	81 (9.2)	1.26 (0.88 to 1.79)	0.20	0.79 (0.50 to 1.26)	0.32

*Adjusted baseline variables: age, diastolic blood pressure, current smoking, hypertension, diabetes mellitus, atrial fibrillation, antihypertensive agents before stroke, stroke-to-needle time, stroke-to-visit time, stroke-to-imaging time, National Institute of Health Stroke Scale (NIHSS) on admission and Trial of Org 10172 in Acute Stroke Treatment (TOAST) types.
ECASS II, second European–Australasian acute stroke study; mRS, modified Rankin Scale; NINDS, National Institute of Neurological Disorders and Stroke; SICH, symptomatic intracranial haemorrhage; SITS-MOST, safe implementation of treatments in stroke-monitoring study.

similar, and even men took longer to get to the hospital and start thrombolysis than women in the acute phase. This situation may account for the fact that women pay more attention to themselves and have a better understanding of stroke signs and symptoms. Thus, it is of considerable significance to strengthen the education of stroke prevention and treatment to the public.

The influence of sex differences in stroke is also related to age. Recent studies proved that the age-related ischaemic stroke (IS) mortality rate of young women is lower than that of men, while of old women is higher than that of men. But the vital cross-over age is various in different studies.[9 16 28] Preclinical research proved that the prognosis of female

mice after middle cerebral artery occlusion was even worse with ageing.[29] However, in the real world, many studies, including ours, have not found a significant difference in outcomes after thrombolysis between women and men concerning age.[16] We believe that the relationship between sex, age and prognosis is not a simple triangle. In fact, a randomised clinical trial named Early versus Late Intervention Trial with Estradiol found out that starting hormone therapy (HT) in newly postmenopausal women (<6 years) is relatively safe and may slow down the progression of atherosclerosis, whereas for women after 10 years of menopause, the effect of HT is not significant.[30] More basic research also provides evidence that the impact of age on sex is not

Table 3 Interaction with poor functional outcome after intravenous thrombolysis in women versus men

	Women n (%)	Men n (%)	mRS score of 3–6 unadjusted OR (95% CI)	P value	Interaction p values	mRS score of 3–6 adjusted OR (95% CI) *	P value	Interaction p values
Age<50 years	17 (34.7)	31 (22.3)	1.85 (0.91 to 3.77)	0.09	0.40	1.57 (0.52 to 4.76)	0.42	0.53
Age≥50 years	226 (47.1)	296 (39.9)	1.34 (1.06 to 1.69)	0.01		1.00 (0.74 to 1.37)	0.98	
Pre-mRS≤2	238 (46.1)	319 (36.8)	1.47 (1.18 to 1.83)	0.0007	0.21	1.02 (0.75 to 1.39)	0.89	0.56
Pre-mRS>2	5 (41.7)	7 (58.3)	0.51 (0.10 to 2.59)	0.42		–	–	
NIHSS≤5	11 (13.4)	14 (9.2)	1.53 (0.66 to 3.54)	0.32	0.89	0.83 (0.26 to 2.68)	0.75	0.97
NIHSS>5	232 (51.9)	313 (42.9)	1.43 (1.13 to 1.82)	0.003		1.05 (0.78 to 1.41)	0.76	
TOAST types					0.54			0.48
LAA	123 (46.2)	214 (40.0)	1.30 (0.97 to 1.75)	0.08		0.95 (0.63 to 1.42)	0.8	
SAO	10 (22.7)	15 (18.5)	1.29 (0.53 to 3.19)	0.57		0.19 (0.04 to 0.95)	0.04	
CE	81 (57.9)	62 (53.5)	1.20 (0.73 to 1.96)	0.48		1.14 (0.6 to 2.19)	0.68	
Others	28 (36.8)	30 (21.9)	2.08 (1.12 to 3.86)	0.02		1.47 (0.61 to 3.55)	0.39	

*Adjusted baseline variables: age, diastolic blood pressure, current smoking, hypertension, diabetes mellitus, atrial fibrillation, antihypertensive agents before stroke, stroke-to-needle time, stroke-to-visit time, stroke-to-imaging time, National Institute of Health Stroke Scale (NIHSS) on admission and Trial of Org 10172 in Acute Stroke Treatment (TOAST) types, except the analysis factor itself.
CE, cardioembolism; LAA, large-artery atherosclerosis; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; SAO, small-artery occlusion; TOAST, the Trial of Org 10172 in Acute Stroke Treatment.
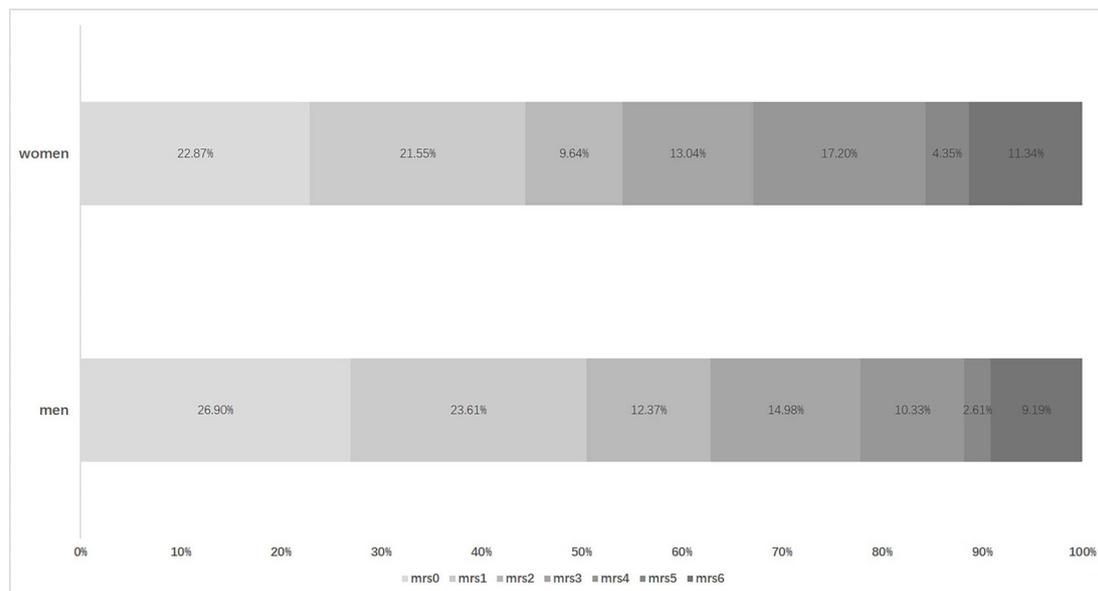
Figure 1 Distribution of modified Rankin scale (mRS) score after intravenous thrombolysis in patients with acute ischaemic stroke (N=1410).

only in hormonal changes but also in systemic inflammation, metabolism and age-related gene expression.[31–33]

Further, our study found that women may benefit more from treatment than men. These observations may be closely tied to the prevalence of cardioembolic stroke, less smoking and better compliance in women. Besides, according to the previous reports, oestrogen plays a crucial role in promoting thrombus recanalisation by lowering the level of platelet activator inhibitors.[34]

Excluding the sociological and physiological factors above, biological sex differences in genetic are particularly noteworthy when confirmed by various evidence. The most convincing results are that sex-specific cell grown in culture media without sex steroids has a mechanistically different response to hypoxia and glucose deficiency, which is a common manifestation of cerebral ischaemia.[35] Moreover, recent work showed an inherent sex disparity in molecular signalling pathways and cell death mechanisms.[36]

This study has several limitations. First, since it was an observational retrospective study, there was no control group without thrombolytic therapy. Second, only Chinese patients were recruited in the programme. We are unable to analyse the differences in thrombolytic prognosis between women and men of different races. Third, due to the limited sample data and size, the aetiological analysis in women and men is not detailed enough. Factly, gender may be a modifier for various stroke causes.[37]

CONCLUSION

For Chinese patients with IS, although women are older and more severe at the time of onset, the prognosis after intravenous thrombolysis is not significantly different from men. It is remarkable to improve women's chances of thrombolysis and strengthen the genetics and molecular biology research of sex differences per se.

Table 4 National Institute of Health Stroke Scale (NIHSS) scores changed over time after intravenous thrombolysis

Outcome	Women (n=541)	Men (n=899)	P value	Adjusted p value*
Median NIHSS on admission	12.3±6.8	11.6±6.7	0.04	–
Median NIHSS 2 hours (±15 min)	9.8±7.0	9.0±7.2	0.004	–
Median NIHSS 24 hours (±2 hour)	9.1±8.3	8.3±7.9	0.07	–
Median NIHSS at discharge or 7 days (±1 day)	6.7±7.8	6.2±7.0	0.41	–
Improving NIHSS 2 hours (±15 min)	2.4±4.5	2.6±5.0	0.66	0.59
Improving NIHSS 24 hours (±2 hours)	3.1±6.7	3.2±6.6	0.91	0.45
Improving NIHSS at discharge or 7 days (±1 day)	5.2±7.1	5.0±6.7	0.20	0.33

*Adjusted baseline variables: age, diastolic blood pressure, current smoking, hypertension, diabetes mellitus, atrial fibrillation, antihypertensive agents before stroke, stroke-to-needle time, stroke-to-visit time, stroke-to-imaging time and Trial of Org 10172 in Acute Stroke Treatment (TOAST) types.
NIHSS, National Institute of Health Stroke Scale.

ORCID iDs
Hongyu Zhou http://orcid.org/0000-0002-9130-889X
Yuesong Pan http://orcid.org/0000-0003-3082-6789
Yue Suo http://orcid.org/0000-0002-0632-0262
Hao Li http://orcid.org/0000-0002-8591-4105
Yongjun Wang http://orcid.org/0000-0002-9976-2341

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