

Stroke Severity, Its Correlates and Impact on Thrombolysis in a Population-Based Study

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Key Words

Stroke severity · Demographics · Etiology · Stroke epidemiology · Thrombolysis

Abstract

Objective: Data about the distribution of stroke severity and its correlates are sparse. In a population-based approach, we determined the NIH Stroke Scale Score (NIHSS) and studied associations with demographic variables, stroke unit care, etiology, the onset assessment interval (OAI), and the rate of thrombolysis. **Methods:** We performed a databank-based post-hoc analysis of data ascertained during the prospective, population-based stroke study among the 188,015 permanent residents of Basel City, Switzerland. **Results:** In 246/269 (91.4%) patients, NIHSS was available. The median NIHSS was 5.0 ± 6.0 . NIHSS 0–6, 7–15, and >15 were present in 156 (63%), 56 (23%), and 34 (14%) patients. Higher NIHSS were associated with advancing age ($p = 0.038$), female gender ($p = 0.04$), stroke unit treatment ($p = 0.003$), cardioembolism ($p < 0.001$), shorter OAI ($p = 0.009$), and thrombolytic therapy ($p < 0.001$). In multivariate regression analyses, age, OAI, and thrombolysis correlated independently with higher NIHSS. Stroke unit patients differed from non-stroke unit patients in shorter OAI, younger age, and higher NIHSS. **Conclusion:** In a geographically defined stroke population, 1/3 patients had moderate-to-severe

stroke. Patients with less severe strokes were younger, sought medical attention later and were less likely to receive thrombolysis. Thus, public stroke awareness programs might consider targeting also younger individuals and stress that also mild-to-moderate strokes benefit from emergency medical care.

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Introduction

Stroke severity as quantified with the NIH stroke scale score (NIHSS) predicts functional outcome after 3 months [1, 2], length of stay [3] and discharge destination [4] in patients with acute ischemic stroke. In addition, NIHSS has been reported to determine time to admission [5–9] and the likelihood of clinical deterioration [10]. In turn, stroke severity seems to be influenced by stroke etiology [11], age [12], and gender [13]. Thus, there are several potential correlates of stroke severity. The aforementioned studies assessed patients admitted to hospitals; population-based data about stroke severity are, however, sparse [14]. Furthermore, studies incorporating the search for correlates of stroke severity in a geographically defined population meeting current standards for epidemiological studies [15] are missing to the best of our knowledge.

Compared to hospital-based studies, a population-based approach enables more realistic estimates about the distribution of the stroke severity among the permanent residents of a community. In turn, an epidemiological study is more labor-intensive. The question whether a stroke unit subgroup is representative for the epidemiological sample is thus of main interest. Epidemiological data are crucial for the planning of acute stroke treatment processes, rehabilitation facilities and the allocation of resources. Furthermore, the thorough search for correlates of stroke severity clarifies whether acute treatment variables such as type of initial stroke care provider, thrombolysis, or onset assessment interval (OAI) are independently associated with stroke severity. Knowledge about the interaction of these variables with stroke severity may allow to optimize prehospital stroke care pathways and to adapt stroke awareness programs.

With these considerations in mind, we performed an explorative, databank-based analysis of stroke severity and its potential correlates, using data obtained during a prospective, epidemiological stroke study in a geographically defined population [16].

Patients and Methods

Study Population

In a population-based approach, we assessed the distribution of stroke severity and sought for an association with demographic variables, interval from stroke onset to clinical assessment, etiology, type of stroke care provider, and thrombolysis. In detail, we performed a post-hoc analysis using the databank setup for the prospective, population-based bipartite study about the epidemiology of (1) first-ever ischemic stroke [16] and (2) aphasia due to first-ever ischemic stroke [17]. The study was restricted to first-ever ischemic strokes. Patients with transient ischemic attacks or intracranial hemorrhages were excluded [16, 17].

The Canton Basel City, Switzerland, is an urban area of 37.1 km² and has 188,015 residents (census 2002). It was considered an appropriate model for such a study due to its geographically well-defined population and the advanced degree of organized stroke care available for all inhabitants.

Multiple, overlapping sources of information were used, as suggested by Sudlow and Warlow [15]. (1) The stroke register of the local University Hospital allowed ascertaining all stroke patients on a daily basis. The University Hospital is the only regional hospital to provide stroke unit care and thrombolysis. As a policy, stroke unit treatment as well as thrombolysis is available for all stroke patients without any age restriction. (2) The register of the stroke rehabilitation unit of Basel City was used to identify all patients with in-hospital rehabilitation for acute stroke regardless of the place of acute stroke treatment. (3) All hospitals in Basel City received quarterly mailings to provide data about their stroke patients treated. (4) Concerning stroke patients who were not hospitalized, all physicians of Basel City taking care of nursing home

residents, or filling in death certificates as required by the law, were also contacted quarterly by mail to report all the stroke patients they had encountered. This approach enabled them to retrieve patients managed outside hospitals (e.g. with mild strokes) or who had died due to stroke prior to hospitalization. (5) The records of a stroke neurologist making stroke ward rounds in a near-by hospital outside Basel City were checked weekly. (6) The sole regional pediatric hospital was contacted for the sake of completeness regarding pediatric strokes. (For further details, see Gostynski et al. [16].)

The diagnosis of first ischemic stroke was verified exclusively by one experienced stroke neurologist (S.T.E.), who reviewed all available source data of the reported patients. First-ever ischemic stroke rather than recurrent one was assumed in patients fulfilling the following criteria: (1) no history of previous strokes according to the patient, his relatives or primary care physician, and (2) no previous records in the stroke registry of the stroke unit, in which all stroke data have continuously been entered since March 1995.

After ethical approval, between June 1, 2002 and May 31, 2003, 269 first-ever ischemic stroke patients were recorded prospectively among the 188,015 residents of the canton Basel City; this amounts to an overall incidence rate of 143 (95% CI 126–160) per 100,000 inhabitants [16].

Stroke Severity

Stroke severity was quantified by means of the NIHSS [18] obtained at the first clinical examination. For all stroke unit patients, the NIHSS was assessed by NIHSS-trained physicians on admission. For patients treated elsewhere, the NIHSS was assessed retrospectively by just one experienced stroke physician (S.T.E.) basing his assessment on the review of medical records and charts described by Baird et al. [19]. In 23/269 patients (8.6%) clinical data on stroke symptoms were not detailed enough to determine NIHSS, which led to the patient's exclusion from further analyses. The mean age of the latter was 83 years (± 10.3) and 19 (82%) of them were female. None of them had thrombolytic treatment or stroke unit care. NIHSS was categorized according to the TOAST publication [1]. Strokes with NIHSS of 7 or more were considered moderate-to-severe strokes.

Potential Correlates of Stroke Severity

Data on age, gender, OAI (i.e. defined as the time lag between first stroke symptoms or – in cases of unknown onset – the point in time when the patient was last seen symptom-free and the clinical assessment of stroke) [20], type of stroke care provider (dichotomized in stroke unit care vs. no stroke unit care; the latter comprised both hospitalization in all other hospitals and non-hospital stroke management), and thrombolytic treatment (intravenous or intra-arterial) was prospectively ascertained as part of the epidemiological study [16, 17]. Stroke etiology was determined applying TOAST criteria [1] by one single rater [17].

Data Analysis

The relations between NIHSS and 6 potential correlates (age, gender, OAI, stroke unit care [yes/no], thrombolysis [yes/no], and etiology according to TOAST [5 categories]) were analyzed by nonparametric tests (Spearman rho). Multivariate regression analysis was applied to detect the influence of age, gender, OAI, etiology, stroke care provider, and thrombolytic treatment on

Table 1. Clinical characteristics of patients cared for in the stroke unit versus those treated elsewhere

Clinical characteristics	All patients (n = 246)	Stroke unit patients (n = 219)	Non-stroke unit patients (n = 27)	p
Demographic data				
Age, median (\pm IQR)	78 (14.3)	77 (14)	84 (13)	<0.001
Male sex, n (%)	110 (45)	100 (46)	10 (37)	0.4
NIHSSS ^a				0.03
Median (\pm IQR)	5.0 (6.0)	5.0 (7.0)	4.0 (4.0)	
Mean (\pm SD)	7.2 (7.3)	7.6 (7.54)	4.4 (3.0)	
Stroke risk factors, n (%)				
Hypertension	170 (69)	151 (69)	19 (70)	1.0
Smoking (current)	49 (20)	47 (22)	2 (7)	0.1
Diabetes mellitus	52 (21)	45 (21)	7 (26)	0.6
Hypercholesterolemia	66 (27)	60 (27)	6 (22)	0.7
Atrial fibrillation	70 (28)	61 (28)	9 (33)	0.6
Coronary heart disease	79 (32)	67 (31)	12 (44)	0.2
Stroke unit care, n (%)	219 (89)	219 (100)	0 (0)	–
Thrombolysis, n (%)	14 (5.7)	14 (6.4)	0 (0)	–
Onset–assessment interval, h ^c				
Median (\pm IQR)	20 (55)	18 (37)	99.5 (293.5)	<0.001
Range	1–1,008	1–996	3–1,008	
<3 h, n (%)	41 (17)	40 (18)	1 (4)	
<6 h, n (%)	66 (27)	65 (30)	1 (4)	
Stroke etiology ^b				
Cardioembolism	85 (35)	77 (35)	8 (30)	0.7
Large-artery atherosclerosis	31 (13)	31 (14)	0 (0)	0.03
Small-vessel occlusion	38 (15)	31 (14)	7 (26)	0.2
Other determined	23 (9)	23 (11)	0 (0)	0.09
Undetermined	69 (28)	57 (26)	12 (44)	0.07

^a Refers to National Institutes of Health Stroke Scale score [18]. ^b According to the TOAST classification [1].
^c Onset–assessment interval is defined as time interval in hours between stroke onset (or time patient was last seen without symptoms) until clinical stroke assessment took place. In 1 patient (0.4%), data were missing. IQR = Interquartile range.

NIHSS and to account for potentially confounding variables. In order to avoid a potential bias, these regression analyses were thereafter performed for the (1) the subgroup of patients with NIHSS <4, and (2) for the subgroup who had stroke unit care. For all statistical tests, $p < 0.05$ (2-sided) was considered significant. Analyses were performed using the SPSS statistical package (SPSS for Windows, version 14) [21]. Data are indicated as median \pm interquartile range (IQR), unless stated otherwise.

Results

Study Population and Stroke Severity

Our geographically determined study population comprised 246 patients. The median age was 78 (IQR \pm 14.3) years; 110 (45%) patients were male. Table 1 summarizes the baseline characteristics. NIHSS ranged from 0 to 42 with a median of 5.0 (\pm 6.0). NIHSS 0–6

were present in 156 (63%) patients; 56 (23%) patients had NIHSS 7–15 and 34 (14%) NIHSS >15 (fig. 1).

Correlates of Stroke Severity

Higher NIHSS was associated with advancing age ($p = 0.038$). Patients aged <65 had a median NIHSS of 3.5 (\pm 4.0) compared to 5.0 (\pm 8.0) for those aged ≥ 65 ($p = 0.048$). Women had a higher median NIHSS (6.0 \pm 8.0) than men (4.0 \pm 5.0) ($p = 0.04$). Table 2 summarizes the distribution of stroke severity according to gender and age considering the demographic distribution of the population in Basel City.

Higher NIHSS were associated with shorter OAI ($p = 0.009$). Patients with NIHSS 0–6 presented within (median) 24 (\pm 75) h, those with NIHSS 7–15 within 15 (\pm 25) h, while those with NIHSS >15 presented within 5.5 (\pm 22.75) h ($p = 0.005$). Only 16/156 (10.3%) of the

Table 2. Distribution of stroke severity among patients with first-ever ischemic stroke (FEIS) according to gender and age categories taking into account the demographic distribution of the population in Basel City, Switzerland

Age	Males		Females		Total	
	n/N	NIHSS median (IQR)	n/N	NIHSS median (IQR)	n/N	NIHSS median (IQR)
≤64 years	27/74,444	3.0 (3.0)	17/74,698	5.0 (5.0)	44/149,142	3.5 (4.0)
65–74 years	32/7,958	3.0 (5.0)	27/10,782	5.0 (5.53)	59/18,740	4.0 (5.0)
75–84 years	35/5,059	4.0 (5.5)	59/9,173	7.0 (9.5)	94/14,232	6.0 (8.0)
85+ years	16/1,509	4.0 (4.25)	33/4,392	6.0 (9.0)	49/5,901	5.0 (8.0)
Total	110/88,970	4.0 (5.0)	136/99,045	6.0 (8.0)	246/188,015	5.0 (6.0)

n = Number of first-ever ischemic stroke patients, derived from Gostynski et al. [16]; N = number of population in each age category, derived from Gostynski et al. [16]; NIHSS = National Institute of Health Stroke Scale score [18]; IQR = interquartile range.

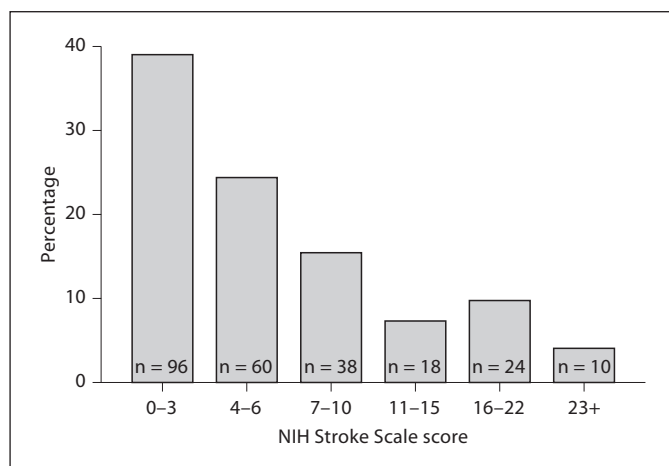


Fig. 1. Distribution of stroke severity among stroke patients in Basel City. NIH stroke Scale score refers to the National Institute of Health Stroke Scale score [18].

group with NIHSS 0–6 presented within 3 h compared to 15/34 (44%) of the patients with NIHSS >15.

NIHSS differed across stroke etiologies ($p < 0.001$). Cardioembolic strokes had higher median NIHSS (7 ± 13) than non-cardioembolic strokes (4 ± 5 ; $p < 0.01$). 219/246 (89%) of the stroke patients were treated in a stroke unit. Stroke unit patients differed from those treated elsewhere in a higher rate of thrombolysis (6.4 vs. 0%), higher median NIHSS (5 ± 7 vs. 4 ± 4 ; $p = 0.03$), shorter OAI (18 ± 37 vs. 99.5 ± 293 h; $p < 0.001$) and younger age (77 ± 14 vs. 84 ± 13 ; $p < 0.001$) (table 1).

Multivariate regression analysis with demographic variables, treatment, OAI, stroke unit care, and etiology in the model revealed that older age ($p = 0.02$), shorter OAI ($p = 0.04$), and thrombolytic treatment ($p < 0.001$) were significantly associated with higher NIHSS, while the other variables were not.

Our administration of thrombolysis in 14 of 188,015 inhabitants within 1 year amounts to a thrombolysis rate of 7.5 per 100,000 population (95% CI 4.1–12.2).

Multivariate regression analysis with demographic variables, treatment, OAI, stroke unit care, and etiology in the model revealed that older age ($p = 0.02$), shorter OAI ($p = 0.04$), and thrombolytic treatment ($p < 0.001$) were significantly associated with higher NIHSS, while stroke care provider ($p = 0.13$) and stroke etiology ($p = 0.08$) were not.

Even after excluding all patients with NIHSS <4 ($n = 96$), thrombolytic treatment remained independently related to higher NIHSS ($p = 0.005$) and shorter OAI ($p = 0.015$). If only patients with stroke unit care were analyzed, still thrombolytic treatment ($p < 0.001$), older age ($p = 0.04$), and OAI ($p = 0.019$) were independently associated with thrombolytic treatment.

Discussion

The following main observations about stroke severity and its correlates for this geographically defined epidemiological population could be made: firstly, only one third of the patients had moderate-to-severe strokes. Sec-

only, advanced age, shorter OAI and thrombolytic treatment were independently associated with higher stroke severity. Thirdly, the stroke unit subgroup cannot be considered an adequate model for epidemiological questions.

The novel approach of this study was the combined assessment of the distribution of stroke severity together with its correlates in an epidemiologically defined population; thereby both stroke patients admitted to different kinds of hospitals and those managed at home were included [16].

One of 3 stroke patients had moderate-to-severe strokes, while the others had milder strokes. This ratio confirms and refines previous study results [14] of a mean NIHSS of 6 for an epidemiological population which, however, included hemorrhagic strokes as well. The assessment of the distribution of stroke severity is a prerequisite allowing to evaluate a possible increase of the rate of thrombolysis when thrombolysis is used in milder strokes as well [22].

The finding that older age is associated with higher NIHSS quantifies earlier observations stating that older stroke patients have a higher rate of coma, paralysis, and dysphagia [12], incontinence and dysphasia [23], or more total anterior circulation infarcts [24] than younger ones.

The observation that patients with more severe strokes sought medical attention earlier than individuals with less severe stroke confirms previous studies [5–9] among hospitalized patients. Furthermore, our data clarified that the inverse relation between stroke severity and delay to medical assessment is not restricted to patients treated in hospitals [5–8] or stroke units [9], but is extendable to the entire community.

Thrombolysed patients had more severe strokes than stroke patients without thrombolytic treatment. This association is explained by a measurable deficit which is at the same time a requirement for thrombolysis. In addition, it may reflect a reluctance to use thrombolysis in less severe stroke patients [25, 26]. However, the approach not to treat the latter is questionable considering the following observations: Firstly, one third of patients with mild stroke and therefore not considered for thrombolysis had an unfavorable outcome [25]. Secondly, of the 19 patients with mild stroke who received thrombolysis all had a favorable course and symptomatic intracranial hemorrhages did not occur, except for one case [27]. Recently, an expert panel suggested to use thrombolytic treatment in patients with NIHSS of ≥ 2 or 3 [22].

In our geographically defined population, thrombolytic treatments for stroke patients amount to 75 throm-

bolytic treatments per 1 million inhabitants a year. The 95% CI indicates that the rate may range from 41 to 122 thrombolytic treatments. These estimates are in line with the thrombolysis rates for some Scandinavian countries obtained by the SITS-MOST registry [28]. From a public health point of view, these data may help to plan further acute stroke care facilities within the community.

More than 8 of 10 patients in our epidemiologically defined population had stroke unit treatment. Stroke unit patients and those treated elsewhere differed significantly in stroke severity and other variables (e.g. age, OAI, thrombolysis rate). Therefore, the stroke unit subgroup cannot be considered exemplary for approximate findings for the entire stroke population.

Half of the stroke patients presented later than 20 h after onset. The subgroup of non-stroke unit patients sought medical attention even later – half of them later than 4 days. These long OAIs indicate the need for more sustained public information, taking into account that late presentation was the most important barrier to thrombolysis [20].

As a limitation, we performed a post-hoc analysis of a stroke register data set. Though most variables were prospectively ascertained, in some patients the NIHSS was either retrospectively determined or could not be determined at all. The latter group of patients was older and had a higher female percentage than the group with analyzable data. These methodological limitations may reduce the reliability of our findings. Due to the small rates of missing (23/269; 8.6%) or retrospectively determined (15/246; 6.1%) NIHSS our main findings are unlikely to be caused by methodological bias. Moreover, no data on recurrent stroke were ascertained, but only such on first ischemic stroke. Although, this approach may be debatable, it still is in line with other epidemiological stroke studies [29, 30].

In conclusion, in this geographically defined stroke population, one of three patients had moderate to severe strokes. Patients with less severe strokes were younger, sought medical attention later and were less likely to receive thrombolysis. Thus, public stroke awareness programs might consider targeting younger individuals and emphasize that mild to moderate strokes benefit from emergency medical care, too.

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