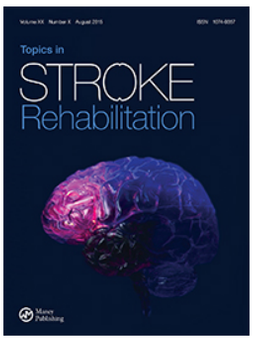

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Early clinical predictors of post-stroke spasticity

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ABSTRACT

Background and Purpose: Up to 40% of stroke patients with paresis develop post-stroke spasticity (PSS), which induces difficult complications including pain, contracture, posture disorder. The most important factor for PSS management is its early initiation, so that early recognition of PSS is required in clinical practice.

Methods: This prospective observational cohort study was conducted with a high standard of PSS assessment and a comprehensive protocol investigating possible predictive factors to identify early predictors of PSS already in the acute phase following stroke (<7 days). PSS was assessed with the Resistance to Passive movement Scale (REPAS) for major joint movements in upper- and lower limbs, based on Ashworth scale, within 7 days following stroke and after 3 months. Binary logistic regression analysis with significant clinical parameters was applied with 95% of confidence intervals (CI) to find predictors of PSS.

Results: Of 145 consecutive first-ever stroke patients, 34 patients (23.4%) exhibited PSS. The Modified Rankin Scale (MRS), National Institutes of Health Stroke Scale (NIHSS), and Mini-Mental State Examination (MMSE) were revealed as strong clinical predictors of PSS. The combination of an MRS >2 (Odds Ratio (OR): 56.538, 95% *CI*: 17.150–186.394), NIHSS >2 (OR: 57.137, 95% *CI*:15.685–208.142) and MMSE <27 (OR: 6.133, 95% *CI*:2.653–14.178) showed positive predictive (95.2%) value for prediction of PSS (sensitivity 94.4%, specificity 93.3%).

Conclusions: Besides evaluating PSS itself with a reliable and valid rating scale the common clinical scales in stroke units practice (NIHSS, MRS, MMSE) allow early identification of patients at high risk for PSS.

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Clinical predictor; stroke; spasticity

Introduction

During the hyperacute phase[1] following a stroke, acute deficiency symptoms like paralysis or speech loss are at highest importance for affected patients, and caregivers. However, already at this time, a gradual process due to lesions in central nerve system has started, which will reach its climax in the coming weeks or months, namely the development of an upper motor neuron syndrome (UMNS) with post-stroke spasticity (PSS).

In the last century, the velocity-dependent increase in muscle tone was defined as spasticity and characterized as one motor dysfunction arising from upper motor neuron lesions.[2–4] While the pathophysiology of PSS is still incompletely understood, it is assumed that all positive features of the UMN syndromes are related to changes in the balance between excitatory and inhibitory signals to the spinal motor neuron pool leading additionally to changes in soft tissue and muscle fiber density.[5]

As velocity-dependent increase in muscle tone defined by Lance [2] represents only one "positive" component of the UMNS more recent definitions include all positive symptoms (increased tendon reflexes, Babinski group reflexes, clonus, spasms, spastic dystonia, and velocity-dependent increase in muscle tone) as spasticity[6] excluding the "negative" components of the UMNS (e.g. paresis) and the complications of the UMNS (e.g. contractures, loss of muscle fibers). In this study, we define PSS as the appearance of velocity-dependent increase in muscle tone as assessed by Ashworth scale (≥1).

Up to 42.6% of all stroke patients with mild to severe paresis will develop PSS.[6–8] The PSS can lead to incorrect joint positions and contractures. Pain, posture disorders, and by this impaired relearning

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of functionally essential actions occurring in the aftermath of stroke are feared long-term consequences of PSS.[3,9–13]

Most important in managing PSS is the early implementation of specific targeted prophylaxes and consequent treatment.[3,14] To date, specialized occupational therapy and physiotherapy together with botulinum toxin (BoNT) injections constitute the therapies of choice.[14–16] The earlier the treatment is initiated, the better the outcome. If PSS is treated too late, incorrect movement patterns and incorrect posture have already been established and can only be corrected with great efforts or surgical measures.[3,14]

Owing to its gradual onset and the associated delay before complete clinical manifestation, PSS is usually detected and treated too late. In clinical practice, specific treatment is often initiated after weeks and months, when the PSS patterns are established and already pronounced. For the treating physicians, it would thus be very useful to know "spasticity predictors" in order to identify patients at high risk of developing PSS.[3,14]

A variety of studies investigated clinical predictors of PSS and identified several risk factors associated with it. Risk factors which were shown to be independently predictive in clinical studies were severe arm paresis,[7–10,17,18] velocity-dependent increase in muscle tone itself measured as increased modified Ashworth Scale (MAS),[7,9,18,19] low Barthel Index (BI),[7,8] hemihypesthesia[8], low EQ-5D (EuroQol – five dimension scale) score,[8] and large infarct volumes.[20] The limitation of these studies is often a retrospective design or a lack of a detailed professional assessment of PSS with reliable and valid instruments.[14]

The current study was therefore conducted with a standardized accepted validated reliable assessment, the Resistance to Passive movement Scale (REPAS) and a comprehensive clinical examination protocol investigating a variety of possible predictive factors to find strong clinical predictors of PSS with a set of already established clinical rating scales.

Methods

Consecutive patients suffering from acute stroke and admitted at the Stroke Unit of the Charité Medical University (Campus Benjamin Franklin Berlin, Germany) were screened and enrolled over a period of 22 months. Patients included had to be affected by an acute ischemic stroke with clinical symptoms and new ischemic lesion on magnetic resonance imaging (MRI) or computer tomography (CT) within 7 days and provide their written informed consent for participating to the study. All participants had to give written consent to the study. Exclusion criteria were as follows: aged under 18 years, recurrent or hemorrhagic stroke, severe cognitive deficits, severe language comprehension disorders, lack of ability to provide informed consent, as well as physical disability already existing prior to the acute stroke or prior infarct areas detected upon acute imaging data (to the event of admission to the Charité Medical University (Campus Benjamin Franklin Berlin, Germany)). The ethics committee of the university approved the study (Ethics number: EA4/112/11). All investigations were carried out in accordance with the Helsinki Declaration.

All patients were examined by the two experienced assessors (a neurologist and a physiotherapist) within the acute phase of stroke (according to Bernhardt et al.) [1] first 7 days after the acute stroke (T0) as well as 3 months post-stroke (T1) using both a standard questionnaire and standard elaborated clinical examination protocol, with the examination lasting about 2 hours. The standard questionnaire included parameters, such as age, gender, medical history, background, home situation, previous infarct events, cardiovascular risk factors like arterial hypertension, diabetes mellitus, hypercholesterolemia, nicotine abuse, atrial fibrillation, cardiac pacemaker, coronary arterial disease (CAD), peripheral obstructive arterial diseases (PAOD) prior carotid artery intervention and visual field disorders at acute event (See Table 1).

The clinical standardized examination consisted of a comprehensive neurological examination including the National Institutes of Health Stroke Scale (NIHSS: 0 to 30) for neurologic impairments, modified ranking scale (MRS: 0–5 and 6 for dead) and Barthel Index (BI: 0–100) for degree of disability or dependence in daily activities, as well as the following operationalized standardized examinations: Cranial nerves, range of gaze, increased proprioceptive reflexes, Babinski sign, sensitivity, Scale

Table 1. Basic data of participants with/without post-stroke spasticity (PSS).

n (%)	all	no PSS	PSS	p
Number	145	111	34	
Sex (female)	63 (43.4)	49 (44.1)	14 (41,2)	>0.05[b]
Age (mean±sd, years)	71 ± 11	71 ± 12	73 ± 10	>0.05[a]
Arterial hypertension	89 (61.4)	71 (64.0)	18 (52.9)	>0.05[b]
Diabetes mellitus	27 (18.6)	23 (20.7)	4 (11.8)	>0.05[b]
Hypercholesterolimia	36 (24.8)	33 (29.7)	3 (8.8)	<0.05[b]
LDL	9 (6.2)	7 (6.3)	2 (5.9)	>0.05[b]
Nikotin abusus	99 (68.3)	86 (77.5)	13 (38.2)	<0.01[b]
Atrial fibrillation	20 (13.7)	15 (13.5)	5 (14.7)	>0.05[b]
Cardiac pacemaker	1 (0.7)	1 (0.9)	0 (0)	>0.05[b]
Coronary artery disease (stent)	15 (10.3)	13 (11.7)	2 (5.9)	>0.05[b]
Peripheral arterial occlusive disease	6 (4.1)	6 (5.4)	0 (0)	>0.05[b]
Carotid endarterectomy	4 (2.8)	4 (3.6)	0 (0)	>0.05[b]
Left hemispheric stroke	63 (43.4)	49 (44.1)	14 (41.2)	>0.05[b]
Right hemispheric stroke	65 (44.9)	50 (45.0)	15 (44.1)	
Both hemispheric stroke	17 (11.7)	12 (10.8)	5 (14.7)	
TOAST classifikation (%)				>0.05[b]
TOAST-I		15.0	14.9	
TOAST-II		14.2	11.4	
TOAST-III		25.0	28.1	
TOAST-IV		0.7	0.9	
TOAST-Va		2.7	1.8	
TOAST-Vb		26.4	26.3	
TOAST-Vc		16	16.6	

mean ± sd: mean values ± standard deviation; LDL: light density lipid
[a]T-Test
[b]Chi-Quadrat Test

for Contraversive Pushing (SCP: 0–3)[21] for pushing symptom to one side, Catherine Bergego Scale (CBS: 0–30)[22] for neglect symptom, Active Range of Motion (AROM: 0 for 0% of normal value to 3 for normal) for active movement of joints including, British Medical Research Council scale for muscle strength (BMRC: 0–5) including muscles for main joint movements of limbs,[23] Arm-Hand-Activity scale (AHAs: 1–5),[24] Esslinger Transfer scale (ET: 0–4)[25] for disability of transfer, Functional Ambulation Category (FAC: 0–5)[26] for gait disorder and Mini-Mental State Examination (MMSE: 0–30).[27] AROM was recorded with the grade of active motion as compared with non-affected side or occasionally standard AROM values; Grade 1 for 0%, Grade 1 for up to 50%, Grade 2 for more than 50%, Grade 3 for the same as non-affected side. The lowest scores of BMRC on affected side in each patient were applied for the statistics. In order to assess velocity-dependent increase in muscle tone, the Resistance to Passive movement Scale (REPAS) was employed, which is a summary rating scale for resistance to passive movement in 8 upper and 7 lower limb joints on both sides. The severity of muscle tone increase was defined as follows: REPAS score greater than zero in one joint represents increased muscle tone.[28] We categorized mild spasticity for 1–3 points of REPAS values, moderate for 4–10 points, and severe spasticity for more than 10 points.

The imaging data of patients (cCT [device] and/or 3 Tesla MRT [Magnetom Trio, Siemens Healthcare]) were evaluated in a standardized manner to identify the presence of ischemic or hemorrhagic lesions, lateralization of stroke, and TOAST classification,[29] while taking into account both medical history and clinical data.

All calculations were performed using the "Statistical Package for the Social Sciences" program, Version 21.0 (IBM). Continuous and normally distributed variables were expressed as mean ± standard deviation; anomalously distributed variables were expressed as median (Q2) with interquartile range (IQR) quartile 1 – quartile 3. The patient groups with and without PSS were compared for scale variables using a Student's t-test or Mann–Whitney U test, and a chi-squared test for categorical variables. Statistical significance was set at $p < 0.05$. The clinical parameters that statistically proved significant differences in the comparison of both groups subsequently underwent the binary logistic regression analysis with

95% of confidence intervals (CI) in accordance to the development of PSS (REPAS ≥1), to find its strong clinical predictors.

This manuscript conforms to the STROBE Guidelines.

Results

Patient inclusion

In total, 764 consecutive patients affected by an acute stroke and admitted at the Stroke Unit of the Charité Medical University (Campus Benjamin Franklin Berlin, Germany) were screened for study eligibility. Overall, 647 suffering from acute ischemic stroke within the past 7 days fulfilled the inclusion criteria. Two hundred and three patients were finally included in the study (Figure 1). Other patients were excluded because of recurrent stroke, severe cognitive deficits, severe language comprehension disorders, and concomitant or preexisting physical disability, etc. Two-hundred and three patients were enrolled after having given their informed written consent; they were then examined and questioned according to a standard study protocol within 7 days post-stroke (T0: 5.4 ± 1.1 days). The follow-up examination took place 3 months after the stroke event (T1: 134.0 ± 14.0 days). At the T1 follow-up examination, 58 (28.6%) patients dropped out. While the reasons varied, they were primarily accounted for by either the patient refusal to undergo further examination or the inability to reach patients (See Figure 1). The study population analyzed at T1 was comprised of 145 stroke patients.

Baseline patient data

In total, 82 (56.6%) of the 145 acute stroke patients were male and 63 (43.4%) female, with an average age of 71 ± 11.3 years. Primary cardiovascular risk factors were arterial hypertension in 89 (61.4%) patients, diabetes mellitus in 27 (18.6%) patients hypercholesterolemia in 36 (24.8%) patients, and nicotine abuse in 99 (68.3%) patients (Table 1)

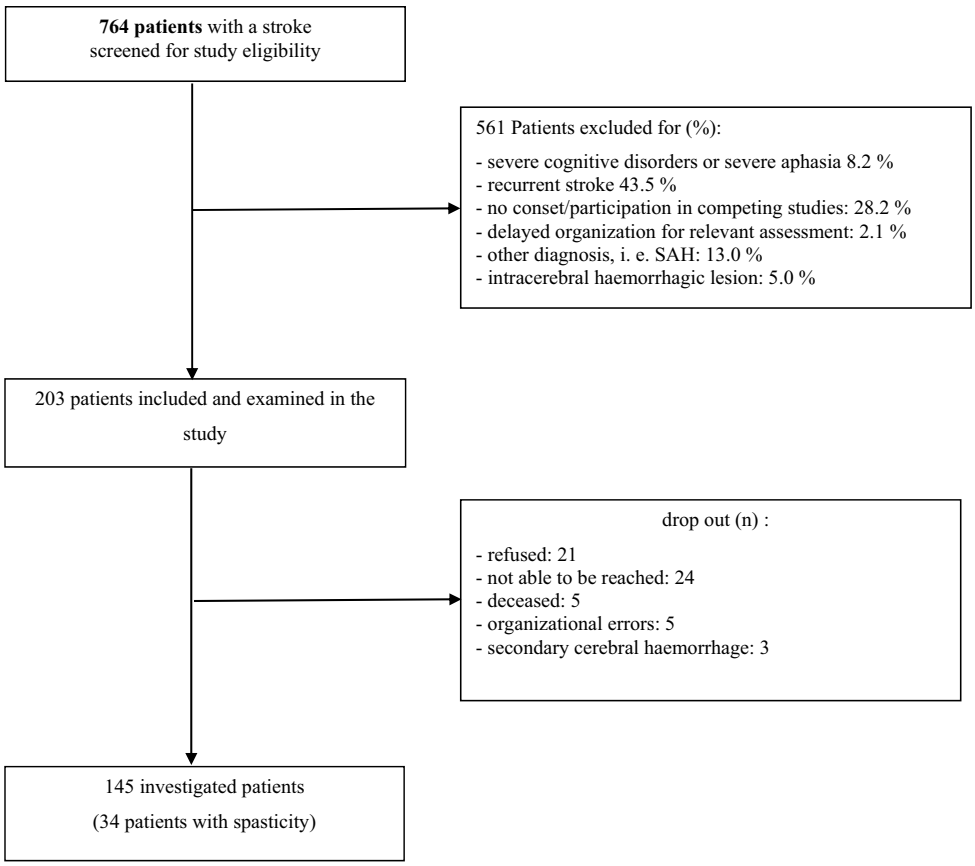


Figure 1. Study flow chart.

Baseline data of stroke

Overall, 131 (90.3%) of the 145 patients underwent 3 Tesla MRI imaging and 14 (9.7%) patients had only CT scanning as acute imaging procedures. Based on the TOAST classification, infarctions of undetermined etiologies were the most common cause, followed by microangiopathic infarctions, macroangiopathic infarctions, and cardio embolic infarctions. The most of patients who had no PSS were affected mildly to moderately in their functionality (Table 1).

Velocity dependent increase in muscle tone

In total, 34 patients (23.4%) exhibited PSS (REPAS ≥1) at the baseline and 3 months later, as compared to 76.6% who did not. Twenty-seven patients had shown moderate (REPAS 4–10 points) to severe spasticity (REPAS >10 points). Overall, 29 (85.3%) of the 34 patients expressed PSS already within the first 7 days following stroke at the baseline, while at 3 months after stroke, five further patients (14.7%) presented with PSS. The PSS in upper limbs was more frequently affected than in the lower limbs (See Table 2). All 34 patients showed velocity-dependent increase in muscle tone in the upper limbs, while 21 (61.8%) additionally displayed increased muscle tone in the lower limbs. Despite the equal distribution of both brain hemispheres, left arm PSS was more frequent than right arm PSS (64.7% *vs.* 35.3%, $p < 0.01$). There were no significant differences regarding right-left leg PSS (35.3% *vs.* 26.5%, $p > 0.05$). In the 34 patients with arm PSS, PSS was mild in 13 (38.3%) (REPAS: 1–3), moderate in 15 (44.1%) (REPAS: 4–10), and severe in six (17.6%) (REPAS: >10).[21] Of the 21 patients, leg PSS was mild in nine (26.5%), moderate in nine (26.5%), and severe in three (8.8%) (Table 2). The shoulder and elbow joints were most often affected by PSS. In the shoulder joint, the PSS mostly induced internal shoulder rotation, while in the elbow joint, it mostly led to elbow flexion (Figure 2)

Individual predictors of PSS

Comparisons of the patient groups without and with PSS were carried out individually for categorized and scaled parameters. All patients with PSS (100.0%)

Table 2. Severity of increased Velocity-dependent muscle tone (PSS) using REPAS.

n (%)			REPAS 1–3	REPAS 4–10	REPAS >10
Arm	Right	12 (35.3)	4 (11.8)	6 (17.6)	2 (5.9)
	Left	22 (64.7)	9 (26.5)	9 (26.5)	4 (11.8)
	All	34 (100)	13 (38.3)	15 (44.1)	6 (17.6)
Leg	Right	9 (26.5)	3 (8.8)	5 (14.7)	1 (2.9)
	Left	12 (35.3)	6 (17.6)	4 (11.8)	2 (5.9)
	All	21 (61.8)	9 (26.5)	9 (26.5)	3 (8.8)

REPAS: the Resistance to Passive movement Scale; PSS: post-stroke spasticity

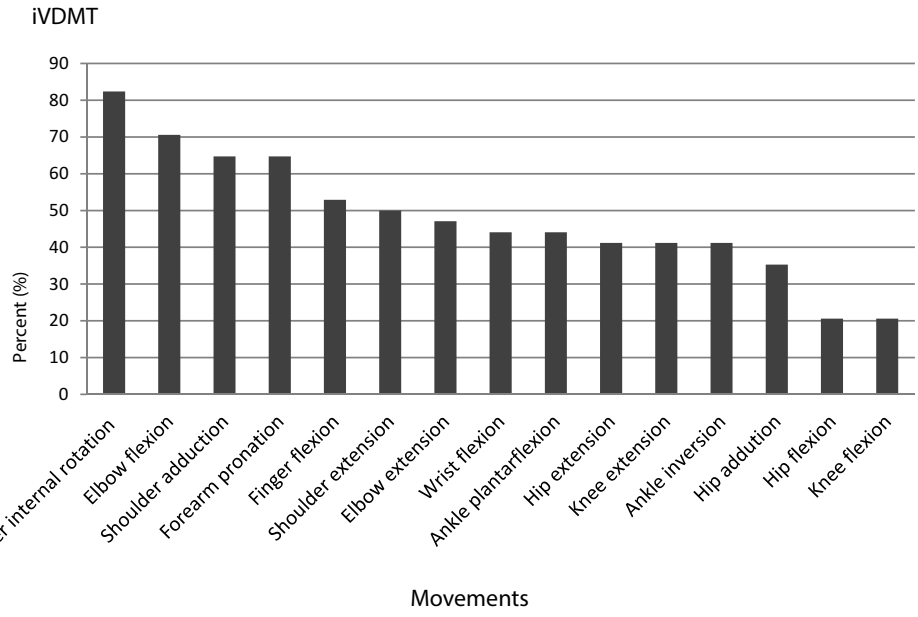


Figure 2. Movements affected by increased velocity-dependent muscle tone (post-stroke spasticity).

exhibited paralysis, whereas only 36.0% of those without PSS were affected by it (Table 3). In addition to the paresis criterion (complaints of patients and BMRC as well as NIHSS item 4 and 5), other clinical manifestations were revealed to be differently prevalent in a significant manner in patients with PSS versus those without, namely at least one disorder of cerebral nerves, increased reflexes, and positive Babinski sign in clinical examination. The following parameters such as NIHSS (National Institutes of Health Stroke Scale), MRS (Modified Rankin Scale), BI (Barthel Index), AROM (Active Range of Motion), BMRC (British Medical Research Council Scale for Muscle Strength), MMSE (Mini-Mental State Examination), SCP (Scale for Contraversive Pushing), CBS (Catherine Bergego Scale for Neglect in everyday life), AHAs (Arm-Hand Activity scale), ET (Esslinger Transfer Scale), as well as FAC (Functional Ambulation Category) were also significant differences between patients groups with and without PSS (Table 3).

Binary logistic regression analysis of significant PSS predictors

The binary logistic regression analysis revealed the following parameters as significant independent PSS predictors: high MRS (Exp(ß): 2.719, $p < 0.01$), high NIHSS (Exp(ß): 1.572, $p < 0.01$) and low MMSE (Exp(ß): 0.704, $p < 0.01$).

Table 3. The distribution of paresis and clinical parameters in patients with/without PSS.

Motor deficit			all	no PSS	PSS	p
Monoparesis	Arm	Left	6 (4.1)	4 (3.6)	2 (5.9)	<0.01[b]
n (%)		Right	9 (6.2)	4 (3.6)	5 (14.7)	
	Leg	Left	2 (1.4)	1 (0.9)	1 (2.9)	
		Right	1 (0.7)	1 (0.9)	0 (0)	
Hemiparesis	Arm	Left	21 (14.5)	11 (9.9)	10 (29.4)	
n (%)		Right	16 (11.0)	10 (9.0)	6 (17.6)	
	Leg	Left	12 (8.3)	5 (4.5)	7 (20.6)	
		Right	5 (3.4)	3 (2.7)	2 (5.9)	
Tetraparesis n (%)			2 (1.4)	1 (0.9)	1 (2.9)	
Total numbers (%)			74 (51.0)	40 (36.0)	34 (100)	
BMRC			145	111	34	<0.01[c]
n, Median (IQR)			5 (3.3–5.0)	5 (4.5–5.0)	0 (0–3.3)	
Disorder of Cerebral Nerves, *n (%)*			65 (44.8)	46 (41.4)	19 (55.9)	<0.01[b]
Increased reflex, *n (%)*			15 (10.3)	6 (5.4)	9 (26.5)	<0.01[b]
Babinski sign, *n (%)*			12 (8.3)	5 (4.5)	7 (20.6)	<0.01[b]
Mean						
Median (IQR)						
MMSE, points			27.2	28.1	24.2	<0.01[c]
			28 (26–30)	29 (27–30)	26 (22–28)	
SCP, points			0.29	0.04	1.05	<0.01[c]
			0 (0–0)	0 (0–0)	0 (0–1.63)	
Neglect (CBS), points			0.48	0.12	1.87	<0.01[c]
			0 (0–0)	0 (0–0)	0 (0–0)	
MRS, grades			1.9	1.0	3.9	<0.01[c]
			1 (0–4)	1 (0–1)	4 (4–5)	
BI, points			80.9	92.3	42.5	<0.01[c]
			100 (75–100)	100 (90–100)	37.5 (19–69)	
AROM, grades			2.4	2.8	0.9	<0.01[c]
			3 (2.3–3)	3 (3–3)	0 (0–2)	
BMRC, grades			3.8	4.5	1.3	<0.01[c]
			5,0 (3.1–5.0)	5.0 (4.5–5)	0 (0–3.3)	
AHAs, grades			4.2	4.8	2.3	<0.01[c]
			5.0 (4.0–5.0)	5.0 (5.0–5.0)	1.0 (1.0–4.3)	
NHPT, seconds			55.5	34.2	125.4	<0.01[c]
			3.0 (19–65)	23 (18–31)	150 (128–150)	
Esslinger Transfer Scale, grades			0.97	0.48	2.62	<0.01[c]
			0 (0–2)	0 (0–0)	3 (2–4)	
NIHSS, points			2.9	1.2	8.6	<0.01[c]
			1(0–4.0)	0(0–1.0)	9(4.8–11.3)	
FAC, *mean ± SD, grades*			3.6 ± 1.8	4.2 ± 1.2	1.4 ± 1.7	<0.05[a]

PSS: post-stroke spasticity; BMRC: British Medical Research Council

[a]T-Test

[b]Chi-Quadrat Test

[c]Mann-Whitney-Test, IQR: interquartile range 25–75, mean ± SD: mean ± standard deviation. MMSE: Mini-Mental State Examination, SCP: Scale for Contraversive Pushing, CBS: Catherine Bergego Scale, MRS: modified ranking scale, BI: Barthel Index, AROM: Active Range of Motion, BMRC: British Medical Research Council for Muscle Strength, AHAs: Arm-Hand Activity scale, NHPT: nine hole peg test, ET: Esslinger Transfer Scale, NIHSS: National Institutes of Health Stroke Scale, FAC: Functional Ambulation Category

Red flags for clinical use

Cutoff values of statistically independent parameters were used. The combination of an MRS > 2 (Odds Ratio (OR): 56.538, 95% *CI*: 17.150–186.394), NIHSS > 2 (OR: 57.137, 95% *CI*: 15.685–208.142) and MMSE <27 (OR: 6.133, 95% *CI*: 2.653–14.178) showed a positive predictive value of 95,2% for prediction of increased velocity dependent muscle tone with a high sensitivity (94.4%) and a high specificity (93.3%). (Table 4; Figure 3a,b).

Overall, in this study 34 (23.4%) out of 145 patients who were affected by first-ever ischemic stroke developed PSS in the next 3 months.

Discussion

Our study found that 23% of stroke patients exhibited velocity-dependent increase in muscle tone as a major "positive" feature of the upper motor neuron syndrome (UMNS) defined as spasticity (Pandyan 2005),[4] with 85% displaying muscle tone increase already at an early stage, notably within the first 7 post-stroke days, whereas additionally 15% developed PSS during a post-acute stage, namely between 7 days and 3 months following stroke occurrence. In other words, the rate of PSS revealed in this study proves to be in the expected range and can not firm its early appearance in the great majority of patients.[6] In our study, PSS in upper limbs is more frequent than in low ones and left arm PSS is more often than right ones as compared to no significant difference in low limbs. PSS in shoulder and elbow was most common and nextly in forearm pronation and wrist flexion.

As shown in former epidemiological studies, we confirmed that patients with increased velocity-dependent muscle tone in the acute phase of stroke carry this to later phases of stroke. In 85% of patients (n = 29) velocity-dependent increased muscle tone was already present in the acute phase in at least one (6 patients) or more (27 patients) involved joints. Accordingly, other investigations that characterized spasticity as a Modified Ashworth Scale (MAS) greater than zero found the prevalence of PSS in the early phase to be in the range of 21 (a week after acute attack) to 24% (2 weeks after acute event).[7,10] In the literature, PSS has been reported with prevalence rates ranging from 19% to 27% for the acute post-stroke phase.[7,10,30] In the chronic phase, the prevalence rates for PSS were reported to range between 20% and 40%, depending on the specific analysis and rating scales for increased muscle tone.[30–32]

We also found that paresis could be highly predictive for PSS occurrence, given that it was observed in 100% of patients developing PSS in the first three months following stroke. However, 36% of patients without PSS also had paresis of limbs contralateral to the cerebral lesion. Therefore, the existence of paresis can be just only a precondition of PSS, but not a predictor. Actually, in other study 42.6% of patients with initial paresis due to stroke showed PSS in 6 months and they suggested that severe paresis at onset would be a strong predictor of PSS.[8] In our study, topical distribution, paresis extent and

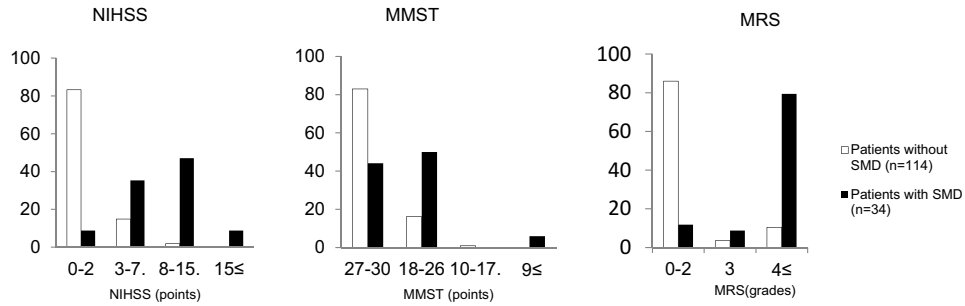
Table 4. Clinical assessments (Category) significantly correlating with post-stroke spasticity (PSS).

n (%)	Values	All	no PSS	PSS	p
MMSE	27–30	107 (73.8)	92 (82.9)	15 (44.1)	<0.01[a]
	18–26	35 (24.1)	18 (16.2)	17 (50.0)	
	10–17	1 (0.7)	1 (0.9)	0 (0)	
	≤ 9	2 (1.4)	0 (0)	2 (5.9)	
NIHSS	0–2	97 (67.0)	94 (84.7)	3 (8.8)	<0.01[a]
	3–7	27 (18.6)	15 (13.5)	12 (35.3)	
	8–15	18 (12.4)	2 (1.8)	16 (47.1)	
	15 ≤	3 (2.0)	0 (0)	3 (8.8)	
MRS	0–2	102 (70.4)	98 (88.3)	4 (11.8)	<0.01[a]
	3	6 (4.1)	3 (2.7)	3 (8.8)	
	≤4	37 (25.5)	10 (9.0)	27 (79.4)	
BI	0–30	18 (12.4)	2 (1.8)	16 (47.1)	<0.01[a]
	35–80	27 (18.6)	15 (13.5)	12 (35.3)	
	85–95	17 (11.7)	14 (12.6)	3 (8.8)	
	100	83 (57.2)	80 (72,1)	3 (8.8)	
BMRC	<4	35 (24.1)	9 (8.1)	26 (76.5)	<0.01[a]
	4	12 (8,3)	31 (28.0)	8 (23.5)	
	5	98 (67.6)	71 (64.0)	0 (0)	
AROM	0	24 (16.6)	4 (3.6)	20 (58.9)	<0.01[a]
	0 < X < 50%	4 (2.8)	1 (0.9)	3 (8.8)	
	50 ≤ X < 100%	6 (4.1)	1 (0.9)	5 (14.7)	
	100%	111 (76.5)	105 (94.6)	6 (17.6)	
AHAs	1–3	31 (21.4)	7 (6.3)	24 (70.6)	<0.01[a]
	4	7 (4.8)	5 (4.5)	2 (5.9)	
	5	107 (73.8)	99 (89.2)	8 (23.5)	
ET	2–4	43 (29.7)	16 (14.4)	27 (79.4)	<0.01[a]
	1	10 (6.9)	8 (7.2)	2 (5.9)	
	0	92 (63.4)	87 (78.4)	5 (14.7)	
FAC	0–3	52 (35.9)	22 (19.8)	30 (88.2)	<0.01[a]
	4	19 (13.1)	19 (17.1)	0 (0)	
	5	74 (51.0)	70 (63.1)	4 (11.8)	
n		145	111	34	

PSS: post-stroke spasticity

[a]: Mann-Whitney-Test, Q2(Q1-Q3), MMSE: Mini-Mental State Examination, SCP: Scale for Contraversive Pushing, CBS: Catherine Bergego Scale, MRS: modified ranking scale, BI: Barthel Index, AROM: Active Range of Motion, BMRC: British Medical Research Council for Muscle Strength, AHAs: Arm-Hand Activity scale, ET: Esslinger Transfer Scale, NIHS: National Institutes of Health Stroke Scale, FAC: Functional Ambulation Category

a) Categories



b) Cutoff values (red flags)

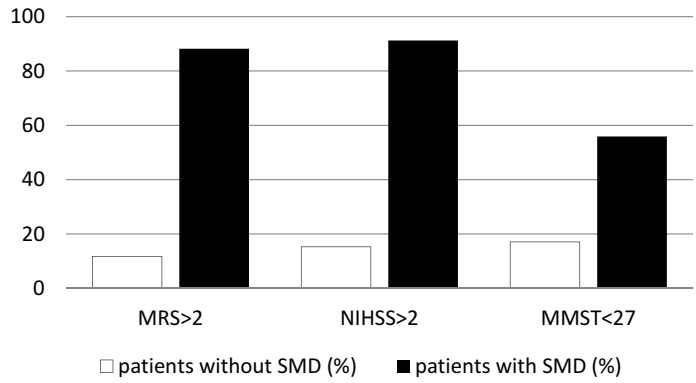


Figure 3. Statistically independent parameters correlating with post-stroke spasticity (PSS).

severity, thereby, severe affected function status from paresis were also crucial factors given that the more severe the paresis and dysfunction in clinical assessments, the higher the proportion of patients that suffer from PSS. Overall, the extent of functional impairment was shown to be a significant predictor of PSS. A high NIHSS score as expression of damaged neurological functions, in addition to low Barthel Index and high Rankin Scale score as the expression of functional limitation and impairment in everyday functions, in addition to a low MMSE score as the expression of reduced cognitive ability, was all associated with PSS occurring in the later post-stroke period. Severe stroke status is associated with their affected life quality i. e. low Barthel Index and with functional impairment i. e. high score for modified Rankin scale and these were often associated with the development of PSS.[8,10,18]

Concerning the individual possible predictors of PSS, certain scores were shown to differently represent the patient proportions with or without PSS (Table 4 and Figure 3). In summary, patients with severe functional impairment as suggested by high NIHSS, MRS and low MMSE, BMRC, BI scores had the highest risk of developing PSS. For instance, when applying the standard scales for neurological post-stroke outcome an NIHSS score greater than 2 was obtained for only 15.3% of patients without PSS versus 91.2% of those with PSS, respectively. On the other hand, an MRS of >2 was recorded for only 11.7% of patients without PSS versus 88.2% of those with PSS.

The MMSE is a clinical assessment of cognitive impairment. In this study, we found most of patients with PSS showed lower scores in the MMSE than without PSS as well as severe functional impairments and we assume that lower

MMSE, when accompanied with high functional impairment can be a strong predictor. We assume concurrently affected MMSE and functional impairment represent a sign of larger cerebral lesions than affected functions alone and therefore it was more correlated with the development of PSS.[20]

Although many studies have recommended different clinical predictors for PSS, there is no confirmation which predictors are better and what their reference values are for the prediction. The study confirms severe affected parese[7–10,17,18,33] as well as poor functional outcome[34,35] as the suspected risk factors of PSS which were suggested in the previous studies. In other studies, poor functional post-stroke status was also shown to be significantly associated with PSS.[7,8,10,32] Paresis was seen as the most relevant predictor,[7–10,17,18,32] as well as a low Barthel index,[7,8,32] or a poor physical care level.[7]

The proposed risk factor hemihypesthesia[8] was not confirmed in the study.

Taken together in this study, the routinely used clinical stroke scales NIHSS and MRS in combination with MMSE allow the positive prediction of patients of high risk for PSS. Using the cutoff values NIHSS greater than 2, MRS greater than 2 and MMSE lower than 27 allows predicting PSS with a positive predictive value of over 95%. These patients could be early identified[1] and would then potentially receive tailored antispastic treatment already in the acute stage. The early treatment with botulinum toxin A and physical measures (occupational therapy, physiotherapy, splints, orthosis) might not prevent PSS, but may prevent secondary complications like severe pain, contractures and even support functional recovery following stroke.[14–16,36]

The most common PSS pattern was internal shoulder rotation, followed by shoulder adduction and flexion in the elbow joint. The fingers and lower extremities were affected less frequently. This reflects examinations of the chronic phase, where the shoulder joint is most frequently affected in adduction and internal rotation and the elbow joint in flexion.[13] Therefore, in the acute phase of stroke, the clinical assessment of velocity-dependent increase of muscle tone should cover also the proximal limb segments (shoulder and arm) and should not be restricted to pronation/supination, wrist, and fingers.

Our current investigation has certain limitations. The study cohort is relatively small due to the prospective study design, the extensive and time-consuming clinical examination and follow-up period. In this context, the exclusion criterion pertaining to severely affected patients who were not able to provide their consent for cognitive reasons, as stipulated by the clinical protocol, resulted in this patient population being discarded from our analysis population. Acute neurological status at their admission was collected and no more evaluation at the baseline (≤7 days) was performed so that the prevalence of several neurologic symptoms such as Babinski sings and increased reflex, which could be often negative at admission, was low.

At baseline, seven patients showed pain in different topics (injuries at stroke onset, disc herniation, rheumatic diseases, etc.) and severity levels with 1–3/10 of visual analogue scale. Especially when pain is located in the paretic limb and exaggerated when moving the limb, e.g., shoulder joint, this could represent different pathologies and is not easy to differentiate especially in the early stage following stroke. Our findings are in line with other studies[37]; however, we did not evaluate, differentiate, and elaborate on pain in the different topics (stretch-induced, nociceptive and neuropathic pain) and in its correlation to PSS at follow-up. As this is an interesting field of research, we would suggest to initiate further epidemiological studies on pain in the early phase following stroke. Additionally, we discussed no rehabilitation intervention between baseline and follow-up visits.

A particularly positive aspect of the current study is that a large number of potential predictive factors were simultaneously investigated in a prospective manner. Both the pre-hospital status including care level and aids, known cardiovascular risk factors, and standard stroke scales, as well as an extended functional clinical examination of patients were all considered in the analysis. The individual predictive parameters that were found to be significant could thus be entered into the multivariable analysis to check for their independence.

Conclusion

Besides the detection of velocity-dependent increase in muscle tone itself, the common clinical

stroke scales in the early phase following stroke such as the modified Rankin Scale, the National Institute for Health Stroke Scale, and Mini-Mental State Examination will allow to identify patients who carry a high risk for post-stroke spasticity (PSS) in the hyperacute phase following stroke. This will allow the earlier introduction of specific antispastic management including physical measures and botulinum toxin A therapy to yield better outcome of rehabilitation and avoid complications of PSS like contractures, pain and therefore improve quality of life following stroke in up to 40% of stroke survivors.

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