Neuroimaging risk factors for participation restriction after acute ischemic stroke: 1-year follow-up study

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ABSTRACT

The aim of the present study was to determine the neuroimaging predictors of poor participation after acute ischemic stroke. A total of 443 patients who had acute ischemic stroke were assessed. At 1-year recovery, the Reintegration to Normal Living Index was used to assess participation restriction. We also assessed the Activities of Daily Living Scale and modified Rankin Scale (mRS) score. Brain MRI measurement included acute infarcts and pre-existing abnormalities such as enlarged perivascular spaces, white matter lesions, ventricular-brain ratio, and medial temporal lobe atrophy (MTLA). The study included 324 men (73.1%) and 119 women (26.9%). In the univariate analysis, patients with poor participation after 1 year were older, more likely to be men, had higher National Institutes of Health Stroke Scale (NIHSS) score on admission, with more histories of hypertension and atrial fibrillation, larger infarct volume, more severely enlarged perivascular spaces and MTLA, and more severe periventricular hyperintensities and deep white matter hyperintensities. Patients with participation restriction also had poor activities of daily living (ADL) and mRS score. Multiple logistic regression showed that, in model 1, age, male gender, NIHSS score on admission, and ADL on follow-up were significant predictors of poor participation, accounting for 60.2% of the variance. In model 2, which included both clinical and MRI variables, male gender, NIHSS score on admission, ADL on follow-up, and MTLA were significant predictors of poor participation, accounting for 61.2% of the variance. Participation restriction was common after acute ischemic stroke despite good mRS score. Male gender, stroke severity, severity of ADL on follow-up, and MTLA may be predictors of poor participation.
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INTRODUCTION

The lifetime risk of stroke in the Chinese population is the highest in the world (approximately 39.3%).[1] According to the International Classification of Functioning, Disability and Health, the consequences of a disease can be categorized into three different dimensions: body function impairments, activity limitations, and participation restrictions. Participation can be defined

SIGNIFICANCE OF THIS STUDY

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT?
⇒ Stroke survivors often experience participation restriction in the chronic phase.
⇒ Several factors contribute to participation restriction after stroke, including cognitive impairment, emotional deficits, stroke severity, functional dependency, and older age.
⇒ The relationship between clinical neuroimaging factors and poor participation in patients who had acute ischemic stroke has rarely been studied.

WHAT ARE THE NEW FINDINGS?
⇒ The present study determined the relationship between neuroimaging factors and participation restriction after acute ischemic stroke.
⇒ Participation restriction was common in patients who had stroke despite having good modified Rankin Scale score.
⇒ Male gender, stroke severity, medial temporal lobe atrophy, and severity of activities of daily living on follow-up were important predictors of poor participation at 1 year after the index stroke.

### HOW MIGHT THESE RESULTS CHANGE THE FOCUS OF RESEARCH OR CLINICAL PRACTICE?
⇒ The advantage of our study was that the relationship between participation and comprehensive MRI variables, which included acute infarct and pre-existing brain abnormalities, was assessed.
⇒ Given the very few studies examining the relationship between clinical neuroimaging factors and poor participation, our findings provide important new knowledge on participation restriction after ischemic stroke.

as 'the person's involvement in a life situation' and includes daily activities and social roles.[2] Stroke survivors often experience participation
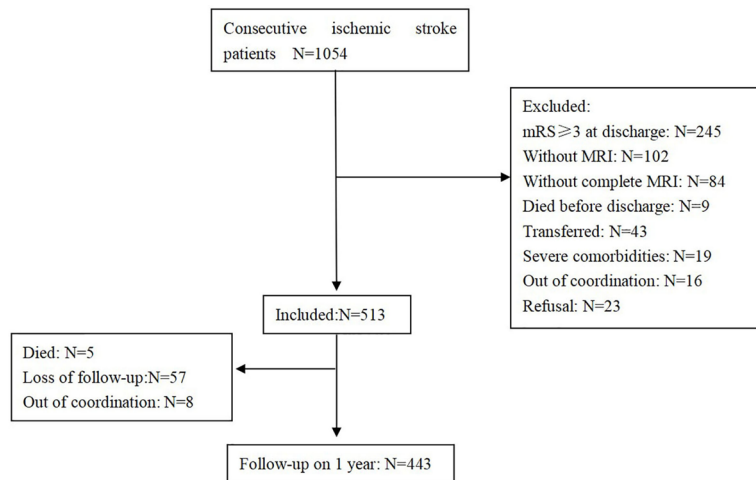
Figure 1 Flow chart of participants. mRS, modified Rankin Scale.

restrictions in the chronic phase, despite having favorable basic activities of daily living (ADL).[3] A Swedish cohort study found that a patient who had a stroke who experienced participation restriction did not want to do everyday occupations,[4] while a Netherlandish study further found that decline in participation might induce incomplete social activities even at 3 years poststroke.[5] Social participation, equally important to cognition, was a strong determinant of quality of life among older adults who had a stroke.[6]

Several factors, including cognitive impairment,[7] emotional deficits,[8] stroke severity,[9] functional dependency,[10] and older age,[11] might contribute to participation restrictions after stroke. However, previous studies largely focused on the relationship of demographic clinical factors with participation restriction. By contrast, the relationship between MRI variables in acute ischemic stroke and participation restriction remains unclear. Thus, the aim of the present study was to determine the relationship between neuroimaging factors assessed by MRI and participation restriction.

MATERIALS AND METHODS
The study was registered at http://www.chictr.org.cn/index.aspx. Valid written consent was obtained from all participants.

Participants and setting
Patients who had acute ischemic stroke admitted to Division I, Department of Neurology, Dongguan People's Hospital from January 1, 2017 to December 30, 2018 were screened. The inclusion criteria were as follows: (1) age >18 years; (2) first or recurrent acute ischemic stroke confirmed by MRI[12] and admitted within 7 days after onset; (3) had complete brain MRI examination; and (4) modified Rankin Scale (mRS) score <3 points at discharge. The exclusion criteria were as follows: (1) transient ischemic attack or hemorrhagic stroke; (2) incomplete or no brain MRI data; (3) mRS score ≥3 points at discharge, including death (mRS=6); (4) patients with severe comorbidities (eg, malignant tumor, etc); (5) patients who were unable to complete the assessment at discharge or follow-up due to severe hearing disabilities, visual disabilities, language

disorders, or cognitive impairment; and (6) patients who refused to provide signed consent.

Demographic data collection
Information on demographic and clinical variables included age, sex, history of stroke, and vascular risk factors. Severity of stroke was assessed with the National Institutes of Health Stroke Scale (NIHSS).[13] Subtype of ischemic stroke was judged according to the Trial of Org 10172 in Acute Stroke Treatment subtype system.[14]

Follow-up of patients
All assessments at follow-up were completed by the patients. Participation restriction was measured by the Chinese version of the Reintegration to Normal Living Index (RNLI).[15] The Chinese version of the RNLI was translated from the RNLI and is an easy-to-understand version with simple words and structures, which ensure patients can finish it, even for those with little or no education.[16] The RNLI is a self-report questionnaire used to quantitatively assess reintegration to normal functioning after stroke.[17] We assessed participation status at 1 year after the index stroke with a good mRS score at discharge. The components of RNLI include 11 questions measuring the different levels of ability for mobility, self-care ability, daily activities, recreational activities, general coping skills, family roles, social activities, personal relationships, and presentation of self to others.[16] Each item is scored from 1 (minimal reintegration) to 10 (complete reintegration). The total score ranges from 11 to 110. A lower RNLI score indicates more severe participation restriction in normal living. We defined poor participation as a score <P25 of the IQR of the RNLI.

We also assessed functional status and disability at 1 year according to the Lawton Activities of Daily Living Scale[18] and mRS.

Neuroimaging data
Neuroimaging data were generated by an MRI examination. All patients were scanned on a 3.0 T system (Sonata; Siemens Medical, Erlangen, Germany)[19] within 7 days after admission. The following sequences were included:

Table 1 Demographic and clinical characteristics of the study patients

Characteristics	N=443
Age (years)*	59.61 (11.59)
Male†	324 (73.1)
NIHSS score on admission‡	2 (1–3)
Time of onset to admission*	23.2 (31.3)
Hypertension†	324 (73.1)
Diabetes mellitus†	132 (29.8)
Atrial fibrillation†	26 (5.9)
Previous stroke†	33 (7.5)
Intravenous thrombolysis†	23 (5.2)
Stroke subtype†	
Large artery	138 (31.2)
Small artery	198 (44.7)
Cardioembolism	25 (5.6)
Other etiologies	10 (2.3)
Unknown etiologies	72 (16.3)
Location of infarcts	
Cortical region†	172 (38.8)
Subcortical region†	302 (68.2)
Infratentorial region†	87 (19.6)
Infarct volume‡	1.1 (0.5–3.4)
BG-EPVS‡	1 (0–2)
CS-EPVS‡	1 (1–2)
PVH‡	1 (0–2)
DWMH‡	1 (0–1)
VBR*	20.3 (5.9)
MTLA‡	0 (0–2)
RNLI score on follow-up‡	103 (98–106)
ADL on follow-up‡	14 (14–15)
mRS score on follow up‡	1 (0–1)

*Mean (SD).
†n (%).
‡Median (IQR).
ADL, activities of daily living; BG-EPVS, enlarged perivascular spaces in the basal ganglia; CS-EPVS, enlarged perivascular spaces in the centrum semiovale; DWMH, deep white matter hyperintensities; mRS, modified Rankin Scale; MTLA, medial temporal lobe atrophy; NIHSS, National Institutes of Health Stroke Scale; PVH, periventricular hyperintensities; RNLI, Reintegration to Normal Living Index; VBR, ventricular-brain ratio.

T1-weighted imaging, T2-weighted imaging, and diffusion-weighted imaging. A neurologist (H-HZ) who was blinded to patients' clinical information reviewed the MRI data. We assessed both the acute infarcts and pre-existing abnormalities, which included enlarged perivascular spaces (EPVS), white matter lesions (WMLs), global brain atrophy, and medial temporal lobe atrophy (MTLA).[19]

Statistical analysis
Statistical analyses were performed using SPSS for Windows (V.24.00). Descriptive data are presented as proportion, mean, or median, as appropriate. A univariate analysis comparing the putative risk factors between patients with poor and favorable participation was performed. Variables with p<0.05 in the univariate analysis were included in further binary multivariate logistic regressions. The significance level was set at p<0.05 (two-sided).

RESULTS
One thousand and fifty-four patients were admitted during the study. Patient selection is described in the flow chart (figure 1). Finally, 443 patients were included in the final analysis. Intrarater reliability (kappa) tests were performed on 10 patients who had a stroke by the same MRI rater. The intrarater agreement for the MRI measurements was good to excellent: volume of infarction intraclass coefficient (ICC) =0.88, EPVS=0.81, WML=0.83, ventricular-brain ratio ICC=0.85, and MTLA=0.86.

There were no differences in gender between the excluded and included patients (men, 72.7% vs 69.1%, respectively; p=0.201), while there were significant differences in age (59.61±11.84 years vs 62.59±14.3 years, respectively; p<0.001) and NIHSS score on admission (2 (1–3) vs 4 (2–10), respectively; p<0.001).

The study sample consisted of 324 men (73.1%) and 119 women (26.9%), with a mean age of 59.61 years (range 26–88). The median NIHSS score at the time of first screening was 2 (range 0–17). The median RNLI score on follow-up was 103, ranging from 11 to 110 (table 1).

Univariate analysis of poor participation
In the univariate analysis, patients with poor participation at 1 year were older, more likely to be men, with higher NIHSS score at admission, and with more histories of hypertension and atrial fibrillation. Further, these patients had a significant larger infarct volume, more severe EPVS and MTLA, and more severe periventricular hyperintensities (PVH) and deep white matter hyperintensities (DWMH). Patients with participation restriction also had poor ADL and mRS score (table 2).

Multiple regressions for poor participation
We conducted two multiple stepwise regression models and the results are presented in table 3. In model 1, after using poor participation as the dependent variable, age, sex, NIHSS score on admission, hypertension, atrial fibrillation, stroke subtype, and ADL at follow-up were entered into the model. mRS score on follow-up was not included because it was significantly correlated with ADL (r=0.725). Age, male gender, NIHSS score on admission, and ADL at follow-up were significant predictors of poor participation at 1 year, accounting for 60.2% of the variance.

Model 2 included both the clinical and neuroimaging variables. PVH and EPVS in the centrum semiovale were not included in the model as they were highly correlated with DWMH score (r=0.695) and EPVS in the basal ganglia (r=0.608), respectively. The results showed male gender, NIHSS score at admission, ADL at follow-up, and MTLA were significant predictors of poor participation at 1 year, accounting for 61.2% of the variance. We further analyzed the interaction of age with MTLA; the OR and 95% CI of the interaction analysis of age and MTLA was 0.996 (0.981 to 1.059), showing that it was not a significant predictor of poor participation.

DISCUSSION
As well as reduced functional outcomes and physical disability, stroke affects multiple other levels of function. In this prospective observational study, we found that many

Table 2 Risk factors for poor participation at 1-year follow-up in the univariate analysis

	Poor participation n=106	Favorable participation n=337	t/z/χ^2	P value
Age (years)*	65.56 (10.95)	57.74 (11.17)	−6.313	<0.001
Male†	68 (64.2)	256 (76)	5.728	0.017
NIHSS score on admission‡	3 (2–4)	2 (1–3)	−3.418	0.001
Time of onset to admission*	26.5 (34.5)	22.2 (30.2)	−1.223	0.222
Hypertension†	87 (82.1)	237 (70.3)	5.666	0.017
Diabetes mellitus†	39 (36.8)	93 (27.6)	3.26	0.071
Atrial fibrillation†	12 (11.3)	14 (4.2)	7.496	0.006
Previous stroke†	12 (11.3)	21 (6.3)	2.999	0.083
Intravenous thrombolysis†	7 (6.6)	16 (4.7)	0.564	0.453
Stroke subtype†			18.79	0.001
Large artery	44 (41.5)	94 (27.9)		
Small artery	37 (34.9)	161 (47.8)		
Cardioembolism	12 (11.3)	13 (3.9)		
Other etiologies	2 (1.9)	8 (2.4)		
Unknown etiologies	11 (10.4)	61 (18.1)		
Location of infarcts				
Cortical region†	46 (43.4)	126 (37.4)	1.225	0.268
Subcortical region†	73 (68.9)	229 (68.2)	0.019	0.891
Infratentorial region†	21 (19.8)	66 (19.6)	0.001	0.97
Infarct volume‡	2.17 (0.64–6.07)	0.98 (0.4–3.04)	−3.287	0.001
BG-EPVS‡	1 (1–2)	1 (0–2)	−2.436	0.015
CS-EPVS‡	1 (1–2)	1 (1–2)	−1.998	0.046
PVH‡	1 (1–2)	1 (0–2)	−2.729	0.006
DWMH‡	1 (0–2)	1 (0–1)	−3.287	0.001
VBR*	20.7 (4.1)	20.2 (6.4)	−0.691	0.49
MTLA‡	1 (0–3)	0 (0–1)	−4.595	<0.001
ADL on follow-up‡	18 (15–29.5)	14 (14–14)	−14.699	<0.001
mRS score on follow-up‡	2 (1–3)	0 (0–1)	−10.94	<0.001

*Mean (SD), t-test.
†n (%), χ^2 test.
‡Median (Qu–QL), Mann-Whitney U test.
ADL, activities of daily living; BG-EPVS, enlarged perivascular spaces in the basal ganglia; CS-EPVS, enlarged perivascular spaces in the centrum semiovale; DWMH, deep white matter hyperintensities; mRS, modified Rankin Scale; MTLA, medial temporal lobe atrophy; NIHSS, National Institutes of Health Stroke Scale; PVH, periventricular hyperintensities; VBR, ventricular-brain ratio.

patients who had a stroke were unable to socially reintegrate, despite having a good mRS score. Further, male gender, stroke severity, MTLA, and severity of ADL were important predictors of poor participation at 1 year after the index stroke. Given the very few studies examining the relationship between clinical neuroimaging factors and poor participation, these data provide important new knowledge on participation restriction after ischemic stroke.

The effect of sex on social participation is controversial. Our findings suggest that men show a greater propensity for participation restriction poststroke than women. In support, women were reported to have a higher subjective well-being than men after stroke.[20] Further, non-white men were shown to have lower participation after stroke.[21] Thus, discussions on the roles of men at home and the difficulties that they may encounter in maintaining these roles after discharge should be considered as an important factor in the part of male groups.

Our data suggest that stroke severity at admission is an important risk factor for participation restriction poststroke, as previously reported.[9 22] However, those studies recruited

patients with a wide range of stroke-related disabilities, resulting in a heterogeneous study sample. By contrast, our study included a more homogenous population of patients who had a stroke with mild, residual disabilities. We found that the more severe the neurological deficits, the worse the participation, despite a favorable recovery. Thus, although patients may recover in terms of physical disability, they may also experience dysfunction in reintegration to normal living.

Comparing with global atrophy, MTLA may be a significant predictor of poor participation in the present study. A previous study showed that the medial temporal lobe, but not global atrophy, is a region that is more susceptible to ischemia and may predict cognitive decline in stroke survivors.[23] We suggest that cognitive impairment may be an important mediator between MTLA and participation restriction.

The present study found that poorer ADL correlated with poor participation to normal life. In a comprehensive study by Mayo et al[24], restriction in ADL was a risk for social isolation, with a further negative implication on patients' health. Complete ADL requires not only dependent basal

Table 3 Multivariate logistic regression of risk factors for poor participation

Variables	β	OR (95% CI)	P value	R^2
Model 1 (without MRI variables)				0.602
Age (years)	0.31	1.031 (1.002 to 1.062)	0.038	
Male	0.745	2.105 (1.078 to 4.112)	0.029	
NIHSS score on admission	0.184	1.202 (1.053 to 1.372)	0.006	
Hypertension	0.198	1.219 (0.562 to 5.825)	0.362	
Atrial fibrillation	0.538	1.713 (0.516 to 5.689)	0.38	
Stroke subtype	−0.162	0.85 (0.661 to 1.093)	0.205	
ADL on follow-up	0.962	2.617 (1.933 to 3.543)	<0.001	
Model 2 (with MRI variables)				0.612
Age	0.016	1.016 (0.985 to 1.049)	0.311	
Male	0.831	2.296 (1.158 to 4.553)	0.017	
NIHSS score on admission	0.184	1.202 (1.056 to 1.369)	0.005	
Hypertension	0.181	1.199 (0.55 to 2.613)	0.649	
Atrial fibrillation	0.492	1.635 (0.477 to 5.608)	0.434	
Stroke subtype	−0.156	0.855 (0.666 to 1.098)	0.22	
Infarct volume	<0.001	1 (0.997 to 1.003)	0.912	
BG-EPVS	0.008	1.008 (0.727 to 1.396)	0.963	
DWMH	0.032	1.033 (0.683 to 1.561)	0.878	
MTLA	0.235	1.265 (1.069 to 1.497)	0.006	
ADL on follow-up	1.001	2.721 (2.018 to 3.671)	<0.001	
MTLA by age	−0.004	0.996 (0.981 to 1.059)	0.577	

ADL, activities of daily living; BG-EPVS, enlarged perivascular spaces in the basal ganglia; DWMH, deep white matter hyperintensities; MTLA, medial temporal lobe atrophy; NIHSS, National Institutes of Health Stroke Scale.

ADL, but also memory function and satisfactory executive function.[25] Impairment in ADL may induce multiple aspects of dysfunction, including memory and executive function, which mediate participation restriction.

Surprisingly, after adjusted MTLA, our study found a conflicting result compared with previous studies, which have reported an increased risk associated with older age.[26 27] Our contrasting findings may relate to the strong relationship between age and MTLA. In model 1, older age was an independent risk factor for poor participation, while in model 2, which included both the clinical and neuroimaging variables, age was not significantly correlated with poor participation. The OR and 95% CI of the interaction analysis of age and MTLA was 0.996 (0.981 to 1.059), which suggested that the association of age and participation restriction reported in other studies may be partly caused by more severe cerebral degeneration. Thus, our data suggest that cerebral atrophy should be considered when studying participation in stroke.

There were several advantages to our study. First, all patients had mild ischemic stroke. In addition, we assessed both acute infarct and comprehensive pre-existing brain abnormalities. There were also some limitations to our study. First, we did not evaluate the cognitive status of our patients at admission or follow-up, which may be correlated with participation restriction. Second, one of the major inclusion criteria is that patients should have complete MRI data. Of the 1054 consecutive patients, 186 were excluded due to lack of MRI or incomplete MRI data. Additionally, our finding is limited to those who had mild-moderate ischemic stroke, who could cooperate to finish the MRI. Third, there were 33 patients who had previous stroke included in the study. We did not assess their prestroke mRS score. However, we had excluded those with significant disability at discharge (mRS ≧3 points), implicating those with

apparent disability before the index stroke were not included in this study.

In conclusion, we found that participation restriction was common after the index mild ischemic stroke. Male gender, stroke severity, MTLA, and severity of ADL may be predictors of poor participation.

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