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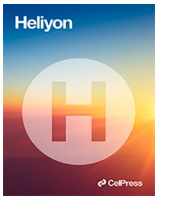

Research article

Sex differences in the correlation between white matter hyperintensity and 3-month outcome in acute stroke patients

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ABSTRACT

Background: The severity of white matter hyperintensities (WMH) has been shown to be an independent predictor of poor stroke outcome, but the effect of sex on this correlation has not been investigated further. Therefore, the purpose of our study was to assess whether there was a sex difference between the severity of WMH and poor stroke outcome.
Methods: This retrospective study included 449 patients with acute ischemic stroke (AIS) who received intravenous thrombolysis. WMH severity was graded based on the Fazekas scale. The association between WMH severity and stroke outcome was explored through multivariable regression analyses in men and women.
Results: Among women, when dividing WMH severity into tertiles, T3 (Fazekas scale >3) had a 5.334 times higher risk for unfavorable outcomes than T1 (Fazekas scale <2) (p-trend = 0.026) in the adjusted model. In addition, moderate-severe WMH (Fazekas scale 3–6) had a 3.391 (1.151–9.991) times higher risk than none-mild WMH (Fazekas scale 0–2) (p = 0.027).
Conclusions: The risk of unfavorable outcomes increased proportionally with the enlargement of the WMH severity in females, suggesting the sex-specific value of the WMH severity in optimizing the risk stratification of stroke.

1. Introduction

Sex differences in functional outcome among acute ischemic stroke (AIS) patients are a significant clinical issue that has attracted

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the attention of academics. Female patients typically experience more severe stroke and worse outcomes than male patients [1–3]. An opportunity to better manage AIS patients with tailored strategies and improve stroke outcome is presented by understanding sex differences in stroke outcome and risk variables related to these disparities.

White matter hyperintensity (WMH), an imaging manifestation of cerebral small vascular diseases, is closely linked to stroke. Previous studies have revealed that WMH lesion burden could predict functional outcome and cognitive impairment following stroke [4–6]. In addition, the structural integrity of normal appearing white matter (NAWM) and sex-specific outcomes following AIS have also been demonstrated. In the study of Mark et al. [7], women were found to have a lower likelihood of excellent prognosis after AIS. They proposed that a potential sex-specific mechanism might be indicated by the association between imaging manifestations of white matter integrity and stroke outcome of female patients. Another of his studies found that an increased NAWM K_2 coefficient, a potential surrogate of blood-brain barrier permeability, was correlated with increased infarct volume and white matter structural integrity in women, but not in men, suggesting that sex differences in white matter microvascular integrity may contribute to sex disparities in stroke outcome [8].

Intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator (r-tPA) is a crucial modality in the treatment of AIS, but it bears the risk of hemorrhage and has a poor prognosis, especially in patients with more extensive WMH [9,10]. However, to our knowledge, few studies have been conducted to explore whether there are sex differences in the severity of WMH lesions and functional outcome of AIS patients undergoing IVT. We aimed to assess sex-related disparities in WMH lesion burden and 3-month outcomes in AIS patients who had received IVT.

2. Material and method

2.1. Patients and population

Our study retrospectively enrolled 489 consecutive AIS patients admitted to our hospital from January 25, 2016 to October 30, 2021, who satisfied the following inclusion criteria: (1) age ≥18 years; (2) received r-tPA intravenous thrombolytic therapy within 4.5 h of onset; (3) without bridging therapy; and (4) with complete imaging data (including magnetic resonance imaging [MRI] of the brain). Furthermore, 40 patients were excluded due to a lack of follow-up data. Ultimately, 449 patients were included in our study (Fig. 1). This study was performed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting observational studies (**Supplement material**) [11].

2.2. Data collection and definitions

Baseline characteristics, including demographics (age, sex, BMI), stroke risk factors (cigarette smoking, alcohol intake, history of hypertension, diabetes mellitus, previous stroke, and atrial fibrillation), and stroke pathogenesis (according to the Trial of Org 10172 in Acute Stroke Treatment [TOAST]) were collected from medical records on admission. The criteria for risk factors were as follows. Hypertension was defined as blood pressure >140/90 mmHg or the diagnosis/treatment of hypertension [12]. Diabetes was diagnosed

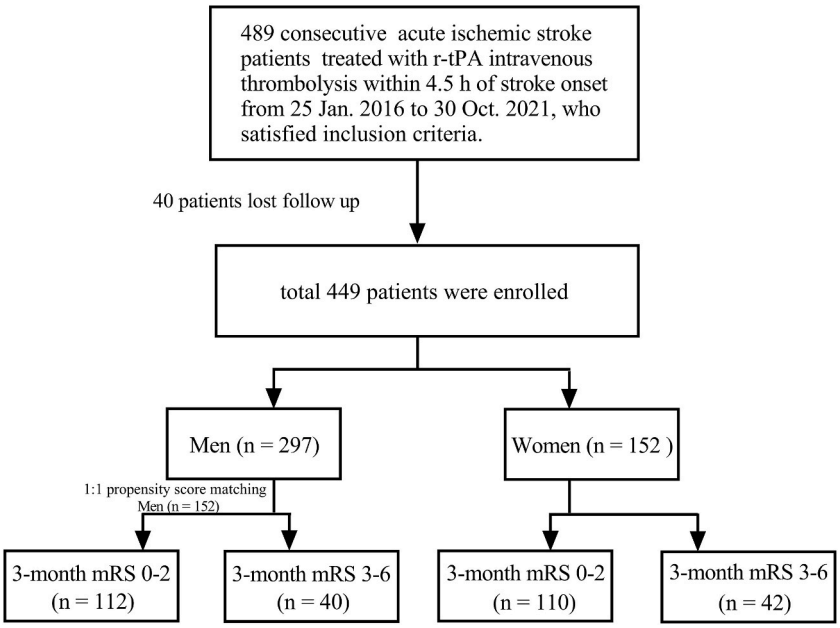

Fig. 1. Flow diagram showing the patient selection process.

as fasting plasma glucose (FPG) $\geq$ 7 mmol/L or HbA1c $\geq$ 6.5 %, and in patients who had previously been diagnosed with diabetes by professional physicians.

National Institutes of Health Stroke Scale (NIHSS) scores were collected on admission for the assessment of initial stroke severity. The 3-month modified Rankin scale (mRS) scores after stroke onset were evaluated by two trained physicians in a phone interview to assess the short-term prognosis, and patients were divided into two groups: the favorable outcomes group (mRS 0–2) and the unfavorable outcomes group (mRS 3–6) [13].

2.3. Neuroimaging Protocol

Standard MRI of the brain, including T1-weighted, T2-weighted, and diffusion weighted imaging (DWI), was obtained within 7 days after thrombolysis. MRI images of brain were acquired by a 1.5 T scanner (MagnetomAvanto, Siemens, Germany). T1-weighted was obtained with a repetition time of 520 ms, an echo time of 11 ms, a field of view of 230 × 230 mm, an image matrix of 256 × 256, a slice thickness of 5 mm with a 1.5-mm interslice gap, and a flip angle of 90°. T2-weighted was obtained with a repetition time of 4370 ms, an echo time of 97 ms, a field of view of 230 × 230 mm, an image matrix of 313.6 × 313.6, a slice thickness of 5 mm with a 1.5-mm interslice gap, and a flip angle of 150°. DWI was obtained by echo-planar imaging with a repetition time of 3000 ms, an echo time of 80 ms, a field of view of 230 × 230 mm, an image matrix of 192 × 192, a slice thickness of 5 mm with a 1.5-mm interslice gap, b values of 0 and 1000 s/mm^2, and a flip angle of 90°.

2.4. Image review and analysis

The T2-weighted images were reviewed independently by two trained neurologists, who were blind to the clinical diagnosis and any follow-up scans. The presence and severities of WMH were evaluated by the Fazekas rating scale, with periventricular WMH (PVH) and deep WMH (D-WMH) rating separately. Briefly, PVH was graded as 0 = absence, 1 = "caps" or pencil-thin lining, 2 = smooth

Table 1
Baseline characteristics stratified by sex.

	Women (n = 152)		*p* value	Men (n = 152)		*p* value
	Favorable (n = 110)	Unfavorable (n = 42)		Favorable (n = 112)	Unfavorable (n = 40)	
Demographic data						
Age (years)	68.00 (57.75–76.25)	75.00 (69.75–86.00)	<0.001	67.00 (62.00–76.00)	76.50 (70.00–82.00)	<0.001
BMI (kg/m^2)	23.12 ± 3.19	22.08 ± 3.30	0.079	23.61 ± 3.09	21.25 ± 2.42	<0.001
SBP (mmHg)	159.98 ± 23.58	169.17 ± 30.37	0.082	156.03 ± 24.76	157.15 ± 17.86	0.760
DBP (mmHg)	88.81 ± 15.32	88.57 ± 21.65	0.948	88.53 ± 15.34	84.30 ± 13.39	0.124
Stroke risk factors (n.%)						
Current Smoking (n.%)	0 (0)	0 (0)	NA	50 (44.6)	11 (27.5)	0.058
Current Drinking (n.%)	8 (7.2)	2 (4.7)	0.728	49 (43.7)	7 (17.5)	0.003
Hypertension (n.%)	71 (64.5)	27 (64.2)	0.976	70 (62.5)	28 (70.0)	0.395
Diabetes (n.%)	19 (17.2)	10 (23.8)	0.359	24 (21.4)	5 (12.5)	0.217
Prior Stroke (n.%)	14 (12.7)	11 (26.1)	0.045	13 (11.6)	6 (15.0)	0.578
Atrial fibrillation (n.%)	16 (14.5)	10 (23.8)	0.175	17 (15.1)	14 (35.0)	0.008
ODT	87.50 (56.00–127.25)	100.00 (70.75–130.75)	0.131	89.00 (61.75–137.00)	87.50 (60.75–133.00)	0.958
ONT	137.00 (101.50–192.25)	163.50 (136.75–207.25)	0.015	152.00 (119.25–196.25)	161.00 (120.75–224.75)	0.403
Stroke subtype, n (%)			0.014			0.050
LAA, n (%)	42 (38.1)	16 (38.0)		51 (45.5)	16 (40.0)	
SAO, n (%)	19 (17.2)	1 (2.3)		21 (18.7)	2 (5.0)	
CE, n (%)	31 (28.1)	21 (50.0)		28 (25.0)	18 (45.0)	
SOE/SUE, n (%)	17 (15.4)	4 (9.5)		12 (10.7)	4 (10.0)	
Evaluation of WMH lesion burden						
Fazekas Scale	2.00 (1.00–3.00)	3.00 (2.00–5.00)	<0.001	2.00 (1.00–4.00)	3.00 (2.00–5.75)	0.007
Moderate-severe WMH	30 (27.2)	24 (57.1)	0.001	41 (36.6)	23 (57.4)	0.022
Infarction lesion side			0.793			0.020
Left	50 (45.4)	22 (52.3)		46 (41.0)	20 (50.0)	
Right	41 (37.2)	16 (38.0)		53 (47.3)	12 (30.0)	
Bilateral	3 (2.7)	2 (4.7)		3 (2.6)	5 (12.5)	
Evaluation of stroke						
Any HT	15 (13.6)	15 (35.7)	0.002	10 (8.9)	12 (30.0)	0.001
ASPECTS	10.00 (9.00–10.00)	10.00 (8.00–10.00)	0.024	10.00 (10.00–10.00)	10.00 (9.00–10.00)	0.005
Admission NIHSS score	6.00 (3.00–9.00)	11.00 (8.00–17.25)	<0.001	5.00 (4.00–8.00)	10.50 (6.00–16.00)	<0.001
24-h NIHSS score	3.00 (1.00–6.00)	11.00 (7.00–16.00)	<0.001	3.00 (1.00–5.00)	10.50 (6.00–14.00)	<0.001
Prestroke mRS score	0 (0–0)	0 (0–0)	0.033	0 (0–0)	0 (0–0)	0.047
3-month mRS score	1.00 (0–1.25)	4.00 (3.00–5.25)	<0.001	1.00 (0–1.00)	4.00 (3.00–4.75)	<0.001

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ODT, onset to door time; ONT, onset to needle time; LAA, largeartery atherosclerosis; SAO, small-artery occlusion; CE, cardioembolism; SOE, stroke of other determined etiology; SUE, stroke of undetermined etiology; WMH, white matter hyperintensity; HT, hemorrhagic transformation; ASPECTS, Alberta Stroke Program Early CT Score; NIHSS, national institute of health stroke scale; mRS, modified Rankin Scale.

"halo", and 3 = irregular PVH extending into the deep white matter. Separate D-WMH were rated as follows: 0 = absence, 1 = punctate foci, 2 = beginning confluence of foci, and 3 = large confluent areas [14]. The total Fazekas score was calculated as the sum of PVH and D-WMH, ranging from 0 to 6. And on this basis, the severity of WMH was categorized as none-mild WMH (Fazekas scale score 0–2) and moderate-severe WMH (Fazekas scale score 3–6) [15].

2.5. Statistical analysis

Statistical analysis was performed via SPSS Statistics 25.0 software (SPSS Inc., Chicago, IL) and R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria). Based on sex, we divided all participants into two groups. The Kolmogorov-Smirnov test was used to assess the normality of the data. Depending on the normal and non-normal distribution of the data, continuous variables were expressed as mean with standard deviation (SD) or median with interquartile range (IQR), respectively, whereas categorical variables were described as *n* (%). For continuous variables, *t*-test or Mann-Whitney *U* test was used to evaluate differences in baseline characteristics between groups, while for categorical variables, the Pearson χ^2-test or Fisher's exact test was used. To explore the factors linked to outcome, the univariate logistic regression analysis was conducted. On this basis, the multivariable regression analyses were performed to assess the correlation between WMH lesion burden and 3-month functional outcome after adjustment for potential confounders, involving all variables with a $p < 0.05$ in univariate analysis. And to explore whether the association between WMH lesion burden and outcome changes in other subgroups, subgroup analyses were conducted.

The study was approved by the Ethics Committee of our hospital and was performed in accordance with the Declaration of Helsinki.

3. Results

3.1. Baseline characteristics of the study population

Baseline characteristics of the study population were presented in tables S1 and S2. The population was comprised of 297 (66.1 %) men and 152 (33.8 %) women. After propensity score matching, the proportion of male and female participants was consistent (both 152). The overall prevalence of unfavorable outcomes was 26.9 %. The prevalence was higher in women than in men (27.6 % vs. 26.3 %). table S3 suggested that there was no statistical difference in WMH burden between the prior stroke group and the non-prior stroke group. The characteristics of the favorable and unfavorable outcome groups were calculated for men and women, respectively (Table 1). Among the women, individuals with unfavorable outcomes were significantly older ($p < 0.001$), and had higher onset to needle time (ONT) ($p = 0.015$), higher Fazekas Scale ($p < 0.001$), greater proportion of moderate-severe WMH ($p = 0.001$), higher admission and 24-h NIHSS score ($p < 0.001$, $p < 0.001$), higher 3-month mRS score ($p < 0.001$), higher proportion of prior stroke ($p = 0.045$), and hemorrhagic transformation (HT) ($p = 0.002$). Among the men, there were similar characteristics. Furthermore, males

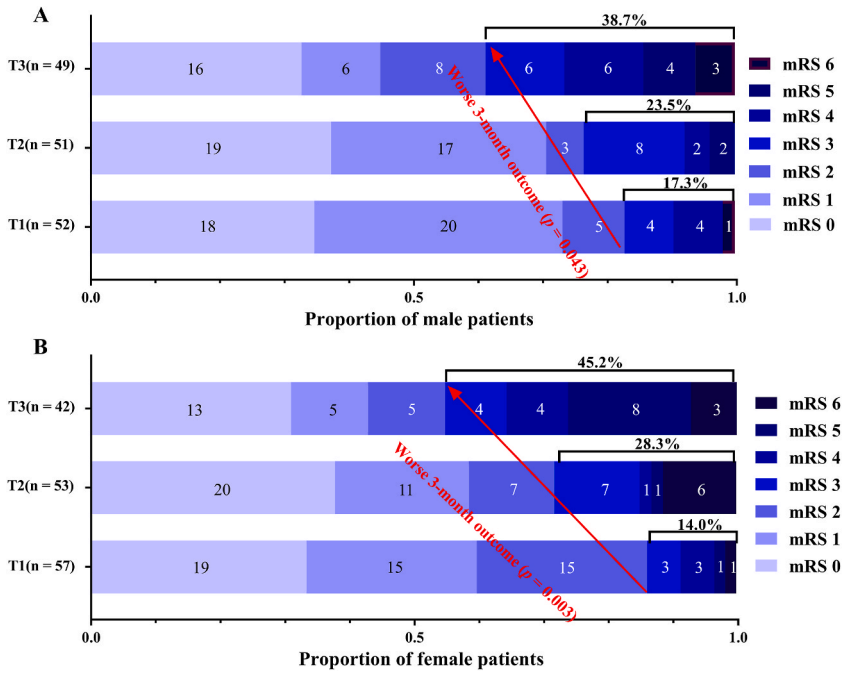

Fig. 2. Association between 3-month modified Rankin scale (mRS) and the severity of white matter hyperintensity (WMH). (A) With increasing WMH lesion burden male patients were more likely to have a higher 3-month mRS score ($p = 0.043$; χ^2-test). (B) With increasing WMH lesion burden female patients were more likely to have a higher 3-month mRS score ($p = 0.003$; χ^2-test).

with unfavorable outcomes had a higher proportion of atrial fibrillation ($p = 0.008$), lower BMI ($p < 0.001$), and lower rate of current drinking ($p = 0.003$).

3.2. Association between WMH lesion burden and stroke outcome

We divided the male patients into tertiles and did the same for the female patients. Both men and women, Fazekas scale scores were <2 on T1, 2–3 in T2, and >3 in T3. For women, the rate of unfavorable outcome in T3 (Fazekas scale >3) was higher than the other two groups (45.2 % vs. 28.3 % vs. 14.0 %, chi-squared test $p = 0.003$). In addition, there were similar results in men (38.7 % vs. 23.5 % vs. 17.3 %, chi-squared test $p = 0.043$) (Fig. 2 A, B).

The results of the univariate analysis were displayed in table S4. Among total population, factors correlated with unfavorable outcomes were older age ($p < 0.001$), lower BMI ($p < 0.001$), higher ONT ($p = 0.033$), lower rate of current drinking ($p = 0.007$), higher proportion of atrial fibrillation ($p = 0.005$), the subtypes of small-artery occlusion (SAO) ($p = 0.004$), cardioembolism (CE) ($p = 0.001$), higher Fazekas scale ($p < 0.001$), higher rate of HT ($p < 0.001$), lower ASPECTS ($p < 0.001$), higher admission NIHSS score ($p < 0.001$), and higher prestroke mRS score ($p = 0.002$).

Multivariable regression analyses were conducted to detect the relationship between WMH lesion burden and unfavorable outcomes in men and women (Table 2, Fig. 3 A-F). Among women, T3 (Fazekas scale >3) had a 4.315 times (95 % CI: 1.220–15.262) greater risk than T1 (Fazekas scale <2) in Model 1 adjusted for age and admission NIHSS. After adjusting for all variables with a $p < 0.05$ in univariate analysis, the risk was rose to 5.334 (95 % CI: 1.251–22.742) (p for trend <0.05) in Model 2. In Model 3, we adjusted variables that might affect stroke outcome but were not significant in univariate analysis, and found that the risk became 4.311 (95 % CI: 1.551–11.988) (p for trend <0.05). However, we found no significant trends across the tertiles in men. In addition, we divided WMH lesion burden into none-mild WMH (Fazekas scale score 0–2) and moderate-severe WMH (Fazekas scale score 3–6). After adjustment all potential confounders in model 2, moderate-severe WMH and continuous WMH were identified as independent factors for unfavorable outcomes in female AIS patients, respectively, but lost statistical significance in men. The results of Model 3 were also similar.

3.3. Subgroup analysis of unfavorable outcome

A subgroup analysis of unfavorable outcomes in AIS patients was shown in Fig. 4. We classified the participants as follows: median age, BMI ≥25 (overweight or obesity), current smoking, current drinking, TOAST, and disease history. Among women, subgroups based on TOAST and disease history revealed that WMH lesion burden had a considerable effect on 3-month unfavorable outcome in individuals without current smoking, drinking, disease history (such as diabetes, prior stroke and HT) or SAO. However, the relationship between elevated WMH lesion burden and a higher risk of unfavorable outcomes was not seen in the subgroups of men.

Table 2
Odds ratio (95 % CIs) of unfavorable functional outcome according to categorical and continuous Fazekas Scale.

	Categorical Fazekas Scale			*p*-trend	Categorical Fazekas Scale		*p*-value	Continuous Fazekas Scale	*p*-value
	T1	T2	T3		None-mild WMH	Moderate-severe WMH			
Women									
Model 1	Ref	1.969 (0.573–6.767)	4.315 (1.220–15.262)*	0.020	Ref	3.381 (1.283–8.905)	0.014	1.369 (1.049–1.787)	0.021
Model 2	Ref	3.212 (0.739–13.956)	5.334 (1.251–22.742)*	0.026	Ref	3.391 (1.151–9.991)	0.027	1.348 (1.005–1.810)	0.046
Model 3	Ref	2.298 (0.854–6.188)	4.311 (1.551–11.988)**	0.005	Ref	3.196 (1.461–6.993)	0.004	1.391 (1.124–1.723)	0.002
Men									
Model 1	Ref	1.391 (0.449–4.303)	1.292 (0.407–4.100)	0.694	Ref	1.112 (0.452–2.735)	0.817	1.085 (0.857–1.375)	0.496
Model 2	Ref	1.263 (0.332–4.812)	1.501 (0.378–5.962)	0.564	Ref	1.119 (0.414–3.021)	0.824	1.128 (0.858–1.483)	0.388
Model 3	Ref	1.388 (0.507–3.797)	2.493 (0.925–6.717)	0.065	Ref	2.095 (0.960–4.568)	0.063	1.262 (1.027–1.551)	0.027

*$p < 0.05$, **$p < 0.01$.
Model 1: adjusted for age and admission NIHSS score.
Model 2: further adjusted for age, BMI, current drinking, atrial fibrillation, ONT, SAO, CE, HT, ASPECT, admission NIHSS score and prestroke mRS score.
Model 3: further adjusted for SBP, DBP, ODT, hypertension and diabetes.
None-mild WMH (Fazekas score 0–2); moderate-severe WMH (Fazekas score 3–6).
Abbreviations: WMH, white matter hyperintensity; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ONT, onset to needle time; ODT, onset to door time; HT, hemorrhagic transformation; ASPECTS, Alberta Stroke Program Early CT Score; NIHSS, national institute of health stroke scale; mRS, modified Rankin Scale; SAO, small-artery occlusion; CE, cardioembolism.

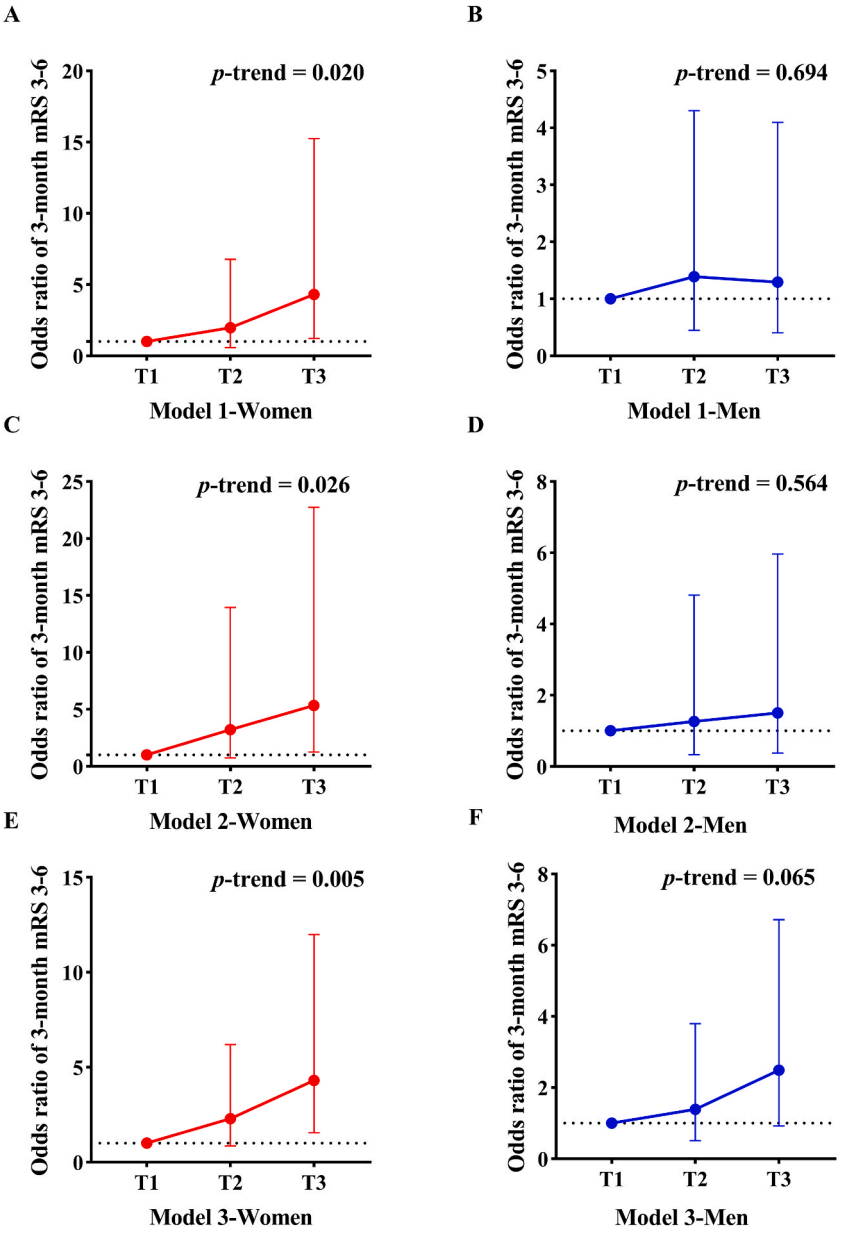

Fig. 3. Probability of unfavorable outcomes (mRS 3–6) based on white matter hyperintensity tertiles according to multivariable logistic regression analysis. (A) presents the results of Model 1-women after adjustment. (B) presents the results of Model 1-men after adjustment. (C) presents the results of Model 2-women after adjustment. (D) presents the results of Model 2-men after adjustment. (E) presents the results of Model 3-women after adjustment. (F) presents the results of Model 3-men after adjustment.

4. Discussion

Our results indicated a sex-specific correlation between WMH lesion severity and the risk of unfavorable outcomes among AIS patients undergoing IVT. These discoveries added to the mixed literature on sex differences in stroke outcome. Women with severe WMH lesions were likely to have a high risk of unfavorable outcomes. But a similar impact of WMH burden on stroke outcome was not observed among men. After adjustment for potential confounders, WMH lesion burden remained an independent predictor of unfavorable stroke outcome in female AIS patients, but lost statistical significance in men.

Our result was consistent with previous studies, which suggested that stroke outcome should be worse for women after AIS [1,2]. These findings were further supported by the multivariable regression analyses demonstrating that severe WMH lesion burden was still correlated with a higher risk of unfavorable outcomes after adjustment. And the correlation was more apparent in T3 (Fazekas scale score >3) compared to T1 (Fazekas scale score <2) and T2 (Fazekas scale score 2–3). There were similar results between the none-mild

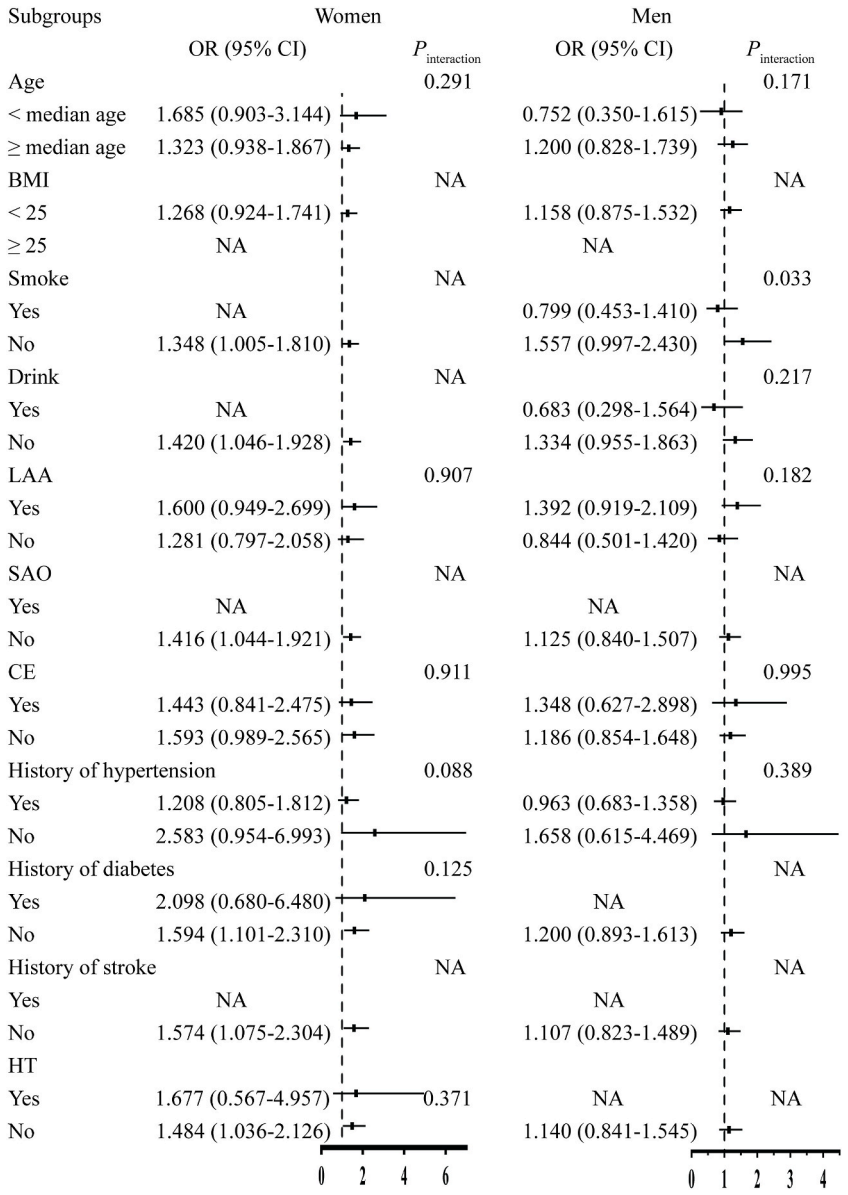

Fig. 4. Subgroup analyses for the risk of unfavorable outcomes (mRS 3–6). The model was adjusted for age, BMI, current drinking, atrial fibrillation, ONT, SAO, CE, HT, ASPECT, admission NIHSS score and prestroke mRS score. Abbreviations: BMI, body mass index; ONT, onset to needle time; SAO, small-artery occlusion; CE, cardioembolism; HT, hemorrhagic transformation; ASPECTS, Alberta Stroke Program Early CT Score; NIHSS, national institute of health stroke scale; mRS, modified Rankin Scale. NA is because there are too few samples in this subgroup to calculate.

(Fazekas scale score 0–2) and moderate-severe WMH groups (Fazekas scale score 3–6). There were several possible explanations for why WMH lesions could predict stroke outcome. (1) Patients with severe WMH lesions have poorer collateral status, due to the underlying cerebrovascular changes associated with cerebral small vessel disease (cSVD), a disease for which WMH lesions are its major radiological hallmark [16]. Moreover, among patients with severe WMH lesions, cSVD also affects small cerebral arteries and capillaries due to the loss of patency of the vascular anastomoses required for adequate collateral circulation, resulting in reduced microvascular reactivity and narrowing or even occlusion of the vascular lumen [16]. As a result, when AIS occurs, patients with severe WMH lesions will aggravate brain cell necrosis due to poor collateral status. (2) Cerebral hypoperfusion correlated with cSVD is one of the factors leading to poor outcomes in patients with severe WMH. A previous study, which performed MRI to assess WMH lesions and measure cerebral blood flow (CBF), exhibited a connection between decreased CBF values in WMH lesions and the NAWM around the lesions [17]. In addition, the study of Marstrand et al. demonstrated that both CBF and cerebrovascular reactivity (CVR) were decreased and mean transit time (MTT) was increased in areas with WMH compared with NAWM [18]. Moreover, using transcranial Doppler sonography (TCD), Tzourio et al. found that the severity of WMH was associated with decreased blood flow velocity in the

middle cerebral artery (MCA) [19]. Therefore, patients with severe WMH may be less resistant to ischemia, which promotes early infarct progression when AIS occurs.

Interestingly, significant sex differences have been reported in WMH, with women usually having higher volumes, as a proportion of the total white matter volume, and faster progression compared to men [20–23]. What is the likely explanation for this sex differences in the severity of WMH burden? Gender-associated neuroendocrine differences have been proposed as a possible explanation [24]. Previous study has suggested that the presence of estrogen might have a protective effect on silent ischemic brain damage such as WMH. Therefore, postmenopausal women who experience estrogen reduction might have increased susceptibility to ischemic brain damage. In addition, considering that both cerebral small and large vessels are exposed to systemic vascular risk factors, the characteristics of cerebral large arteries might theoretically be associated with cSVD [25]. Furthermore, as the upstream vessels of the cerebral small vessels, large arteries play a role in transporting blood flow. Therefore, the hemodynamics of small downstream vessels are altered due to structural and functional changes in large upstream arteries [26]. On the basis of these premises, it could be inferred that changes in the brain large arteries might be related to cSVD. As the main blood supply to the brain, the carotid artery is usually used to estimate the arteriosclerosis of the cerebral arteries. Previous studies have shown that carotid arteriosclerosis and compliance were related to WMH and silent brain infarcts [27–30]. Sex differences in the pathological process of atherosclerosis have been reported [31]. Men are more prone to develop atherosclerosis compared with women, while women are more likely to exhibit smaller carotid arteries and thinner arterial walls than men [32–35]. These sex differences may also be influenced by different levels of sex hormones [36]. Therefore, we concluded that differences in WMH severity and 3-month prognosis may be related to sex differences in WMH burden. In brief, the sex differences found in our study could be explained by a mix of factors, and WMH lesion burden may be a vital indicator in optimizing the risk classification of stroke outcome in women. However, further study should be carried out to verify these results.

Our study illustrated sex differences between WMH lesion burden and stroke outcome. Although previous studies have demonstrated that WMH severity could be an independent predictor of stroke prognosis, they have not further explored the effect of sex on these correlations. Sex differences are a crucial clinical issue. According to previous literature, there were sex differences in stroke risk factors, incidence, and outcome [37–39]. Therefore, a better understanding of these factors related to sex differences is essential for managing patients with tailored strategies to help them improve their prognosis.

However, there were several limitations to our study. First, the relatively small sample size of our study may lead to some inevitable statistical deviations. Second, our research was a single-center study, and whether the results were applicable to the entire population also needs further validation. Third, the association between WMH severity and stroke outcome has only been briefly discussed, but the causality of this relationship still needs to be determined through further longitudinal studies. Additionally, we were only able to clarify several factors linked to these sex differences. More research was required to determine the detailed mechanisms.

5. Conclusion

Our study reflected a potential correlation between the severity of WMH lesions and stroke outcome and demonstrated that severe WMH lesions were associated with a high risk of unfavorable outcomes in females, but not in males. These findings indicated the potential incremental value of WMH severity in optimizing risk stratification for stroke, which could provide crucial information to lessen stroke burden in females.

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Ethical approval

The study was approved by the Ethics Committee of our hospital and was performed in accordance with the Declaration of Helsinki (YJ2020034).

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

CRediT authorship contribution statement

Junli Ren: Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Xia Zhang:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Haobo Xie:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Xinbo Zhou:** Writing – review & editing, Data curation. **Jiahan Xu:** Writing – review & editing, Data curation. **Haojie Qiu:** Writing – review & editing, Data curation. **Jielin Zhou:** Writing – review & editing, Data curation. **Wei Xie:**

Writing – review & editing, Data curation. **Siqi Chen:** Writing – review & editing, Data curation. **Xin Lu:** Writing – review & editing, Data curation. **Yichuan Fan:** Writing – review & editing, Data curation. **Dehao Yang:** Writing – review & editing, Supervision, Conceptualization. **Guangyong Chen:** Writing – review & editing, Supervision, 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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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e30190.

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