Sex differences in Asian stroke registries for thrombolyzed acute ischemic stroke patients: an individual patient data pooling study

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Supplemental File

Supplemental Table 1. Patient characteristics by sex in the included stroke registries

Supplemental Table 2. Included stroke registries

Supplementary Table 3. Characteristics of eligible studies but not included in the review

Supplemental Table 4. Subgroup analysis of associations of sex and ordinal modified Rankin Scale scores at 90 days

Men as reference group

Adjusted for age, baseline National Institutes of Health Stroke Scale (NIHSS) scores, baseline systolic blood pressure (SBP), premorbid mRS, etiological Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification, and prior hypertension and atrial fibrillation [AF]

Supplemental Figure 1. Flow chart of patient inclusion

Supplemental Figure 2. Associations of sex and all the possible dichotomizations of modified Rankin Scale scores at 90 days

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Supplemental Table 1. Patient characteristics by sex in the included stroke registries

	Japan		Mainland China		Taiwan		Philippines		Korea		Singapore	
	Male (n=377)	Female (n=223)	Male (n=841)	Female (n=458)	Male (n=321)	Female (n=191)	Male (n=97)	Female (n=60)	Male (n=905)	Female (n=621)	Male (n=220)	Female (n=139)
Recruitment period	2005-2008		2007-2012, 2017-2018		2006-2010, 2017-2018		2014-2016		2009-2013		2013-2018	
Age, years	69 (11.6)	76 (11.1)	62 (10.8)	66 (11.2)	65 (13.3)	69 (12.1)	59 (12.9)	63 (15.4)	66 (11.9)	72 (1.25)	60 (12.2)	67 (14.1)
Systolic BP, mmHg	150 (20.9)	151 (18.9)	148 (19.5)	147 (20.1)	149 (23.0)	153 (28.0)	151 (25.4)	157 (27.3)	147 (26.8)	149 (28.7)	157 (26.0)	162 (24.1)
NIHSS	12 (7-18)	13 (8-20)	8 (4-13)	9 (5-15)	11 (7-18)	12 (7-17)	12 (6-16)	13 (7-18)	10 (6-16)	12 (7-17)	15 (10-21)	17 (12-21)
Prior hypertension	62.7	59.3	58.9	64.9	72.3	78.5	81.4	80.0	62.7	68.8	74.6	82.7
Prior atrial fibrillation	39.0	51.9	11.3	21.8	33.3	45.0	15.5	25.0	34.8	49.8	32.3	36.7
Pre-morbid modified Rankin scale												
0-1	92.6	82.1	79.5	83.4	91.9	88.0	-	-	92.0	87.1	-	-
2-5	7.4	17.9	20.5	16.6	8.1	12.0	-	-	8.0	12.9	-	-
TOAST classification												
Large-artery atherosclerosis	15.1	15.3	55.7	46.4	19.0	17.7	-	-	30.8	22.2	30.0	27.3
Small-vessel occlusion	47.8	4.9	17.5	15.2	17.7	13.7	-	-	7.0	4.8	5.9	5.8
Cardioembolism	65.5	59.6	11.8	22.0	25.3	45.1	-	-	36.6	48.8	40.0	46.0
Others	14.6	20.2	15.0	16.5	38.0	23.5	-	-	25.6	24.2	24.1	20.9

Data are n (%), mean ± SD, or median (IQR). P values from univariate analyzes based on Chi-square or Wilcoxon signed-rank test

BP denotes blood pressure, NIHSS National Institutes of Health Stroke Scale, mRS modified Rankin scale, TOAST Aetiological Trial of Org 10172 in Acute Stroke Treatment

Supplemental Table 2. Included stroke registries

Study	Country/Region	Definition of symptomatic intracerebral hemorrhage (sICH)
SAMURAI (Stroke 2012;43:253-255)	Japan(national)	SICH associated with neurological deterioration corresponding to an increase of ≥4 points from baseline National Institute of Health Stroke Scale (NIHSS) score
TIMS3 (Stroke 2014;45:2354-2358)	Mainland China(national)	Per original NINDS study, a hemorrhage that was not seen on a previous CT scan and there had subsequently been either a suspicion of hemorrhage or any decline in neurological status
Changhua Christian Hospital stroke Registry (J Thromb Haemost 2012;10(7):1270-5)	Taiwan(regional)	Per original NINDS study, a hemorrhage that was not seen on a previous CT scan and there had subsequently been either a suspicion of hemorrhage or any decline in neurological status
Philippines stroke Registry (Neurology Asia 2018; 23(2):115–120)	Philippines(national)	SICH associated with increased in NIHSS by 4 points at any time after thrombolysis and confirmed by non-contrast CT scan
Korea stroke Registry (Stroke. 2015;46:2541-2548)	Korea(national)	A cerebral hemorrhage documented by neuroimaging study and accompanied by an increase of ≥4 points on the NIHSS score compared with baseline or from the lowest NIHSS score in the individual subject before the development of sICH
Stroke Registry in Chang Gung Healthcare System	Taiwan(regional)	SICH associated with neurological deterioration corresponding to an increase of ≥2 points from baseline NIHSS score
Stroke Registry from Singapore	Singapore (national)	Appearance of blood on CT brain scan with a significant neurologic deterioration, defined as documented objective evidence of neurological decline with an increase of ≥4 points from most recent NIHSS score
Shengyang Stroke Registry	Mainland China(regional)	Per ECASS II, any ICH with neurological deterioration (>4 points on the NIHSS) from baseline or death within 24 to 36 hours

SAMURAI denotes for the Stroke Acute Management with Urgent Risk-Factor Assessment and Improvement rt-PA registry; TIMS3: the Thrombolysis Implementation and Monitor of Acute Ischemic Stroke in China; NINDS: the National Institute of Neurological Disorders and Stroke study; ECASS: European Cooperative Acute Stroke Study

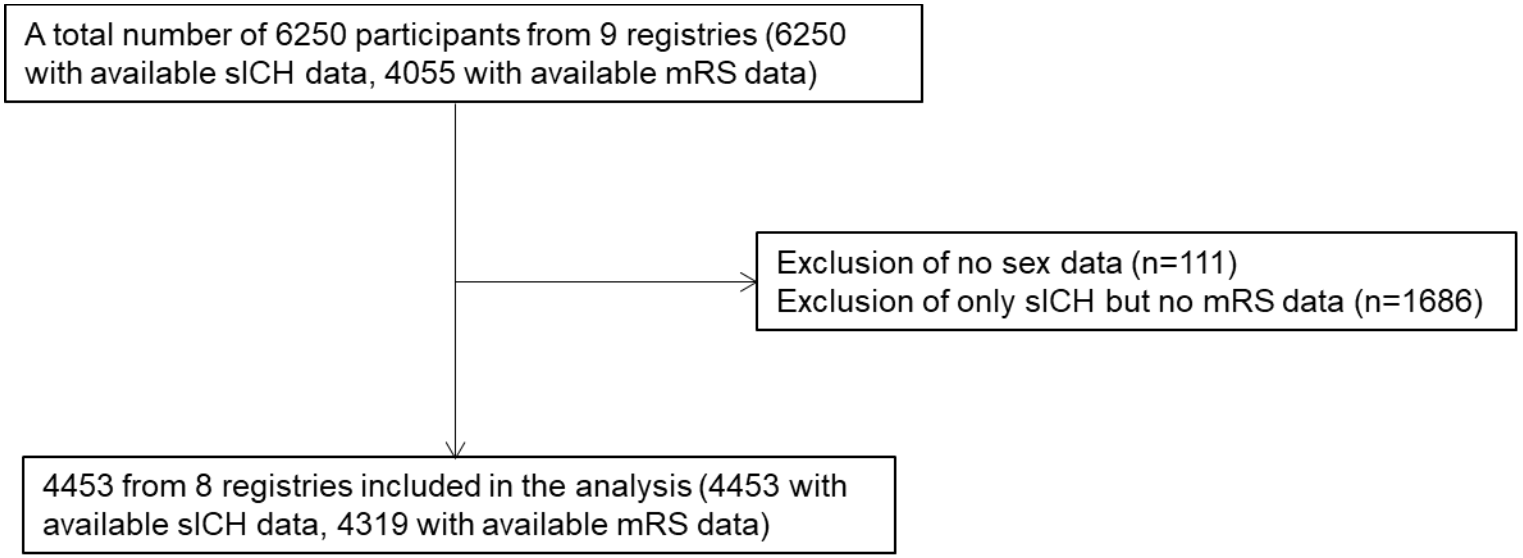
Supplementary Table 3. Characteristics of eligible studies but not included in the review

Publication	Origin	Cases	TPA dose, mg/kg	Results
Yamaguchi et al 2006[8]	Japan	103	0.6	In patients receiving 0.6 mg/kg alteplase, the outcome and the incidence of sICH were comparable to published data for 0.9 mg/kg
Chao et al 2010[28]	Taiwan	241	0.72±0.07 vs. 0.90±0.02	Standard dose of 0.9 mg/kg alteplase may not be optimal for treating aged Chinese patients
Nakagawara et al 2010[10]	Japan	7492	0.6	0.6 mg/kg intravenous alteplase within 3 hours of stroke onset could be safe and effective in routine clinical practice for the Japanese
Nguyen et al 2010[29]	Vietnam	121	0.6-0.86 vs. 0.9	Intravenous thrombolysis, particularly in a lower dose, is safe and feasible in the treatment of AIS in selected Vietnamese population
Zhou et al 2010[30]	China	105	0.6-0.7 vs. 0.8 vs. 0.9	There was a higher proportion of patients with good functional outcomes in the 0.9mg/kg group, but not significant
Chen et al 2012[31]*	Taiwan	261	<0.85 vs. ≥0.85	Standard-dose thrombolysis for AIS in an Asian population carries no increased risk of sICH when compared with the low dose
Chao et al 2014[32]	Taiwan	1004	0.6 vs. 0.7 vs. 0.8 vs. 0.9	In elderly patients (71-80 years), a lower dose of 0.6 mg/kg is associated with a better outcome

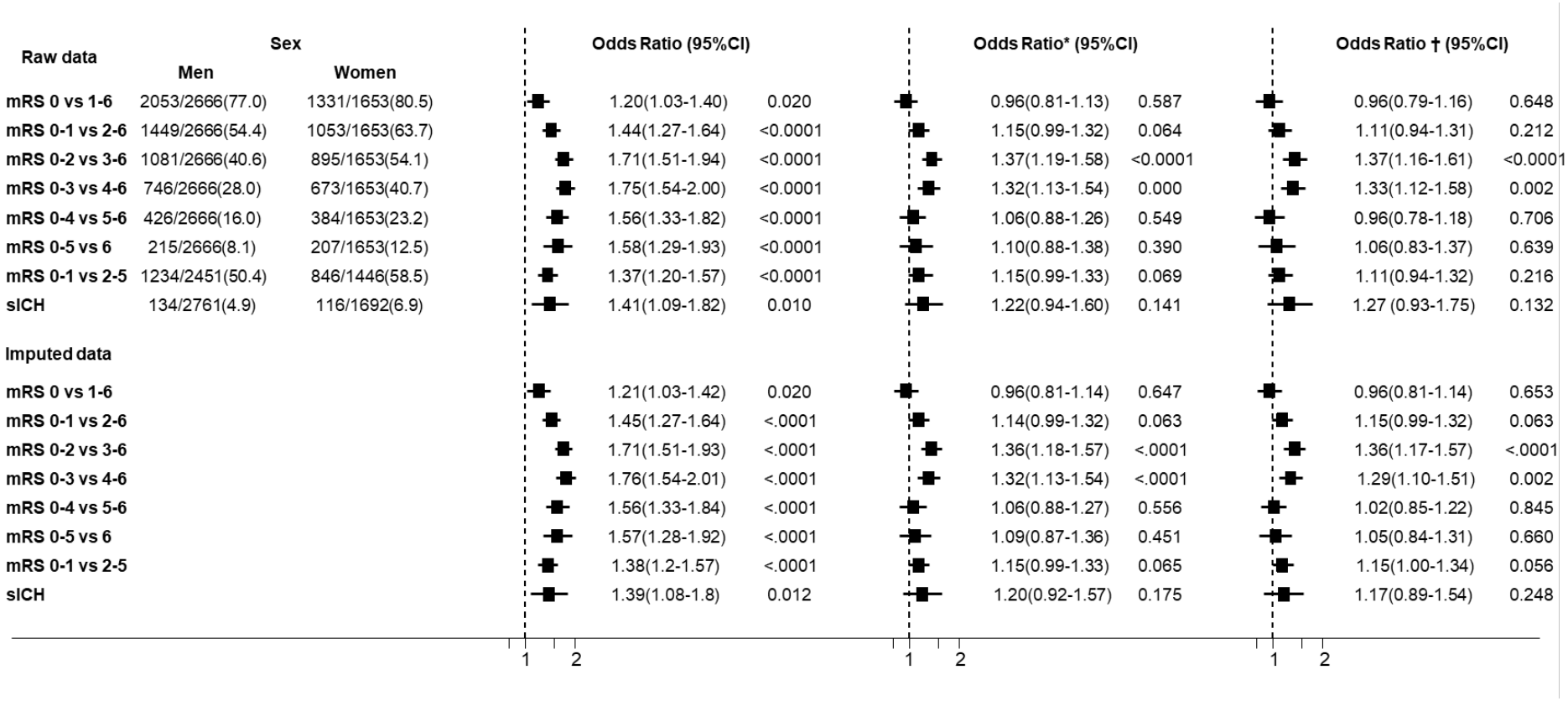
AIS acute ischemic stroke; alteplase: recombinant tissue plasminogen activator; sICH: symptomatic intracranial hemorrhage.
*The study was conducted in National Cheng Kung University Hospital and Changhua Christian Hospital, but only Changhua Christian Hospital provided data

Supplemental Table 4. Subgroup analysis of associations of sex and ordinal modified Rankin Scale scores at 90 days

	P for interaction
Age	0.022
NIHSS	0.294
Prior hypertension (Y vs. N)	0.062
Prior atrial fibrillation (Y vs. N)	0.466
Pre-morbid mRS (0-1 vs. 2-5)	0.251
TOAST classification (large-artery atherosclerosis vs. small-vessel occlusion vs. cardioembolism vs. others)	0.868



Supplemental Figure 1. Flow chart of patient inclusion



Supplemental Figure 2. Associations of sex and all the possible dichotomizations of modified Rankin Scale scores at 90 days