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Research article

The association of gender with functional outcome in thrombolysed stroke: A secondary analysis of INTRECIS study

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ABSTRACT

Background and Purpose: Sex differences in acute ischemic stroke have been widely investigated, but the difference in acute ischemic stroke patients who received intravenous thrombolysis is not well understood. The current study was to investigate the issue based on a prospective cohort.

Methods: From the Intravenous Thrombolysis Registry for Chinese Ischemic Stroke within 4.5h onset (INTRECIS) cohort, a total of 953 eligible patients with acute ischemic stroke were enrolled in final analysis. Based on 3-month modified Rankin scale score (mRS), patients were classified into good outcome group (mRS 0–1) and poor outcome group (mRS 2–6). Univariate and multivariate logistic regression analyses were used to identify predictive factors for clinical outcome in male or female patients.

Results: Of the 953 patients treated with intravenous thrombolysis, 314 (32.9 %) were women. At day 90, we found no significant gender differences in good outcome (72.5 % vs 65.6 %, adjusted $p = 0.414$). We got the same results after propensity score matching (69.5 % vs 63.4 %, adjusted $p = 0.637$). Furthermore, we found that initial National Institute of Health Stroke Scale (NIHSS) score (odd ratio [OR] 0.877; 95 % CI 0.847–0.909, $p < 0.001$) and serum creatinine (OR 0.993; 95 % CI 0.986–1.000, $p = 0\,0.043$) were found to be independent risk factors for poor outcome in male patients, while initial NIHSS score (OR 0.879; 95 % CI 0.839–0.920, $p < 0.001$), age (OR 0.970; 95 % CI 0.946–0.995, $p = 0.017$), systolic blood pressure (OR 0.984; 95 % CI 0.972–0.996, $p = 0.007$) and small artery occlusion (OR 2.718; 95 % CI 1.065–6.936, $p = 0.036$) in female patients.

Conclusions: In this study, we found no gender difference in clinical outcome of thrombolysed stroke patients, but a difference in risk factors predicting outcome in male vs female patients was identified for the first time.

1. Introduction

Intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator (rt-PA) has been recommended to treat acute ischemic stroke (AIS) by guidelines [1–3]. A lot of studies have found the gender difference in etiology, risk factors, clinical manifestations, delay in prehospital and in-hospital treatment, implementation of thrombolytic therapy, complications related to thrombolytic therapy, and prognosis of AIS patients [4–8]. It is of clinical importance to determine the gender difference in AIS, which will be

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helpful to improve the individualized management including the implementation of thrombolytic therapy in male vs female AIS patients.

However, the effect of gender on outcome of thromblysed AIS patients is still controversial [5,9]. Therefore, the current study was designed to investigate whether the gender has effect on outcome of AIS patients who received intravenous rt-PA, and made the first attempt to analyze the predictive factors of outcome in male vs female patients.

2. Methods

2.1. Study population

Intravenous Thrombolysis Registry for Chinese Ischemic Stroke within 4.5h onset (INTRECIS) [10] is a prospective, multicenter cohort study. From this cohort, we consecutively enrolled eligible AIS participants with over 18 years who received 0.9 mg/kg rt-PA. The inclusion criteria were (1) age ≥18 years; (2) diagnosis of AIS; (3) treatment with standard dose of rt-PA (alteplase, 0.9 mg/kg up to a maximum of 90 mg/kg) within 4.5h of symptom onset; (4) complete clinical data. Patients with any of the following conditions were excluded: (1) receiving endovascular therapy; (2) lack of complete clinical data. The INTRECIS study was centrally approved by General Hospital of the Northern Theater Command (the former General Hospital of ShenYang Military Region), and was registered at Clinicaltrials.gov (NCT 02854592). Signed informed consents were obtained from the patients or their legally authorized representative.

2.2. Data collection

From electronic data capture system, we collected demographic and clinical data, including sex, age, smoking history, drinking history, time of onset, onset-to-needle time (ONT), National Institute of Health Stroke Scale (NIHSS) scores, Trial of ORG 10172 in

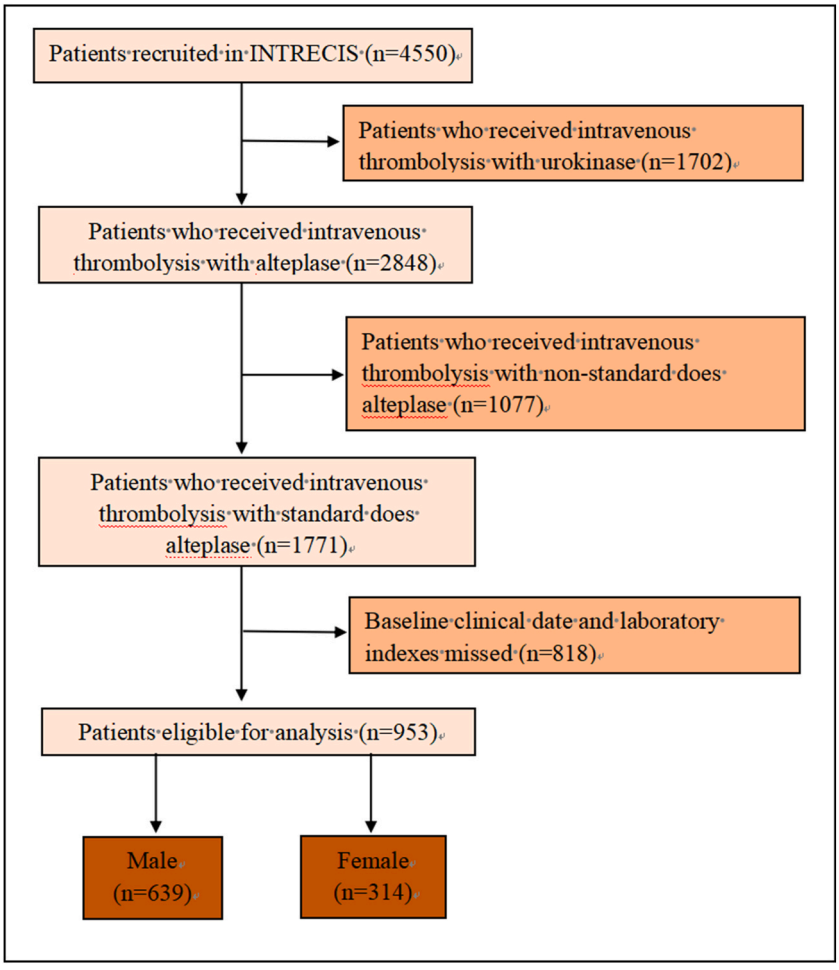

Fig. 1. The flow diagram.

Acute Stroke Treatment (TOAST) classification, past medical history, and laboratory indexes. All patients were assessed at 3-month using modified Rankin Scale (mRS). Good outcome was defined as a mRS score of 0 or 1 at 90 days, while poor outcome as a score of 2 or greater on the mRS at 90 days. The safety outcome was symptomatic intracranial hemorrhage (sICH) within 48h, defined as an increase in the NIHSS score of ≥4 points as a result of intracranial hemorrhage according to the ECASS-3 study [11].

2.3. Statistical analysis

Continuous variables were shown as mean ± standard deviation and median (interquartile range) in normal and non-normal distributions, respectively, and categorical variables were shown as frequency (proportion). Differences in normally and non-normally distributed continuous variables were identified using the Student t tests and Mann-Whitney *U* test, respectively, while the chi-squared test was used for categorical variables. The demographic and clinical characteristics between male and female patients with ischemic stroke, including age, smoking history, drinking history, initial NIHSS scores, ONT, TOAST classification, past medical history, and laboratory indexes, were compared. Univariate and multivariate logistic regression analyses were applied to calculate the odds ratio (OR) and relative 95 % confidence interval (CI) to assess the association between gender and outcome. Potential variables that may be related to outcomes and those with a P-value <0.1 in the univariate regression analysis were further validated by multivariate regression analysis. As the sensitivity analysis, propensity score matching (PSM) was used to balance the baseline characteristics between male and female. We used 1:1 propensity score matching with a caliper width of 0.1, matching for variables with a P-value <0.05. In addition, we apply logistic regression analyses to compared the differences in factors predictive of outcome after intravenous thrombolysis in male and female patients. A P-value of <0.05 was considered to reflect statistical significance, and all data were analyzed using IBM SPSS version 25.0 (SPSS Inc., Chicago, IL, USA).

3. Results

As shown in Fig. 1, a total of 953 eligible patients were enrolled in the current study after excluding 3597 patients with different

Table 1
Baseline characteristics and clinical characteristics after intravenous thrombolysis in AIS patients according to gender.

	Before PSM			After PSM		
	Male (n = 639)	Female (n = 314)	P value	Male (n = 243)	Female (n = 243)	P value
Age, y (IQR)	62 (54–70)	69 (59–78)	**<0.001**	66 (59–73)	65 (56–74)	0.363
Smoking history, n (%)	338 (52.9)	18 (5.7)	**<0.001**	130 (53.5)	15 (6.2)	**<0.001**
Drinking history, n (%)	242 (37.9)	2 (0.6)	**<0.001**	80 (32.9)	2 (0.8)	**<0.001**
Previous stroke, n (%)	118 (18.5)	57 (18.2)	0.906	44 (18.1)	40 (16.5)	0.631
Hypertension, n (%)	349 (54.6)	198 (63.1)	**0.013**	135 (55.6)	146 (60.1)	0.312
Diabetes mellitus, n (%)	98 (15.3)	71 (22.6)	**0.006**	43 (17.7)	54 (22.2)	0.212
Coronary artery disease, n (%)	88 (13.8)	66 (21)	**0.004**	36 (14.8)	43 (17.7)	0.389
Atrial fibrillation, n (%)	40 (6.3)	60 (19.1)	**<0.001**	23 (9.5)	32 (13.2)	0.198
Body mass index, kg/m^2 (IQR/mean ± SD)	24.2 (22–26.1)	23.4 (20–26.33)	**0.008**	23.67 ± 0.21	23.93 ± 0.26	0.449
Heart rate, bpm (IQR)	76 (70–84)	78 (70–87)	0.117	76 (68–84)	78 (70–88)	**0.012**
Systolic blood pressure, mmHg (IQR/mean ± SD)	150 (137–166)	155 (138–170)	**0.071**	152.47 ± 1.43	155.38 ± 1.54	0.167
Diastolic blood pressure, mmHg (IQR)	90 (80–100)	87 (79–96)	**0.006**	88 (80–98)	89 (80–98)	0.851
TOAST, n (%)			**<0.001**			0.909
Large artery atherosclerosis	308 (48.2)	141 (45)		110 (45.3)	113 (46.5)	
Cardioembolism	61 (9.5)	63 (20.1)		33 (13.6)	39 (16)	
Small artery occlusion	217 (34)	87 (27.8)		81 (33.3)	74 (20.5)	
Other determined	15 (2.3)	4 (1.3)		5 (2.1)	4 (1.6)	
Undetermined	38 (5.9)	18 (5.8)		14 (5.8)	13 (5.3)	
Median NIHSS on admission	5 (3–10)	7 (3–13)	**0.001**	6 (3–10)	7 (3–13)	0.123
Onset-to-needle time, m (IQR)	171 (130–212)	170 (130–202)	0.647	161 (120–203)	171 (135–210)	0.133
Random blood sugar, mmol/L (IQR)	6.65 (5.76–8.31)	7.1 (5.9–8.95)	**0.004**	6.76 (5.8–8.7)	7.1 (5.84–9.3)	0.122
White blood cell, x10^9/L (IQR)	7.51 (6.11–9.38)	7.15 (5.75–8.83)	**0.010**	7.11 (5.76–9.18)	7.17 (5.76–9.2)	0.969
Hemoglobin, g/L (IQR)	147 (136–157)	130 (123–139)	**<0.001**	141 (129–150)	132 (125–141)	**<0.001**
Albumin, mg/L (IQR)	39.5 (36–42.2)	38.7 (35.5–42)	**0.049**	39 (35.8–41.7)	38.8 (36–42.1)	0.907
Blood urea nitrogen, mmol/L (IQR)	5.5 (4.55–6.71)	5.49 (4.6–6.53)	0.655	5.4 (4.5–6.46)	5.45 (4.6–6.59)	0.538
Creatinine, μmol/L (IQR)	73 (63–86.4)	59.65 (49–71)	**<0.001**	67 (58–79.3)	60 (49–72)	**<0.001**
Urate, μmol/L (IQR)	312 (239–393)	263 (200–336)	**<0.001**	291 (226–357)	265 (201–341)	**0.015**
C-reactive protein, mg/L (IQR)	1.6 (0.4–5)	1.7 (0.5–5)	0.482	1.7 (0.5–5)	1.4 (0.49–5)	0.638
Cholesterol, mmol/L (IQR)	4.39 (3.8–5.09)	4.6 (3.99–5.27)	**0.002**	4.44 (3.89–5.32)	4.63 (4–5.24)	0.105
Triglyceride, mmol/L (IQR)	1.4 (0.96–1.96)	1.28 (0.87–1.85)	**0.048**	1.24 (0.84–1.88)	1.34 (0.89–1.88)	0.479
Low density lipoprotein, mmol/L (mean ± SD)	2.68 ± 0.36	2.82 ± 0.52	**0.029**	2.72 ± 0.06	2.83 ± 0.06	0.191
High density lipoprotein, mmol/L (IQR)	1.09 (0.92–1.31)	1.21 (1.04–1.40)	**<0.001**	1.12 (0.96–1.39)	1.21 (1.04–1.42)	**0.003**
mRS≤1 at 3months, n (%)	463 (72.5)	206 (65.6)	**0.03**	169 (69.5)	154 (63.4)	0.150
Symptomatic intracranial hemorrhage	19(3)	5(1.6)	0.201	9(3.7)	5(2.1)	0.278

AIS, acute ischemic stroke; IQR, interquartile range; TOAST, trial of org 10,172 in acute stroke treatment; NIHSS, national institute of health stroke scale; mRS, modified Rankin scale.

reasons. The median age of all participants was 64 (interquartile range, 55, 73) years, and 314 patients (32.9 %) were women. Demographic and baseline characteristics according to gender were presented in Table 1. Many baseline characteristics were not balanced between male and female, but only several variables were imbalanced after PSM (Table 1). After adjusting these imbalanced variables, multivariate logistic regression analysis showed that gender was not associated with good functional outcome (Before PSM: 72.5 % vs 65.6 %; adjusted OR 0.834, 95 % CI 0.540–1.288, p = 0.414, Fig. 2A; After PSM: 69.5 % vs 63.4 %, adjusted OR 1.118, 95 % CI 0.703–1.777; p = 0.637, Fig. 2B) or sICH (Before PSM: adjusted OR 1.879, 95 % CI 0.681–5.184, p = 0.294; After PSM: adjusted OR 1.457, 95%CI 0.377–5.631, p = 0.586).

Table 2 exhibited baseline and clinical characteristics according to outcome in male vs female patients. Among men, poor outcome was associated with older age, larger artery atherosclerosis (LAA) etiology, more history of previous drinking, and atrial fibrillation, higher initial NIHSS score, white blood cells (WBC), body mass index (BMI), serum hemoglobin, albumin and random blood glucose (RBG). Among women, poor outcome was associated with older age, previous stroke, more LAA etiology, atrial fibrillation, higher systolic blood pressure, heart rate, NIHSS on admission, RBG, serum creatinine, and blood urea nitrogen ($p < 0.05$).

In Table 3, univariate analysis found that age, drinking, atrial fibrillation, LAA, small artery occlusion (SAO), initial NIHSS score, WBC, hemoglobin, and creatinine were significant predictors of poor outcome in male patients, while age, LAA, SAO, atrial fibrillation, heart rate, systolic blood pressure, initial NIHSS score and RBG in female patients. Multivariate analysis showed that initial NIHSS score (OR 0.877; 95 % CI 0.847–0.909, $p < 0.001$) and serum creatinine (OR 0.993; 95 % CI 0.986–1.000, p = 0 0.043) were independent risk factors for poor outcome in male patients (Table 4), while initial NIHSS score (OR 0.879; 95 % CI 0.839–0.920, $p < 0.001$), age (OR 0.970; 95 % CI 0.946–0.995, p = 0.017), systolic blood pressure (OR 0.984; 95 % CI 0.972–0.996, p = 0.007) and SAO (OR 2.718; 95 % CI 1.065–6.936, p = 0.036) for poor outcome in female patients (Table 5).

As the sensitivity analysis, we further analyzed the association of gender with outcome of thrombolysed stroke in patients with 18–80 years old. Similar results were observed (sTable 1–5).

4. Discussion

Previous studies have investigated the relationship between gender and functional outcome after IVT, but the results are conflicting. For example, in the Safe Implementation of Treatments in Stroke-International Stroke Thrombolysis Register (SITS-ISTR), gender was not found to show influence on the functional outcome after IVT, though there was a higher bleeding risk among men [5]. A pooled analysis of randomized IVT trials also found no appreciable effect of gender on outcome after IVT [12]. However, in the study of IVT registries of 12 European tertiary hospitals, women more often had poor functional outcome compared with men [5]. Our study found no effect of gender on outcome in AIS patients who received intravenous thrombolysis. Collectively, these conflicting results suggest that the association of gender with outcome of AIS was complex and warrant further investigation [13]. Furthermore, we found a difference in dependent risk factors predicting poor outcome in male vs female patients.

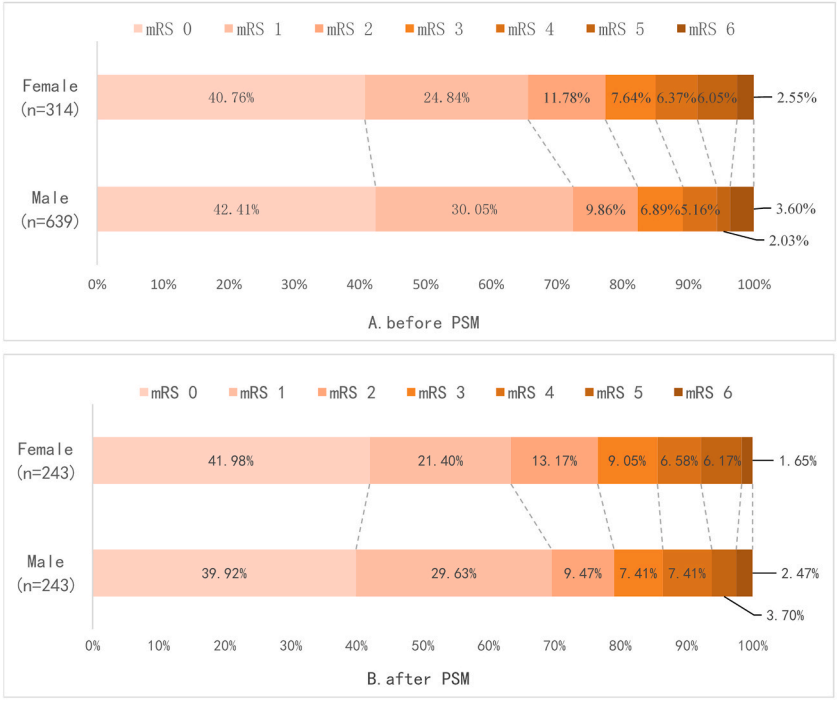

Fig. 2. Distribution of modified Rankin scale (mRS) score.

Table 2
Baseline characteristics and clinical characteristics after intravenous thrombolysis in AIS patients.

	Male (n = 639)			Female (n = 314)		
	mRS 0–1 (n = 463)	mRS ≥2 (n = 176)	P value	mRS 0–1 (n = 206)	mRS ≥2 (n = 108)	P value
Age, y (IQR)	62 (53–70)	65 (56–73)	**0.002**	66 (56–77)	74 (66–81)	**<0.001**
Smoking history, n (%)	211 (45.6)	90 (51.1)	0.208	11 (5.3)	7 (6.5)	0.679
Drinking history, n (%)	190 (41)	52 (29.5)	**0.007**	1 (0.5)	1 (0.9)	0.641
Previous stroke, n (%)	83 (17.9)	35 (19.9)	0.568	31 (15)	26 (24.1)	**0.049**
Hypertension, n (%)	245 (52.9)	104 (59.1)	0.161	130 (63.1)	68 (63)	0.980
Diabetes mellitus, n (%)	71 (15.3)	27 (15.3)	0.998	42 (20.4)	29 (26.9)	0.193
Coronary artery disease, n (%)	62 (13.4)	26 (14.8)	0.651	40 (19.4)	26 (24.1)	0.366
Atrial fibrillation, n (%)	22 (4.8)	18 (10.2)	**0.011**	30 (14.6)	30 (27.8)	**0.005**
Body mass index, kg/m2 (IQR)	24.2 (22.5–26.3)	23.7 (21.5–25.95)	**0.018**	23.4 (21–26.7)	22.85 (20.3–25.85)	0.151
Heart rate, bpm (IQR)	76 (70–84)	76 (68–86)	0.771	76 (69–85)	80 (71–91)	**0.029**
Systolic blood pressure, mmHg (IQR)	150 (136–166)	153 (138–168)	0.361	150 (136–167)	160 (142–177)	**0.016**
Diastolic blood pressure, mmHg (IQR)	90 (80–100)	90 (80–99)	0.906	85 (78–95)	89 (80–98)	**0.098**
TOAST, n (%)			**<0.001**			**<0.001**
Large artery atherosclerosis	204 (44.1)	104 (59.1)		85 (41.5)	56 (51.9)	
Cardioembolism	39 (8.4)	22 (12.5)		26 (12.7)	37 (34.3)	
Small artery occlusion	180 (38.9)	37 (21)		75 (36.6)	12 (11.1)	
Other determined	10 (2.2)	5 (2.8)		3 (1.5)	1 (0.9)	
Undetermined	30 (6.5)	8 (4.5)		16 (7.8)	2 (1.9)	
Median NIHSS on admission	5 (3–7)	10 (5–15)	**<0.001**	5 (3–9)	12 (9–17)	**<0.001**
Onset-to-needle time, m (IQR)	175 (130–213)	165 (122–208)	0.348	165 (125–200)	174 (145–215)	0.114
Random blood sugar, mmol/L (IQR)	6.55 (5.62–8.05)	6.8 (6.0–8.9)	**0.029**	6.9 (5.8–8.61)	7.44 (6.2–10.1)	**0.026**
White blood cell, x10^9/L (IQR)	7.47 (6.1–9.2)	7.91 (6.45–9.99)	**0.057**	7.07 (5.7–8.79)	7.2 (5.96–9.40)	0.220
Hemoglobin, g/L (IQR)	148 (137–158)	144 (132–154)	**0.003**	130 (123–139)	131 (122–141)	0.843
Albumin, mg/L (IQR)	40 (36.5–42.4)	38.25 (35.33–41.96)	**0.006**	38.85 (35.48–41.7)	38.55 (35.68–42.2)	0.887
Blood urea nitrogen, mmol/L (IQR)	5.48 (4.5–6.55)	5.7 (4.68–7.06)	**0.057**	5.27 (4.39–6.35)	5.82 (4.95–7.1)	**0.002**
Creatinine, μmol/L (IQR)	72.3 (63–85)	74 (62.63–90.98)	0.116	58 (48–69)	63 (52–73)	**0.036**
Urate, μmol/L (IQR)	319 (247.8–394)	300.5 (227.5–385)	0.349	264.8 (201.75–340.88)	252.2 (191.68–334.7)	0.354

AIS, acute ischemic stroke; IQR, interquartile range; TOAST, trial of org 10,172 in acute stroke treatment; NIHSS, national institute of health stroke scale; mRS, modified Rankin scale.

Table 3
Univariate logistic regression analysis of the 90-day outcome after intravenous thrombolysis in AIS patients.

Parameter	mRS≤1 at 3months					
	Male (n = 639)			Female (n = 314)		
	OR	95%CI	P value	OR	95%CI	P value
Age	0.976	(0.961–0.991)	**0.001**	0.957	(0.937–0.977)	**<0.001**
Smoking history	1.250	(0.883–1.769)	0.208	0.814	(0.306–2.163)	0.680
Drinking history	0.603	(0.415–0.875)	**0.008**	1.916	(0.119–30.933)	0.647
Previous stroke	1.136	(0.732–1.764)	0.569	1.790	(0.999–3.208)	**0.051**
Hypertension	1.285	(0.904–1.827)	0.162	0.994	(0.614–1.610)	0.980
Diabetes mellitus	1.000	(0.618–1.619)	0.998	1.433	(0.832–2.470)	0.195
Coronary artery disease	1.121	(0.683–1.839)	0.651	1.316	(0.752 2.304)	0.337
Atrial fibrillation	2.284	(1.194–4.370)	**0.013**	2.256	(1.274–3.998)	**0.005**
Body mass index	1.060	(1.007–1.115)	**0.025**	1.050	(0.990–1.113)	0.106
Heart rate	0.996	(0.984–1.009)	0.576	0.984	(0.969–0.999)	**0.036**
Systolic blood pressure	0.997	(0.989–1.005)	0.416	0.990	(0.980–1.000)	**0.048**
Diastolic blood pressure	1.003	(0.990–1.016)	0.702	0.989	(0.973–1.006)	0.210
Large artery atherosclerosis	0.545	(0.383–0.775)	**0.001**	0.658	(0.412–1.051)	**0.080**
Small artery occlusion	2.389	(1.589–3.593)	**<0.001**	4.615	(2.376–8.966)	**<0.001**
NIHSS on admission	0.862	(0.833–0.893)	**<0.001**	0.860	(0.823–0.897)	**<0.001**
Onset-to-needle time	1.001	(0.998–1.004)	0.420	0.999	(0.996–1.002)	0.456
Random blood sugar	0.961	(0.910–1.015)	0.153	0.932	(0.875–0.992)	**0.027**
White blood cell	0.944	(0.889–1.002)	**0.056**	0.942	(0.864–1.028)	0.182
Hemoglobin	1.011	(1.003–1.020)	**0.012**	1.001	(0.987–1.016)	0.896
Albumin	1.005	(0.992–1.018)	0.421	0.997	(0.982–1.012)	0.657
Blood urea nitrogen	0.942	(0.871–1.019)	0.139	0.977	(0.913–1.044)	0.487
Creatinine	0.990	(0.984–0.997)	**0.004**	0.993	(0.982–1.005)	0.241
Urate	1.000	(0.999–1.002)	0.524	1.001	(0.999–1.003)	0.226

AIS, acute ischemic stroke; NIHSS, national institute of health stroke scale; mRS, modified Rankin scale; OR, odds ratio; CI, confidence interval.

Table 4
Multivariate logistic regression analysis of the 90-day outcome after intravenous thrombolysis in male patients.

Parameter	mRS≤1 at 3months		
	OR	95%CI	P value
Age	0.994	(0.976–1.012)	0.500
Drinking history	0.742	(0.419–1.123)	0.158
Atrial fibrillation	1.495	(0.672–3.325)	0.324
Body mass index	1.048	(0.989–1.110)	0.112
Large artery atherosclerosis	0.781	(0.446–1.368)	0.387
Small artery occlusion	1.384	(0.740–2.592)	0.309
NIHSS on admission	0.877	(0.847–0.909)	**<0.001**
White blood cell	0.953	(0.890–1.020)	0.167
Hemoglobin	1.007	(0.997–1.018)	0.157
Creatinine	0.993	(0.986–1.000)	**0.043**

NIHSS, national institute of health stroke scale; mRS, modified Rankin scale; OR, odds ratio; CI, confidence interval.

Table 5
Multivariate logistic regression analysis of the 90-day outcome after intravenous thrombolysis in female patients.

Parameter	mRS≤1 at 3months		
	OR	95%CI	P value
Age	0.970	(0.946–0.995)	**0.017**
Previous stroke	1.682	(0.842–3.360)	0.141
Atrial fibrillation	1.015	(0.460–2.240)	0.970
Systolic blood pressure	0.984	(0.972–0.996)	**0.007**
Heart rate	0.993	(0.976–1.012)	0.481
Large artery atherosclerosis	0.779	(0.380–1.600)	0.497
Small artery occlusion	2.718	(1.065–6.936)	**0.036**
NIHSS on admission	0.879	(0.839–0.920)	**<0.001**
Random blood sugar	0.966	(0.897–1.040)	0.362

NIHSS, national institute of health stroke scale; mRS, modified Rankin scale; OR, odds ratio; CI, confidence interval.

A lot of studies have investigated the risk factors for predicting outcomes after IVT in AIS patients [14,15]. This is the first to investigate whether there is a difference in dependent risk factors predicting outcome in male vs female patients. We unexpectedly found that serum creatinine was a dependent risk factor of predicting outcome in only male patients who received IVT. The reason for the difference remains elusive. Creatinine is one of components contributing to the total antioxidant capacity [16]. We have not identified a study on the effect of creatinine on gender-related prognosis of acute ischemic stroke. However, the impact of creatinine has been studied in patients with traumatic brain injury and sex-related differences have been observed, in accordance with what we have discovered [17]. One possible explanation may be due to the mild effect of oxidative stress for women with brain injury, which need further exploration.

Unlike male patients, age, systolic blood pressure, and small vessel occlusion were found to be independently associated with only female patients. One possible explanation is a difference in endogenous fibrinolysis because of differences in gender hormones between men and women. Estrogen has an indirect influence on the controlling of the fibrinolytic system, as well as a direct neuroprotective activity [18–21]. In humans, studies showed that the sooner the hormone replacement therapy was started after menopause or at younger age, the lower was the incidence of vascular events, suggesting a neuroprotective effect from higher estrogen levels [22]. Thus, with the increase of age, the protective effect of estrogen in women gradually disappears, so it is more likely to affect the prognosis in female patients. More basic studies have also provided evidence that age affects gender not only in hormonal changes, but also in systemic inflammation, metabolism, and age-related gene expression [23]. These may further explain more cardiovascular involvement in high blood pressure, worse arteriosclerosis, and larger impairment of automatic regulation of cerebral blood flow in women, compared with men [24]. Therefore, this may explain the association of systolic blood pressure and small artery occlusion with the outcome of female stroke patients. Collectively, the gender differences in predicting factors for functional outcomes after intravenous thrombolysis warrant to be confirmed in prospective, big sample, clinical trials.

Our study has some limitations. First of all, this is retrospective study, which is prone to bias, although our data were collected based on a prospective cohort. Second, there is some missing clinical data and laboratory indicators, which would produce selection bias. Third, this finding would be of limited applicability to younger populations given the included patients with median age over 60 years old in this study. Finally, the sample size of male and female patients was significantly different, which could have influenced the conclusions.

5. Conclusions

In this study, gender was not found to have effect on outcome in AIS patients who received intravenous thrombolysis. Furthermore, we found a difference in dependent risk factors predicting outcome in male vs female patients.

Statement of ethics

This study was approved by the Institutional Review Board of General Hospital of Northern Theater Command (IRB: k2016-11).

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Data availability statement

The data underlying this article will be shared upon reasonable request to the corresponding author.

CRediT authorship contribution statement

Tong Chen: Writing – original draft, Formal analysis, Data curation. **Yu Cui:** Formal analysis, Data curation. **Hui-Sheng Chen:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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