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Research Article

Recent Minor Ischemic Stroke with an NIHSS Score of 0 in Neurologic Outpatients: Prevalence, Risk Factors and Outcome

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Abstract

Background: Recent minor ischemic stroke (MIS) with a National Institutes of Health Stroke Scale (NIHSS) score of 0 was previously unstudied. Our aim was to identify the prevalence, outcomes of, and risk factors for recent MIS with an NIHSS score of 0.

Methods: A prospective cohort of neurologic outpatients treated from 2012-2016 was selected for study. We diagnosed patients with recent MIS using magnetic resonance imaging (MRI) and categorized them based on whether they had NIHSS scores of 0 or 1-3.

Results: Among 3209 patients with minor brain events, 42.8% (1372/3209) had recent MIS verified by MRI. While, 34.3% (1102/3209) had recent MIS with an NIHSS scores of 0, and 8.4% had an NIHSS scores of 1-3. Middle age (Odds ratio [OR], 1.10; 95% confidence interval [CI], 1.05-1.18), nonfocal neurologic symptoms (OR, 0.51; 95% CI, 0.30- 0.67), and increased systolic blood pressure (OR, 1.04; 95% CI, 1.02-1.17) were significantly associated with recent MIS with an NIHSS score of 0. During the 3-month follow-up, recent MIS with an NIHSS score of 0 had more favorable outcomes compared with those with an NIHSS score of 1-3 (Rankin Scale score 0 to 2, 99.6% vs. 71.3%, p< 0.001), but the recurrence events was 22.3% in recent MIS with an NIHSS score of 0 and 28.3% in recent MIS with an NIHSS score of 1-3 (p=0.043).

Conclusions: The disability rate of MIS with an NIHSS score of 0 is very low, but its high prevalent rate and high recurrence events seriously threatens the health of middle-aged.

Keywords: Minor ischemic stroke; Prevalence; risk factors; Outcomes; Magnetic resonance imaging

Introduction

Since the second half of the twentieth century, the clinicopathologic features of minor ischemic stroke (MIS) have been described in the medical literature [1]. A previous study reported that lacunar infarcts and partial anterior circulation stroke are attributable to MIS [2], but most recent studies have considered small infarcts or small lacunes associated with minor symptoms in patients with very low baseline National Institutes of Health Stroke Scale (NIHSS) scores (≤3) to be mainly ascribed to MIS [3-7]. Deep brain gray and white matter is typically involved, as well as white matter near the cortex. Moreover, MIS is not limited to traditional lacunar infarcts; other stroke subtypes can also be attributed to MIS, including arteriothrombotic, cardioembolic, and non-small vessel disease (non-SVD) due to other etiology [2,5]. Unfortunately, some MIS patients are hospitalized and have a worse prognosis [3,6-9] due to atheromatous stenosis or acute occlusion of larger arteries, such as the basilar or middle cerebral artery. However, the face validity of NIHSS scores of 0-3 in the investigations of patients with recent MIS with an NIHSS score of 0 is not well known. We hypothesized that at the first-ever visit, the presence of symptoms accounting for an NIHSS score of 0 would indicate a health-threatening MIS due to its high prevalent rate and high recurrence events. We tested these hypotheses by conducting a study of neurologic outpatient admissions in Northern China over the past 4 years. The aim of this study was to investigate the prevalence, outcomes of, and risk factors for MIS in patients with an NIHSS score of 0.

Methods

Study population

A prospective cohort of consecutive patients was selected for the study between January 2012 and January 2016. All patients were registered neurologic outpatients (including stroke and nonstroke patients) treated at a tertiary teaching hospital; thus, the sample consisted of males and females aged >25 years or older residing in 38 villages or towns and one urban population in Shuyang, Northern China. The inclusion criteria for recent MIS were defined as follows [3,4,7]: (1) First-ever visit indicating recent mild brain symptoms, no positive signs or only minor positive signs, measured as a score of 0-3 on the NIHSS at the time of the initial visit; (2) Magnetic resonance imaging (MRI) study with evidence of recent MIS. We excluded patients with a previous history of stroke, transient ischemic attack (TIA), or peripheral vertigo and patients with ischemic stroke with

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NIHSS scores >3. The study was approved by the ethical committee on clinical research of the Affiliated Shuyang Hospital of Xuzhou Medical University. Because the study involved only a review of records obtained as a part of routine medical care, did not require all patients to write the information consent.

Image analysis

All patients underwent MRI of the brain within 6 hours of the first visit. MRI was performed with 1.5-T equipment (Siemens), including diffusion-weighted imaging (DWI) or fluid-attenuated inversion recovery (FLAIR) images, T2- and T1-weighted images. For the purposes of this study, the radiographic inclusion criteria for recent MIS were defined as follows: DWI increased signal, reduced signal on apparent diffusion coefficient map (ADC), and as an acute small infarction or lacunar lesion (usually ≤20mm in diameter) located in cerebral cortex, subcortical white matter, basal ganglia, thalamus, brainstem, or cerebellum [10,11].

All MRI studies were reviewed by a neuroradiologist and a neurologist who were blinded to the study. The examiners looked specifically for lesions on DWI, FLAIR/T2, and ADC maps and measured the maximum diameters (in mm). The maximum diameters of the lesions, number of lesions and lesion location on DWI and FLAIR were recorded in detail for each patient.

Clinical assessment

The NIHSS was used to assess the severity of stroke. The NIHSS scores were calculated for all MIS patients and were measured within 1 hour of the time of the initial neurologic outpatient visit. According to the findings of the initial NIHSS score, the study population was divided into two groups: MIS with an NIHSS score of 0 and with NIHSS scores of 1-3.

The following risk factors and symptoms were recorded by an experienced neurologist: gender, age, body mass index (BMI), history of hypertension, diabetes mellitus, or heart disease, alcohol use, smoking, systolic blood pressure (SBP), diastolic blood pressure, headache/migraine, dizziness/vertigo, dizziness with headache, numbness or sensory abnormality, and weakness or motor hemiparesis. The periodic duration of symptoms in all patients was also recorded.

For outcome analyses, the modified Rankin Scale (mRS) scores at 90 days of follow-up were assessed (scores range from 0 to 6; no symptoms=0, slight symptoms=1, restriction=2, slight disability=3, moderate disability=4, severe disability=4-5, death=6). All patients with recurrence events in the first 90 days after initial event were assessed by a neurological specialist. The recurrence events included TIA-like symptoms, nonfocal neurological symptoms, and recurrence stroke. The follow-up information was gathered by a neurological specialist who conducted inquiries by phone (90 days after the initial visit).

Related definitions

A minor brain symptom was defined as a neurological symptom without distinct disability. We define an NIHSS score of 0 according to a total score on NIHSS equal to 0, including from onset to initial visit no focal symptoms and signs rather than asymptomatic MIS. Asymptomatic MIS was defined as a small stroke with high intensity on T2-weighted images without clinical symptoms, which included nonfocal symptoms and focal symptoms.

In the present study, we defined a TIA as an episode of <24 hours of neurologic dysfunction caused by focal brain, spinal cord, or retinal ischemia without new infarction.

We identified these nonlocal neurological symptoms based on the National Institute of Neurological Disorders and Stroke (NINDS) criteria and related documents [12,13]. Transient symptoms with infarction (TSI) indicated transient symptoms associated with abnormal lesions on DWI [14]. Transient nonfocal neurological symptoms indicated an attack with temporary (<24 hours) nonfocal neurological symptoms including TIA-like symptoms or TSI.

Nonfocal neurological symptoms could be attributed to a recent MIS and were based on the following medical documents: dizziness or vertigo is associated with an increased risk of developing vascular events [15]; dizziness is a posterior circulation symptom but is also an anterior circulation symptom [12,14,16] that can be attributed to central causes. Migraine/headache is a common symptom and risk factor for cerebrovascular disease [17]. Other nonfocal neurological syndromes, such as numbness or tingling, slurred speech, dysarthria, and confusion, as well as common focal neurological syndromes, such as motor hemiparesis and hemidysesthesia, were also included in this study.

Statistical analysis

Numeric variables were expressed as the mean ± standard deviation (SD) or median (interquartile range [IQR]). Continuous variables were compared using the t-test. Fisher's exact test and Mann-Whitney U test were used to explore the relationship among baseline patient variables. Multivariate-adjusted Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated with the use of a logistic regression model if they were significant in the univariate analysis. The disability rate in the first 90 days was also compared between groups. Statistical calculations were performed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA), with the level of significance set at $P<0.005$.

Results

Patient population

A total of 3209 patients who presented for an initial visit due to minor brain symptoms were admitted to our neurologic outpatient department between January 1, 2012, and January 1, 2016. We excluded 1015 patients with a final diagnosis of TIA, 410 patients with primary migraine without infarction, 307 patients with peripheral vertigo, 42 patients with cervical vertebral disease, 32 patients with other brain episodes, and 31 patients with infarction and initial NIHSS scores >3. Ultimately, 1372 (42.8%) patients satisfied the inclusion criteria for this validation cohort study. Among them, we diagnosed 1102 (34.3%, 1102/3209) patients with recent MIS with an NIHSS score of 0 events and 270 (8.4%, 270/3209) patients with recent MIS with NIHSS scores of 1-3 events. 70% of MIS patients who had an NIHSS of 0 were received alone antiplatelet treatment at home, rest 30% of these patients with more frequent symptoms were admitted to stroke ward. Yet, most of MIS patients who had an NIHSS of 1-3 were admitted to stroke ward, but no patients received

Table 1: Baseline characteristics of neurologic outpatients with MIS (n=1372).

Characteristic	Value
Age, (years, mean ±SD)	60.7 ±11.3
Female sex, n(%)	716(51.7)
MRI findings	
Median time of onset to MRI (days, range)	7(0.16-19.8)
Median number of lesions (range)	2(1—13)
Median size of ischemic lesion (mm, range)	5.0(0.3-20.0)
Multiple infarction (%)	982(71.6)
Brain atrophy (%)	22(1.6)
Leukoaraiosis (%)	91(6.6)
Location of MIS	
ACA	761(55.5)
PCA	169(12.3)
ACA+PCA	442(32.2)
MIS with an NIHSS score of 0, n (%)	1102(80.3)
MIS with an NIHSS score of 1-3, n (%)	270(19.7)
1 score	219(16.0)
2 score	38(2.8)
3 score	13(0.9)

MIS: Minor Ischemic Stroke; ACA: Anterior Circulation Artery; PCA: Posterior Circulation Artery.

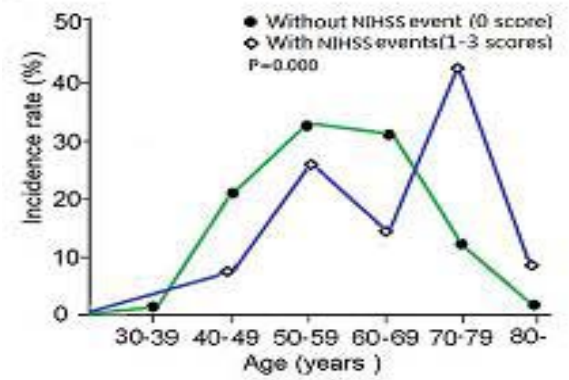

Figure 1: The incidence peaked in the age group of patients who were 40-59 years and had NIHSS scores of 0, while the incidence peaked in the group of patients with NIHSS scores of 1-3 in the subgroup of patients aged 70-79 years.

intravenous thrombolysis because this hospital did not implement thrombolytic treatment at that time.

The baseline characteristics of neurologic outpatients with recent MIS are shown in Table 1. The median time from symptom onset to assessment, NIHSS score and MRI was 5 days (range: 0.16-19.8 days). The mean age was 60.7 ±11.3 years. Furthermore, the prevalence of recent MIS increased with younger age, and there were differences among patients with an NIHSS score of 0 compared with those with NIHSS scores of 1-3 ($p<0.001$). The prevalence peaked in the age group of patients who were 40-59 years and had NIHSS scores of 0, while the incidence peaked in the group of patients with NIHSS scores of 1-3 in the subgroup of patients aged 70-79 years (Figure 1).

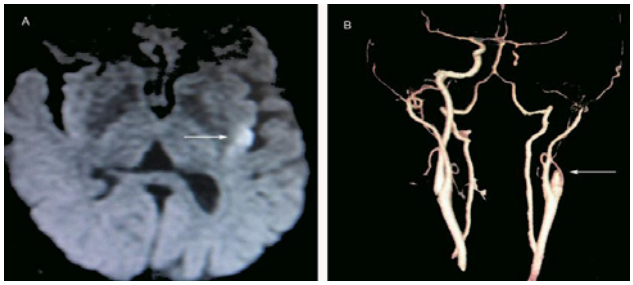

Figure 2: A 55-year-old male with acute vertigo for 2 hours, NIHSS score=0, and recent small infarct (0.5mm) in the left insula (A, arrow) on the head MRI-DWI and CT vascular imaging display in the beginning of the left internal carotid artery stenosis (B, arrows).

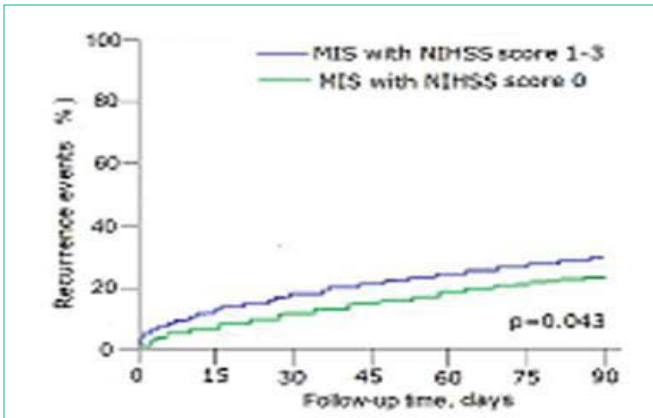

Figure 3: Recurrences events during the first 90 days of follow-up after initial visit for patients with an NIHSS score of 0 or with an NIHSS score of 1-3 (22.3% vs. 28.3%, P = 0.043).

Results of the validity analysis in patients with recent MIS in both subgroups of NIHSS score events

The symptoms of patients with recent MIS with or without NIHSS score events are shown in Supplementary Table 1. The common clinical symptoms of recent MIS in neurologic outpatients were nonfocal neurologic symptoms, such as dizziness/vertigo, dizziness with headache, and headache/ migraine. Among patients with nonfocal neurologic symptoms, more than 70% of patients had transient nonfocal symptoms. The Figure 2 shows a 55-year-old male due to acute vertigo for 2 hours (NIHSS score of 0) with recent MIS lesion (0.5mm in diameter) on DWI and with left internal carotid proximal occlusion.

Univariate analysis indicated that middle age, median time of symptom onset to MRI, increased SBP, impaired fasting glucose, nonfocal neurologic symptoms, and numbness, were more frequent in patients with an NIHSS score of 0 than in patients with NIHSS scores of 1-3 (Table 2). However, only nonfocal neurologic symptoms (OR, 0.51; 95% CI, 0.30- 0.67), middle age (OR, 1.10; 95% CI, 1.05- 1.18), and increased SBP (OR, 1.04; 95% CI, 1.02-1.17) were established by logistic regression as independent risk factors for recent MIS with an NIHSS score of 0 (Table 3).

Outcome analysis

During the 90-day follow-up after the initial visit, survival data were available for our patients with recent MIS (1.3% lost to follow-

Table 2: Characteristics of risk factors and symptoms in MIS patients with or without NIHSS score events (n=1372).

Variable	MIS with NIHSS score of 0 (n=1102)	MIS with NIHSS score of 1-3 (n=270)	*P Value*
Male sex, n(%)	539(49.8)	127(47.0)	0.588
Age (y, mean ± SD)	58.4±10.7	68.1±11.4	<0.001
BMI (kg/m^2, mean ± SD)	24.0±3.3	23.9±2.3	0.562
Duration of hypertension (years, mean ± SD)	2.9±4.8	4.3±5.7	<0.001
Diabetes mellitus, n(%)	80(7.3)	35(13.0)	0.004
Dyslipidemia, n(%)	615(55.8)	176(65.2)	<0.001
Heart disease (%)	24(2.2)	12(4.4)	0.053
Atrial fibrillation (%)	16(1.5)	4(1.4)	1
Metabolic syndrome (%)	357(32.4)	109(40.4)	0.015
Current smoking (%)	267(24.2)	59(21.9)	0.426
Heavy alcohol consumption (%)	247(22.4)	45(16.7)	0.004
SBP	150±21.1	157±23.8	<0.001
DBP	96.2±11.5	94±10.9	<0.001
Blood glucose	5.7±1.6	6.1±2.6	<0.001
Median time of symptoms to MRI (days, range)	7.6(0.16-28.8)	5.1(0.16-20.8)	0.265
Nonfocal neurologic symptoms, n(%)	1102(100.0)	141(52.2)	<0.001
Focal neurologic symptoms, n(%)	0(0)	129(47.8)	<0.001
Initial median NIHSS score (range)	0(0)	1.1(0-3)	<0.001

MIS: Minor Ischemic Stroke; NIHSS: National Institutes of Health Stroke Scale; BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure.

Table 3: Multivariate analysis of risk factors for MIS with or without NIHSS score events.

Variable	MIS with NIHSS score of 0 (n=1102)	MIS with NIHSS score of 1-3 (n=270)	HR (95% CI)	*P Value*
Nonfocal symptoms, n(%)	1061(96.3)	204(75.7)	0.5(0.357-0.750)	0.001
Age, mean ± SD	58.4±10.7	68.1±11.4	1.1(1.046-1.099)	<0.001
Increased SBP, mean ± SD	150±21.2	158±22.0	1.0(1.002-1.026)	<0.001

MIS: Minor Ischemic Stroke; HR: Hazard Ratio; CI: Confidence Interval; SBP: Systolic Blood Pressure.

up). The total recurrence rate for recent MIS was 23.5% (318/1354), with 22.3% recurrence event (243/1098) in patients with an NIHSS score of 0 and 28.3% recurrence event (75/265) in patients with an NIHSS score of 1-3 (p=0.043) (Figure 3).

The survival rate was 100% in the two groups during the first 90 days of follow-up. The disability rate in patients with an NIHSS score of 0 was significantly lower than that in patients with NIHSS scores of 1-3 (0.36% vs. 28.7%, p<0.001) (Table 4). The factors associated with outcome in patients with recent MIS, according to the NIHSS score, are exhibited in Supplementary Table 2.

Discussion

A high prevalence of MIS and TIA (55-74%) is currently recorded in metropolitan areas [18,19]. The present study showed that patients with recent MIS accounted for 42.8% of neurologic outpatient patients at the first visit, suggesting that this location is likely to be a high prevalence area of MIS events [20].

Although most of the studies have defined NIHSS scores of 0-3 as diagnostic criteria for MIS [3,7,21], the present data showed that 34.3% of MIS patients with nonfocal symptoms alone had an NIHSS scores of 0, and among them, all patients with an NIHSS score of 0 events had mRS scores of 0-2 during the 90-day follow-up. These findings from our data strongly support that recent MIS with an NIHSS score of 0 events are more likely to suit the definition of nondisabling MIS.

Our data analysis of conventional risk factor profiles (age, BMI, hypertension, smoking, blood glucose, dyslipidemia, nonfocal neurologic symptoms, etc.) showed significant differences between the groups of patients with MIS with an NIHSS score of 0 and with NIHSS scores of 1-3. However, in the multiple logistic regression analysis, the different prevalence rates in patients with an NIHSS score of 0 and with NIHSS scores of 1-3 suggest that among MIS patients with an NIHSS score of 0, the risk factors were significantly correlated with middle age, nonfocal neurologic symptoms, and increased SBP.

To the best of our knowledge, hypertension is a traditional stroke risk factor that has been recognized, but middle age and nonfocal neurologic symptoms were have not been previously reported as risk factors for MIS with an NIHSS score of 0.

Some studies have confirmed that stroke risk increases with aging, and older patients have an increased stroke prevalence [22,23]. However, our current study showed that the prevalence of MIS with an NIHSS score of 0 were more likely to spread in the middle-aged population (incidence peaking between 40-59 years), showing that MIS with an NIHSS score of 0 seriously threatens the health of middle-aged people and has become a public health problem that cannot be ignored in outpatient populations.

Table 4: mRS score at 90 days following-up in patients with or without NIHSS score events.

Variable	MIS with NIHSS score of 0 (n=1089)	MIS with NIHSS score of 1-3 (n=265)	*P Value*
Lost to follow-up, n(%)	13(1.2)	5(1.9)	0.374
mRS score at 90 days			
0-2, n(%)	1085(99.6)	189(71.3)	<0.001
3-5, n(%)	4(0.36)	76(28.7)	<0.001
6, n(%)	0(0)	0(0)	NA
Recurrence events in 90 days, n(%)	243(22.3)	75(28.3)	0.043
Disability in 90 days, n(%)	4(0.36)	76(28.7)	<0.001

MIS: Minor Ischemic Stroke; NIHSS: National Institutes of Health Stroke Scale; mRS: Modified Rankin Scale.

The present study shown that MIS patients with an NIHSS score of 0 was commom in the neurologic outpatient clinic, but they more frequently had nonfocal neurologic symptoms than those patients with NIHSS scores of 1-3. This finding is in accordance with the results of some epidemiological studies published in recent years that have confirmed a high prevalence of ischemic stroke or cerebral angiopathy in patients with dizziness and/or headache [12-17]. Thus, our findings suggested that a large number of MIS patients with an NIHSS score of 0 was almost always visit in neurologic outpatient, which was mainly due to high prevalent minor nonlocal symptoms. This was further confirmed by a recent study [24].

A previous study showed that the functional outcomes of patients with MIS with nonlocal symptoms were favorable [12]. Our current study also confirmed that MIS with nonlocal symptoms with an NIHSS score of 0 was associated with a favorable outcome. However, several previous studies have shown that even minor stroke can yield poor outcomes and require thrombolysis [3,6,7]. Moreover, some studies have confirmed that the prognosis for ischemic stroke related to the burden of atherosclerosis [25,26]. Really, not only does the genetic factors are important mechanisms of atherosclerosis [27], but also presence of vascular risk factors may accelerate the progress of atherosclerosis [9,25,28]. A recent study showed that the overall rate of recurrent stroke in patients with symptomatic intracranial atherosclerosis disease was nearly 20%, even with advances in medical treatment [29]. Unfortunately, the recurrence rate in MIS patients with an NIHSS score of 0 was previously understudied. However, our study shown that the recurrence events was 22.3% in recent MIS with an NIHSS score of 0, and there was almost no difference compared with those 28.3% with an NIHSS score of 1-3, showing that a high recurrence rate seriously threatens the health of MIS patients with an NIHSS score of 0.

Because of the research design, it was difficult to determine the indicator associated with recurrence events. However, in the present study, high recurrence events in recent MIS involves the following two important issues. First, some MIS with an NIHSS score of 0 with frequent nonlocal symptoms may also have severe atherosclerotic burden because only those frequency of recurrent events have related to intracranial/extracranial artery stenosis [9,25,26,29]. Perhaps, another reason for the high recurrence rate was due to that these patients did not be getting the best effective treatment (e.g., statins regularly).

Some limitations of our study should be mentioned. First, some MIS patients with stenosis of the basilar or middle cerebral artery have a worse prognosis [3,6,9], but the majority of our neurologic outpatients did not accepted the vascular imaging examine. Therefore, future research is needed to confirm this atherosclerotic burden from recurrence events with an NIHSS of 0. Second, the studied population was only from a single center, although the sample size was large. However, we believe that this sample is representative of a general population because this institution is a unique regional national tertiary hospital, and the study population was enrolled based on estimates of the population of older than 25 years (including males and females), and 93% of subjects were from 38 villages or towns, while only 6% were from country towns. This allowed us to determine the proportion of MIS patients who were admitted to neurologic outpatient clinics. This institution is located in a high prevalence zone of cerebrovascular disease [20], suggesting that the prevalence of MIS with an NIHSS score of 0 might not have been overestimated in our study population. In addition, instances of unexpected stroke are often routed directly by ambulance to the emergency room, especially when motor function is involved [30]. This decrease may be a cause of the NIHSS score of 1-3 events in our general neurology outpatients.

Conclusion

The disability rate of MIS with an NIHSS score of 0 is very low, but it seriously threatens the health of middle-aged people as its high prevalent rate and frequent recurrence events. Our finding is research novelty because the entity of recent MIS with an NIHSS score of 0 is more likely to suit the definition of nondisabling MIS. In contrast, those patients with NIHSS scores of 1-3 may have a risk of disability.

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