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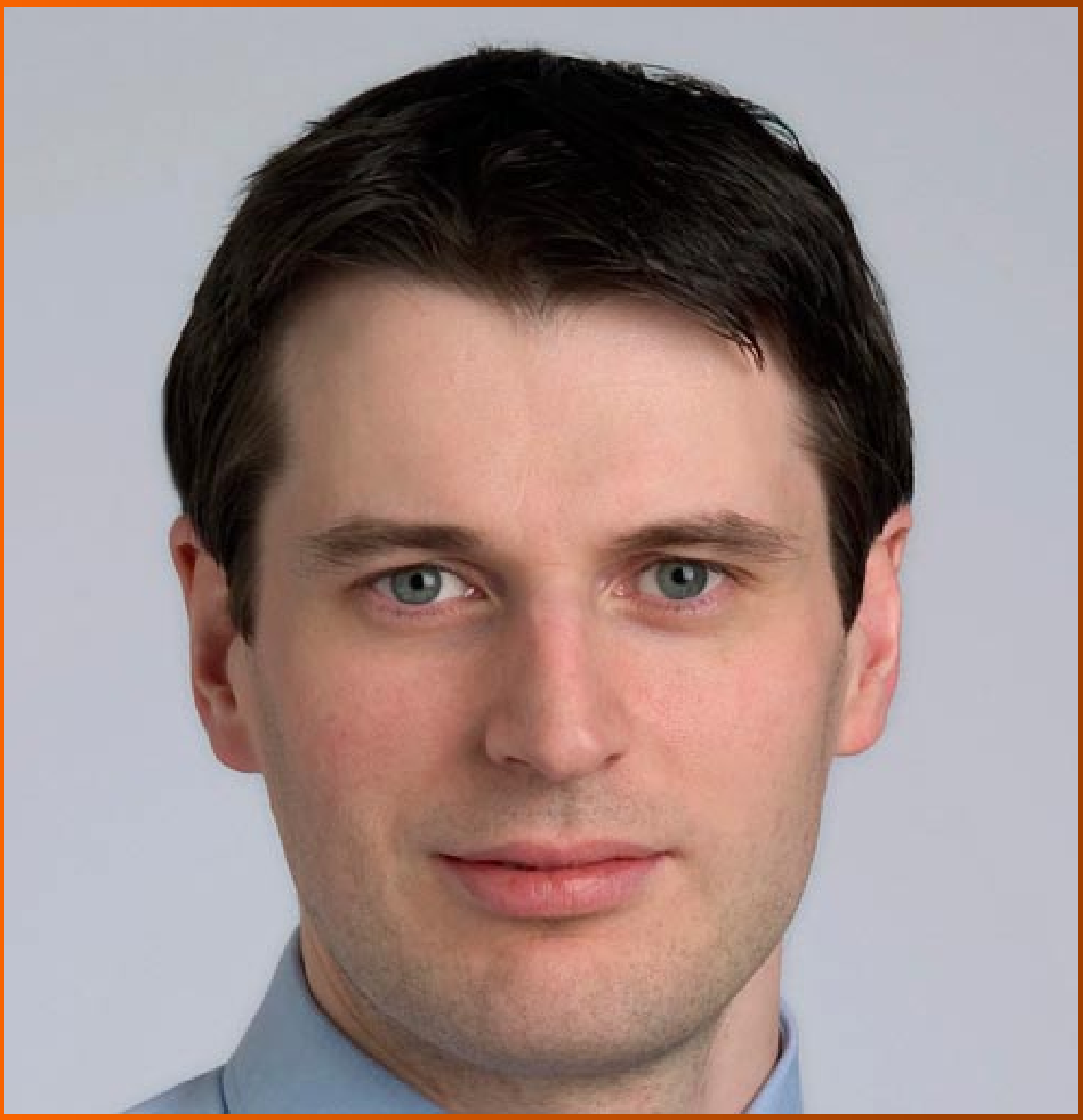

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Contents

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Thrombolysis for mild stroke

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Abstract

The term "mild stroke", or "minor stroke" refers to the acute ischemic stroke patients with mild and nondisabling symptoms. Currently there is still no unanimous consensus on the exact definition of mild stroke. Patients with mild stroke are assumed to have a good prognosis in natural course, so they are routinely not given thrombolysis despite early emergency department arrival. Recent studies have revealed that, however, approximately one third of so-called mild stroke patients who are not treated with thrombolysis have significant disability whereas those treated are more likely to achieve a good recovery. Thus excluding all mild strokes from thrombolysis is probably not justified. Those mild stroke patients who are likely to experience early deterioration or end with disability are mostly characterized by imaging findings. Therefore, selected patients with these characteristics based on neuroimaging to be given thrombolysis might be more justified. Meanwhile, new definition should be developed to exclude those who are at a higher risk of poor outcome. Applying information from imaging may make it come true. Using neuroimaging information to define mild stroke and select patients with mild symptoms to thrombolysis may be a future direction.

Key words: Definition; Mild stroke; Minor stroke; Neuroimaging; Thrombolysis

Core tip: Clinically, mild stroke patients are routinely excluded from thrombolysis, for the considering that they are too mild and expected to have a good outcome even left untreated. Recent studies showed that mild strokes might also benefit from thrombolysis. However, unlike major stroke, about two thirds of mild stroke patients will have good outcome in nature course; about the one third will end with poor outcomes but they are found to be mostly characterized by imaging features. So we proposed that neuroimaging-based approaches to define mid stroke and selecting mild stroke patients to thrombolysis may be future directions.

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INTRODUCTION

Evidences have confirmed that thrombolysis is the

most effective therapeutic approach for acute cerebral infarction[1,2]. However, a number of stroke victims arriving in hospital within the time window are withheld thrombolytic treatment for several contraindications. "Mild stroke", or "minor stroke", is one of the most common reasons[3]. Yet there is no unanimous consensus on the exact definition for mild stroke and whether mild stroke patients should be given thrombolysis remains a widely controversial issue as the pivotal studies on reperfusion treatment routinely excluded such patients, leading to scarce data available from randomized controlled trials concerning the optimal management. Some studies in the recent reported that patients with mild stroke might also benefit from thrombolysis. This may bring remarkable public health impact as approximately half of the patients with an acute stroke are categorized as mild stroke[4]. We therefore write this review to elaborate the current researches on mild stroke including the definition, the present situation in the treatment and especially the clinical researches on thrombolysis for mild strokes. We also discuss potential approaches to define or treat mild strokes and ultimately hope that a better understanding of mild stroke will foster the development of innovative therapeutic strategies for mild stroke patients.

WHAT IS MILD STROKE?

A deficit measured on the National Institutes of Health Stroke Scale score of ⩽ 3 is the most commonly used definition

The term "minor stroke" was first mentioned 40 years ago by Perdue *et al*[5] referring to the mild neurologic deficits preceding catastrophic cerebral infarction. Since then, the definitions used to identify minor stroke or mild stroke varied from one study to another and some even did not provide a definition[6]. Majority of the existing definitions are based on the symptoms or baseline National Institutes of Health Stroke Scale (NIHSS) in acute stage (Table 1). Regardless of the exact definitions, most these given definitions share an identical meaning - acute ischemic stroke patients with mild and nondisabling symptoms. A deficit measured on the NIHSS score of ⩽ 3 seems to be the most commonly used definition by literature available[6].

An ideal definition of a "minor stroke", just as Fischer *et al*[6] assert, should reflect the following 5 aspects: "(1) it should capture patients with mild and nondisabling symptoms in acute stage and favorable short-term and medium-term outcomes; (2) it should be valid for different subgroups of stroke patients; (3) it should imply both qualitative and quantitative dimensions; (4) it should be simple and useful in daily clinical practice; and (5) it should not overlap with the definition of a transient ischemic attack". Fischer *et al*[6] also assessed the 6 commonly used definitions and concluded that "NIHSS ⩽ 3" is one of the two most suitable (the other is "score ⩽ 1 on each NIHSS item and normal consciousness"). However, it also has several important limitations: (1) NIHSS score of 3 could represents a severe deficit in one NIHSS item or mild deficits in several items. Some physicians generally consider the prior situation more severe than the latter; (2) using 3 as a specific cut point might be arbitrary because the difference of 90 d outcome between patients with a NIHSS score of 3 and 4 is not evident[7]; (3) what's more, approximately one third of patients with an NIHSS score of ⩽ 3 can not be discharged home and a quarter have a poor outcome[8]. As a result, the definition of NIHSS ⩽ 3 could not well reflect the real severity and outcome of acute ischemic patients with mild symptoms.

Patients with mild stroke symptoms as defined by an NIHSS ⩽ 5 are most commonly excluded from thrombolysis in clinical practice and trials

The definition of stroke severity is clinically relevant as "mild stroke" which is a frequently mentioned contraindication. However, it is never clarified and left to the clinicians' judgement although "acute ischemic stroke with a baseline NIHSS ⩽ 3" is a widely applied definition. Thus when stratifying patients based on the severity of the neurologic deficit, clinicians find themselves in hesitation: is an NIHSS of 3 mild but an NIHSS of 4 or 5 not? National Institute of Neurological Disorders and Stroke rt-PA Stroke Study[1] and III European Cooperative Acute Stroke Study[2] exclude NIHSS scores of < 5 from enrollment on the presumption that this represents the mild subgroup. According to the hospital records from 16 adult area hospitals in a study by Khatri *et al*[16], among 437 patients with acute ischemic stroke that presented to emergency departments within 3.5 h, 247 (57%) had a base line NIHSS ⩽ 5 and only 4 were treated with rt-PA. Moreover, in the American Heart Association Get With the Guidelines Registry (GWGR) nationwide program from 2003 to 2009, among 73044 cases arriving to emergency departments within 2 h of symptom onset but excluded from rt-PA treatment, 29612 (41%) were not treated solely due to mild or improving symptoms, and 75% of these had a baseline NIHSS < 5[3]. Many of the stroke patients who are regarded too mild to treat actually have a higher baseline NIHSS than 3. Mild strokes with a NIHSS ⩽ 5 at baseline are more likely to be excluded from thrombolysis in clinical practice and trials[17]. In this aspect, the definition of NIHSS ⩽ 5 can better reflect the clinical profile that a large number of patients are excluded from thrombolysis just because of the mild symptoms. Hence several eminent epidemiological studies employed this definition[4,11,12].

OUTCOME OF PATIENTS WITH MILD STROKES MIGHT NOT BE AS BENIGN AS GENERALLY ASSUMED

MIS are excluded from thrombolysis because they are expected to have good functional outcome. However,

Table 1 Most commonly used definitions for mild stroke by literature

Based on baseline NIHSS	All patients with baseline NIHSS ≤ 3[6-9]
	All patients with baseline NIHSS ≤ 4[7,10]
	All patients with baseline NIHSS ≤ 5[4,11,12]
	All patients with baseline NIHSS ≤ 6[7,13]
	All patients with baseline NIHSS ≤ 9[14]
	All patients with a score 0 or 1 on every baseline NIHSS score item and normal consciousness[6,14]
Based on syndromes	All patients with a lacunar-like syndrome (presumed small vessel occlusive disease) such as pure sensory syndrome, pure motor hemiparesis, sensorimotor syndrome, ataxic hemiparesis, and dysarthria-clumsy hand syndrome[6,14]
	All patients with only motor deficits (can include dysarthria or ataxia) with or without sensory deficits. These patients can have only a combination of motor, coordination, and sensory deficits without any deficits in the spheres of language, level of consciousness, extinction or neglect, horizontal eye movements, or visual fields, deficits generally ascribed to larger territories of focal ischemia[6,14]
	All patients with baseline NIHSS in the lowest (least severe) quartile of severity (NIHSS ≤ 9), excluding all patients with aphasia, extinction, or neglect, or any points on the level-of-consciousness questions[6,14]
Based on imaging	Major stroke: A proximal cerebral artery occlusion on the CTA or MRA; if no occlusion, imaging evidence of significant parenchymal ischemia on NCCT or DWI[15]
	Minor stroke: all of the others except major stroke[15]

NIHSS: National Institutes of Health Stroke Scale; CTA: Computered tomography angiography; MRA: Magnetic resonance angiography; NCCT: Non-contrasted computered tomography; DWI: Diffusion-weighted imaging.

studies indicate that outcome of patients with mild strokes might not be as benign as generally assumed. Khatri *et al*[17] reviewed a prospective cohort of 136 consecutive patients with mild deficits (NIHSS ≤ 5), 40 (29%; 95%CI: 22%-38%) had poor outcomes (modified Rankin Scale score 2-6) at 90 d and early worsening within 5 d were more common among those with poor outcome; Smith *et al*[3] analyzed the outcome of 29200 patients of mild stroke enrolled in GWGR programme who were excluded from thrombolysis, 28.3% were unable to be discharged home and 28.5% were unable to ambulate without assistance at discharge; Multiple studies have confirmed that approximately 25% to 35% of these patients are disabled at the time of discharge or 90 d despite presenting with mild neurological deficits at acute phase.

TREATING MILD STROKES WITH RT-PA - GRADUALLY ACCEPTED BY CLINICIANS

Mild stroke is one of the most common exclusions for thrombolysis. Prior studies have estimated that 30% to 50% of acute ischemic stroke patients arriving within 3 h of symptom onset are not treated with rt-PA just because of "mild stroke" or "rapidly improving stroke symptoms"[3,18]. However, there is a lack of criteria about what is "mild stroke" and such a contraindication is consensus-based, not evidence-based. Across the Specialized Program of Translational Research in Acute Stroke (SPOTRIAS) network, there was a significant variability in the proportion of patients with mild stroke (NIHSS score 0-3) treated with rt-PA, which ranged from 2.7% to 18.0% across the entire consortium[19]. The main reason is the threshold for the decision to treat a mild stroke differs between physicians at the various centers and between centers overall. In the recently published Promoting Acute Thrombolysis in Ischemic Stroke trail, mild stroke was a less frequent ambiguous contraindication in the intervention hospitals compared with the nonintervention ones (17% *vs* 26%)[20]. All these phenomena reflect a paucity of data on how to best treat mild stroke patients and highlight the demand for a randomized trial to clarify the effect of thrombolysis for mild stroke patients.

On the other hand, having recognized the poor outcomes of mild stroke, many medical centers realize that it is unreasonable to leave them untreated and sometimes they inform patients of the medical knowledge about thrombolysis and may follow their choice[21]. Thus an increasing number of patients with mild stroke are treated. The proportion of mild strokes (NIHSS score 0-3) treated with rt-PA increased from 4.8% in 2005 to 10.7% in 2009 across the SPOTRIAS network[19]; In Sweden, an increase in the proportion of patients with mild stroke (NIHSS ≤ 5) treated with thrombolysis has contributed to rising overall thrombolysis rates - the proportion with mild stroke among patients treated with thrombolysis increased from 22.1% in 2007 to 28.7% in 2010[11]; Over the past two decades period, the initial severity of stroke patients enrolled in the large clinical trails has declined gradually[1,2,22]. These trends may reflect the trend toward the use of thrombolytic agents in patients who have less severe acute ischemic stroke. Many investigators therefore proposed that current thrombolysis guidelines need revision[21].

DOES MILD STROKE BENIFIT FROM THROMBOLYSIS?

Currently no randomized, placebo-controlled trial has yet been implemented to test the efficacy and safety of rt-PA administered in patients with mild stroke. Some studies that retrospectively analyse the outcome of mild stroke patients received thrombolysis have attempted to evaluate the safety and efficacy. Some show that the patients treated with thrombolysis tend to aquire better outcomes, while the others do not show advantages. However, nearly all the studies show that the rate of

Table 2 Studies on thrombolysis in mild stroke

Ref.	Definition of mild stroke	Patients		Favorable outcome (t-PA *vs* Placebo)	*P*	SICH (t-PA *vs* Placebo)	*P*
		rt-PA	Placebo				
NINDS rt-PA Stroke Study Group[14]	Score ≤ 1 on each NIHSS item and normal consciousness	21	7	100% *vs* 86%	< 0.02	0% *vs* 0%	-
	Presumed small-vessel stroke	51	30	69% *vs* 60%	< 0.02	4% *vs* 0%	-
	Only motor deficits ± sensory deficits	220	219	61% *vs* 46%	< 0.02	3% *vs* 0.5%	-
	NIHSS score ≤ 9, minus all with aphasia, extinction/neglect, or any points on the level of consciousness questions	97	76	81% *vs* 74%	< 0.02	3% *vs* 0%	-
	NIHSS ≤ 9	99	78	82% *vs* 74%	< 0.02	3% *vs* 0%	-
Köhrmann *et al*[10]	NIHSS ≤ 4	32	-	94%	-	0%	-
Hassan *et al*[13]	NIHSS ≤ 6	27	24	92.6% *vs* 50%	< 0.03	3.7% *vs* 4.2%	1
Hassan *et al*[23]	NIHSS ≤ 10	52	98	74% *vs* 34%	< 0.009	2% *vs* 3%	-
[1]Steffenhagen *et al*[24]	NIHSS ≤ 5	78	16	74.7% *vs* 81.3%	0.75	2.6% *vs* -	0.572
[2]Khatri *et al*[25]	NIHSS ≤ 5	42	16	78.6% *vs* 81.3%	-	2.4% *vs* 0%	-
[2]Huisa *et al*[26]	NIHSS ≤ 5	59	74	57.6% *vs* 68.9%	0.871	5%	-
[3]Helsinki Stroke Thrombolysis Registry[7]	NIHSS 0-2	58	-	88%	-	0%	-
	NIHSS 3-4	194	-	86%	-	2.6%	-
	NIHSS 5-6	236	-	78%	-	2.1%	-
Greisenegger *et al*[27]	NIHSS ≤ 5	445	445	41% *vs* 29%	< 0.001	2.5% *vs* 0%	-
Urra *et al*[28]	NIHSS ≤ 5	119	84	83% *vs* 81%	> 0.05	0% *vs* 0%	-
Logallo *et al*[29]	NIHSS ≤ 5	158	1633	38% *vs* 31%	0.07	1.9% *vs* 0.1%	< 0.001

[1]Steffenhagen *et al*[24] compared the functional outcome of mild stroke patients using the modified Rankin scale (mRS) with severe (NIHSS score > 5) groups. Symptomatic intracerebral hemorrhage was low (2.6% *vs* 4.7%; *P* = 0.572). Favorable outcome (mRS score < 2) at 3 mo was more frequent (74.7% *vs* 34.7%; RR = 2.2, 95%CI: 1.8-2.5, *P* < 0.001) and mortality rate was lower (8% *vs* 22.9%; RR = 0.35, 95%CI: 0.16-0.76, *P* = 0.002). Favorable outcomes were not different (81.3% *vs* 74.7%, mRS score < 2, *P* = 0.75) compared to a placebo-treated group with baseline NIHSS scores ≤ 5 (*n* = 16) from the NINDS t-PA trial; [2]In Khatri's study, 4 of the 58 minor strokes had baseline disability (mRS > 2), and all were in the rt-PA group. In Huisa's study, the NIHSS score at admission was higher in the t-PA treated group compared to that in untreated group (3.4 ± 1.4 *vs* 1.9 ± 1.3; *P* < 0001). Thus the selective bias in the two studies might underestimate the effects of thrombolysis; [3]In Helsinki Stroke Thrombolysis Registry, they did not give the definition of mid stroke. Fifty-eight mild stroke patients with NIHSS score 0-2 were treated with thrombolysis only when hyperdense cerebral artery sign, artery occlusion on computed tomography (CT) angiography, or perfusion deficit on perfusion CT scan presented. NIHSS: National Institutes of Health Stroke Scale; t-PA: Tissue plasminogen activator; SICH: Symptomatic intracranial hemorrhage.

intracranial hemorrhage will not increase significantly in rt-PA groups, which indicates that thrombolysis for mild stroke should be safe (Table 2).

HOW TO TREAT MILD STROKE? - NEUROIMAGING-GUIDED THROMBOLYSIS FOR MILD STROKE MAY BE A POTENTIAL WAY

Unlike major stroke, about two thirds of mild strokes have good functional outcomes in their natural course. Considering the probability that these patients may not benefit much but will be exposed at risks of hemorrhage if given rt-PA, it seems to be not reasonable if all mild strokes are given thrombolytic therapy. On contrary, those who will have a poor outcome and can be figured out ideally might derive the greatest benefit from thrombolysis if treated. A number of studies have tried to find out the the causes and characteristics of mild stroke patients with poor outcomes.

Ohara *et al*[30] retrospectively studied the clinical data of mild strokes (NIHSS ≤ 5) who presented within 3 h after onset and did not receive intravenous rt-PA and found that major vessel occlusion (OR = 6.90; 95%CI: 1.31-47.51; *P* = 0.022) and NIHSS > 3 (OR = 8.00; 95%CI: 1.20-79.31; *P* = 0.031) were independent predictors of poor outcomes. Rajajee *et al*[31] revealed that persisting large-vessel occlusion substantially increases the risk of early worsening (OR = 18; 95%CI: 1.6-209; *P* = 0.02) and poor functional outcome(OR = 7; 95%CI: 1.2-38; *P* = 0.04) in mild stroke patients(NIHSS ≤ 5) while Coutts *et al*[32]'s study indicated that intracranial or extracranial vessel occlusion or ≥ 50% stenosis was associated with poorer outcome (RR= 2.92; 95%CI: 1.81-4.71). A study in Changhua, Taiwan, also demonstrated that mild or rapidly improving patients with initial NIHSS score ≥ 3 had high risk of unfavorable outcome (OR = 5.95; 95%CI: 1.10-32.12)[33].

Moreover, several studies have obtained amazing results through analyzing multimodal MRIs of mild strokes. A study by Khatri *et al*[17] showed that mild strokes (NIHSS ≤ 5) with poor outcome had larger DWI infarcts at baseline and more frequent lesions growth and NIHSS worsening from baseline to 5 d, increase in DWI infarct volume (OR = 3.57; 95%CI: 1.17-10.9; *P* < 0.03) was an independent predictor of poor 90-d outcome. Similarly, in Asdaghi *et al*[34]'s study, early "recurrence" of mild stroke (NIHSS ≤ 5) was much more likely in patients with larger baseline diffusion-weighted imaging (DWI) or perfusion-weighted imaging (PWI) lesions and all new lesions developed within the

baseline PWI infarcts. Interestingly, both Asdaghi *et al*[34] and Rajajee *et al*[31]'s studies showed that baseline large DWI lesion or DWI-PWI mismatch were frequently accompanied by large vessel occlusions in those mild patients who underwent early neurologic deterioration with infarct expansion and ended with poor functional status. These findings suggest that majority of "recurrent" events or deteriorations over the first few days after the mild strokes are related to progression of the original infarct within the territory of the penumbral deficit due to consistent vessel occlusion, rather than new cerebrovascular events[35]. Thrombolysis may restrain this progression and bring potential benefit.

Studies above illustrate that baseline NIHSS > 3, major vessel occlusion or severe stenosis, relatively large DWI or PWI lesions are strongly associated with early deterioration and poor prognosis, which suggests that selecting mild strokes with these characteristics to treat might be more justified. Specifically, strokes with baseline NIHSS > 3 but without contraindications perhaps all should be given thrombolysis[36], while patients with baseline NIHSS $\leqslant$ 3 should be given thrombolysis or other reperfusion therapies as well on condition that major vessel occlusion, relatively large DWI and PWI lesions or significant DWI/PWI mismatch be visualized with rapid neuroimaging methods[37]. Certainly, justification of this selective approach awaits clinical validation in more studies.

RETHINK THE DEFINITION OF MILD STROKE

To supplement NIHSS, many studies have proposed imaging-based methods to evaluate and classify acute cerebral infarction[38]. However, few such studies have yet to be performed for mild stroke. Torres-Mozqueda *et al*[15] proposed a neuroimaging-based ischemic stroke classification system - Boston Acute Stroke Imaging Scale (BASIS). The rationale underlying this classification system is that if proximal cerebral artery occlusions are identified on the computered tomography angiography or Magnetic Resonance Angiography, or significant parenchymal abnormalities are identified by examination of the non-contrasted CT or diffusion MR imaging, patients will be classified as having a major stroke. All of the other patients are classified as having a mild stroke. Compared to NIHSS and other widely accepted imaging-based scale such as Alberta Stroke Programme Early CT Score[39], BASIS is found to be highly effective in predicting outcomes and applicable to both anterior and posterior circulation strokes[40]. What's more, it focuses on the primary cause of the infarct - arterial occlusion[15], which will give physicians more clues than NIHSS to determine whether thrombolysis should be given or not, especially for patients with mild symptoms. Clearly, definition solely based on baseline NIHSS or symptoms seems not to be a good choice. Using neuroimaging methods might be more reasonable and superior to using NIHSS in terms of suggesting prognosis and helping to guide therapy in individual patient. Advances in the field of neuroimaging have made it quite feasible and achievable[38], but few such studies have yet to be performed and it may be a future direction to define mild stroke.

CONCLUSION

The definition of mild stroke is not uniform yet. The term "mild stroke" or "minor stroke" might not be suitable for all those stroke patients who are currently deemed too mild to treat as a significant percentage of them will be disabled if left untreated. Definitions on the basis of NIHHS solely might not be a good choice. An ideal definition should better differentiate those who are at a higher risk for clinical deterioration and poor prognosis from the patients presenting with mild neurological deficits or low NIHSS. Applying information from neuroimaging may help it come true.

The available studies on rt-PA for mild stroke inform us that thrombolysis may be beneficial and with minimal side effects. Considering the fact that most of them have favorable functional outcomes in their natural course, selecting patients who are most likely to be early worsening and disabled to treat might be more justified. Current studies have identified some characteristics of these patients and efforts of neuroimaging-guided thrombolysis in mild stroke have been made. We think that it will be a future direction for treating mild strokes.

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