

# Predictors of early mortality after acute ischaemic stroke

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## Summary

**Background:** The study set out to identify clinical, laboratory and radiological predictors of early mortality after an acute ischaemic stroke (AIS) and to analyse medical and neurological complications that caused death.

**Methods:** A total of 479 consecutive patients (mean age 63 ± 14 years) with AIS underwent stroke examination and treatment. Examination included clinical evaluation, laboratory tests, and brain CT and/or MRI. Follow-up data at 30 days were available for 467 patients (93%) who were included in the present analysis.

**Results:** The median National Institute of Health Stroke Study (NIHSS) score on admission was 6. A total of 62 patients (13%) died within 30 days. The cause of death was the initial event in 43 (69%), pneumonia in 12 (19%), intracerebral haemorrhage in 9 (15%), recurrent stroke in 6 (10%), myocardial infarction in 2 (3%), and cancer in 1 (2%) of the patients.

In univariate comparisons, advanced age ( $p < 0.001$ ), hypertension ( $p = 0.013$ ), coronary dis-

ease ( $p = 0.001$ ), NIHSS score ( $p < 0.001$ ), undetermined stroke etiology ( $p = 0.031$ ), relevant comorbidities ( $p = 0.008$ ), hyperglycemia ( $p < 0.001$ ), atrial fibrillation ( $p < 0.001$ ), early CT signs of ischemia ( $p < 0.001$ ), dense artery sign ( $p < 0.001$ ), proximal vessel occlusion ( $p < 0.001$ ), and thrombolysis ( $p = 0.008$ ) were associated with early mortality. In multivariate analysis, advanced age (HR = 1.12; 95% CI 1.05–1.19;  $p < 0.001$ ) and high NIHSS score on admission (HR = 1.15, 95% CI 1.05–1.25;  $p = 0.002$ ) were independent predictors of early mortality.

**Conclusions:** We report 13% mortality at 30 days after AIS. More than two thirds of the deaths are related to the initial stroke. Advanced age and high NIHSS score are the only independent predictors of early mortality in this series.

**Key words:** acute stroke; predictors; early mortality; outcome

## Introduction

Despite significant achievements in the acute management and treatment of stroke, it remains the third leading cause of death in industrialised countries [1, 2]. Nowadays, up to 10% of patients with an acute ischaemic stroke die within 30 days of the ictus [3]. The identification of early mortal-

ity predictors is of paramount importance for clinicians, so that specific therapies and management strategies can be applied to patients at high risk of dying. However, only limited information is available for predictors of short-term mortality after acute ischaemic stroke [3–7].

## Patients and methods

Consecutive patients who presented within 24 hours after symptom onset to our University Hospital-based stroke center with a first-ever acute ischaemic stroke were prospectively included from October 2003 to May 2007. The local ethics committee approved the study.

Ischaemic stroke was diagnosed when neurological deficits were accompanied by corresponding abnormal

findings depicted on brain computed tomography (CT) and/or magnetic resonance imaging (MRI).

Patients with symptoms that had completely resolved within 24 hrs (TIAs) were excluded.

Baseline clinical investigations included neurological and physical examinations, routine blood analyses, and 12-lead ECG. Stroke severity on admission was assessed with

the National Institute of Health Stroke Scale (NIHSS) [8]. Stroke etiology was classified using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria [9].

After initial clinical evaluation, patients underwent nonenhanced CT followed by CT angiography (n = 229), or multimodal MRI including axial T1-, T2-, and intermediate-weighted SE images, diffusion-weighted images (DWI), perfusion-weighted images (PWI), time-of-flight magnetic resonance angiography (TOF-MRA), and gadolinium diethylenetriamine penta-acetic acid enhanced T1-weighted images (n = 234), or both CT and MRI (n = 16).

One stroke neurologist who was blinded to clinical details and outcomes, retrospectively analysed the images. Early parenchymal CT signs of ischaemia were defined according to the criteria by von Kummer et al. [10]. DWI-PWI mismatch was considered present when visual inspection indicated that the volume of the perfusion abnormality on the time-to-peak map exceeded the volume of diffusion abnormality on the b = 1000 image by 20% or more. Vessel occlusions at the time of initial CT angiography, TOF-MRA or digital subtraction angiography were classified into:

1. Proximal: a) Internal carotid artery (ICA), b) M1 and M2 segments of the middle cerebral artery (MCA), c) A1 segment of the anterior cerebral artery (ACA), d) V4 segment of the vertebral artery (VA), e) basilar artery (BA), and f) P1 segment of the posterior cerebral artery (PCA)

2. Distal: the more distal branches of the MCA, ACA, and PCA, as well as cerebral infarcts with no visible vessel occlusions.

Further diagnostic examination was left to the discretion of the treating physician and included transoesophageal or transthoracic echocardiography (TEE or TTE), 24-hours ECG, laboratory screening for cerebral vasculitis, thrombophilia, and carotid ultrasound imaging.

The following stroke risk factors were assessed: age; gender; hypertension (defined as a history of antihypertensive treatment or a history of hypertension – systolic

blood pressure [BP] >140 mm Hg, diastolic BP >85 mm Hg, or both –); diabetes mellitus (defined by preadmission history or venous plasma glucose concentration of  $\geq 7.0$  mmol/l after an overnight fast on at least two separate occasions, and/or  $\geq 11.1$  mmol/l two hours after the ingestion of 75 g of oral glucose and on one other occasion during the 2-hour test), current cigarette smoking, hypercholesterolemia (defined by preadmission history and/or total cholesterol [TC] >5 mmol/l, and/or HDL-cholesterol <1 mmol/l, and/or LDL-cholesterol >3 mmol/l, and/or TC/HDL ratio >5), history of coronary artery disease, and positive family history of cerebrovascular ischaemic events.

Patients were treated according to European and American guidelines and recommendations for acute stroke treatment, secondary prevention and neurorehabilitation [11–13].

Information on serious medical and neurological complications and the cause of death was obtained prospectively from the medical records in our institution, other hospitals or nursing homes where the patients were discharged to, or the family physician. All deaths occurring within 30 days after stroke were classified as due to stroke, unless an undeniable other cause of death (myocardial infarction, malignancy, car accident, etc.) was the obvious cause of death [14].

### Statistical analysis

Quantitative data are expressed as mean values  $\pm$  standard deviation. The NIHSS score for each patient at admission is given as a median value. Data are reported in frequency tables. Differences between groups and the effect of patient characteristics on clinical outcome were assessed using the Fisher Exact test (for comparison of proportions), Student's *t* test (for comparison of continuous variables), and the Mann-Whitney *U* test (for comparison of ordinal variables). The Cox proportional-hazards survival regression, which included variables that showed statistical difference  $p \leq 0.1$  on univariate comparison, was performed.

## Results

### Study population

During the study period, 479 patients (mean age  $\pm$  SD,  $63 \pm 14$  years; range 18 to 92 years) were admitted to our institution with a first-ever acute ischaemic stroke. There were more men than women (63% vs 37%). Of the 479 patients, 254 (53%) arrived within 3 hours, and 134 (28%) presented within 3 to 6 hours of symptom onset. Twenty-six patients (5%) underwent intravenous thrombolysis and 119 (25%) intra-arterial thrombolysis. Intravenous (<3 hours of symptom onset) and intra-arterial thrombolysis (<6 hours of symptom onset) were administered according to international guidelines and institutional protocols [15, 16]. The remaining 334 patients (70%) received either 100–300 mg acetylsalicylic acid or 75 mg clopidogrel within 24 hours after the stroke onset.

Follow-up data for mortality within 30 days were available for 467 (97%) patients. These patients were included in the following univariate and multivariate comparative analyses.

### Baseline clinical characteristics

Table 1 shows the baseline clinical characteristics of the 467 patients with first-ever acute ischaemic stroke. Hypertension was the most prevalent vascular risk factor (64%), followed by hypercholesterolemia (55%), coronary artery disease (34%), current cigarette smoking habit (32%), positive family history of cerebrovascular ischaemic events (30%), and diabetes mellitus (14%).

The median NIHSS score was 6 (range 1–38).

Seventy-four percent of all strokes were localized in the distribution of the carotid arteries. The remaining 26% were localised in the vertebro-basilar circulation.

The identified causes of stroke were cardiac embolism in 33%, large artery arteriosclerosis in 14%, small vessel disease in 10%, other determined etiologies in 11%, and multiple causes in 1%. Stroke etiology remained undetermined in 30% of cases despite extensive examination.

**Table 1**

Presenting clinical characteristics of 467 patients with a first-ever ischaemic stroke.

Characteristics, n (%)	Survivors (n = 405)	Deceased within 30 days (n = 62)	p-value
Male gender	259 (64)	37 (60)	0.51
Mean age, yr (SD)	61 (14)	74 (10)	<0.001
Vascular risk factors			
Hypertension	251 (62)	50 (80)	0.013
Diabetes mellitus	51 (13)	14 (23)	0.069
Hypercholesterolemia	223 (55)	33 (54)	0.86
Current cigarette smoking	134 (33)	14 (23)	0.27
History of coronary artery disease	124 (31)	35 (57)	0.001
Positive familial history	117 (29)	23 (38)	0.48
Median NIHSS score (range)	6 (1–38)	14 (1–38)	<0.001
Stroke location			
Carotid artery territory	298 (74)	46 (74)	0.92
Vertebrobasilar territory	107 (26)	16 (26)	0.92
Stroke etiology			
Large artery atherosclerosis	59 (15)	7 (11)	0.49
Cardiac embolism	131 (32)	24 (39)	0.32
Small vessel disease	44 (11)	2 (3)	0.06
Other determined	49 (12)	3 (5)	0.09
Undetermined	115 (28)	26 (42)	0.031
Multiple causes	7 (2)	–	0.3
Charlson index, median (range)	0 (0 to 6)	1 (0 to 15)	0.008

SD: standard deviation.

NIHSS: National Institutes of Health Stroke Scale.

**Table 2**

Ancillary Examinations and Thrombolysis in 467 patients with a first-ever ischaemic stroke.

Characteristics	Survivors (n = 405)	Deceased within 30 days (n = 62)	p-value
Blood glucose on admission, mean (SD), mmol/l	7.1 (2.3)	8.1 (2.1)	<0.001
BP on admission, mean (SD), mm Hg			
Systolic	155 (25)	160 (31)	0.38
Diastolic	80 (16)	84 (16)	0.11
Atrial fibrillation, n (%)	62 (14)	25 (40)	<0.001
Early parenchymal CT signs of ischemia <sup>1</sup>	81 (41)	26 (79)	<0.001
Dense artery sign	32 (15)	18 (54)	<0.001
DWL/PWI mismatch <sup>2</sup>	85 (39)	15 (45)	0.49
Proximal vessel occlusion	148 (37)	43 (70)	<0.001
Thrombolysis			
Intra-arterial	93 (23)	24 (39)	0.008
Intravenous	21 (5)	5 (8)	0.36
Symptomatic intracerebral haemorrhage after thrombolysis	6 (5)	8 (28)	<0.001

<sup>1</sup> From 245 patients who underwent CT and CT angiography.<sup>2</sup> From 250 patients who underwent MRI and MR angiography.**Baseline ancillary examinations**

Table 2 gives the results of the baseline ancillary examinations. The mean blood glucose on admission was  $7.24 \pm 2.3$  mmol/l. The mean systolic BP at presentation was  $156 \pm 26$  mm Hg, and the diastolic BP was  $81 \pm 16$  mm Hg. Atrial fibrillation was diagnosed in 44 patients (9%). Early parenchymal CT signs of ischaemia were present in 107 of 245 patients (44%), who underwent CT and CT angiography on admission. A dense artery sign was visualised in 40 CT scans (16%). Among the 250 patients who underwent an MRI and MRA, a DWI/PWI mismatch was present in 100 (40%) patients. Overall, 191 patients (41%) showed a proximal vessel occlusion on CT and/or MR angiography.

**Early mortality**

Sixty-two patients (13%) died within 30 days of their first stroke. The cause of death was the initial event in 43 of 62 patients (69%), pneumonia in 12 (19%), intracerebral haemorrhage in 9 (15%), recurrent stroke in 6 (10%), and myocardial infarction in 2 (3%). One patient (2%) died of carcinoma of the kidney. Stroke etiology was large artery disease in 7 patients (11%), small artery disease in 2 patients (3%), cardioembolism in 24 patients (39%), other determined etiology in 4 patients (6%), and undetermined cause in 25 patients (40%).

**Predictors of early mortality**

In univariate analysis, advanced age ( $p < 0.001$ ), hypertension ( $p = 0.013$ ), coronary artery disease ( $p = 0.001$ ), high NIHSS score on admission ( $p < 0.001$ ), undetermined stroke etiology despite extensive diagnostic examination ( $p = 0.031$ ), relevant comorbidities as measured with the Charlson index ( $p = 0.008$ ), hyperglycaemia on admission ( $p < 0.001$ ), atrial fibrillation ( $p < 0.001$ ), early parenchymal CT signs of ischaemia ( $p < 0.001$ ), dense artery sign ( $p < 0.001$ ), proximal vessel occlusion as seen on CT or MR angiography ( $p < 0.001$ ), and intra-arterial thrombolysis ( $p = 0.008$ ) were associated with early mortality.

Cox-proportional hazards survival regression revealed advanced age and a high NIHSS on admission as independent predictors of early mortality (table 3).

**Table 3**

Independent predictors of early mortality in 467 patients with first-ever ischaemic stroke.

Variable	Hazard ratio	95% CI	p-value
Advanced age	1.12	1.05–1.19	<0.001
High NIHSS on admission	1.15	1.05–1.25	0.001

## Discussion

In this sample of 467 patients, 13% died within 30 days of their first-ever stroke. The initial event was by far the most common cause of death (69% of patients). Other causes were pneumonia (19%), intracerebral haemorrhage (15%), recurrent stroke (10%), myocardial infarction (3%), and cancer (2%). Advanced age and high NIHSS on admission were the only predictors of early mortality. These are the main results of the present study.

How does the 13% mortality rate, in this sample, rank in the light of previous studies? A recent study assessed the 30-day mortality in the original Framingham and the Framingham offspring cohorts [1]. Over a follow-up period of 50 years, 30-day mortality decreased significantly in men (from 23% to 14%), but not significantly in women (from 21% to 20%). In the present series, we did not observe gender differences in early mortality after ischaemic stroke (13% in men and 15% in women,  $p = 0.51$ ). In a study from the Department of Veterans Affairs (VA), 34 866 patients with first-ever ischaemic stroke were retrospectively identified. The authors reported 8.2% mortality at 30 days after the stroke [4]. De Jong et al. observed similar rates (10% mortality at 30 days) in 998 patients with first-ever cerebral infarction [3]. At the same time, Rothwell et al. reported a 17.2% case-fatality due to initial stroke in the Oxford Community Stroke Project (OCSP, 1981–1984) and 17.8% in the Oxford Vascular Study (OXVASC, 2002–2004) [2]. The 30-day mortality rate in this study is in the lower range of the figures reported in the literature. Our findings show a lower stroke mortality rate in Switzerland compared with other industrialised and developing countries from different parts of the world [17]. However, such a comparison is unjustified, because patients admitted to a tertiary care center are highly selected.

Several factors are known to influence early mortality. Among them, age and stroke severity have been most consistently reported. The age range of a first stroke in the Framingham and the Framingham offspring cohorts was 69–76 years in men and 69–81 years in women [1]. The study did not explicitly assess the influence of age on 30-day mortality; although a previous study from Framingham had shown that advanced age at initial stroke was independently associated with a high 30-day mortality [18]. Collins et al. grouped their patients with ischaemic stroke into five age categories: under 45 years (2.4%), 45–54 years (10.3%), 55–64 years (21.9%), 65–74 years (39.1%), and 75 years and older (26.3%) [4]. The risk factor associated with the highest hazard for a 30-day mortality was advanced age (75 years and older) (HR 4.47; 95% CI 3.03–6.60). Advanced age, along with diabetes and stroke subtype, was also an independent predictor of 30-day case fatality in the study by de Jong et al. [3]. In a recent study of 469 older patients (mean age: 80 years), 130 subjects

(27.7%) died within 30 days after stroke [7]. Multivariate logistic regression analysis indicated that short-term mortality was associated with age, altered level of consciousness and congestive heart failure. In the current sample, the mean age was 63 years in men and 64 years in women. Increasing age was significantly associated as a hazard for early mortality (HR = 1.12; 95% CI 1.05–1.19).

Stroke severity on admission is a well-established predictor of mortality. Several clinical variables that reflect the severity of the neurologic lesion have been analysed to predict the clinical outcome. Level of consciousness was the main clinical predictor of early mortality in many previous studies [19–23]. Dysphagia and body temperature have also been reported to predict 30-day mortality after stroke [24–27]. Prognostic models taking into account the severity of motor paresis are scarce. The NIHSS scale, which is a validated tool for assessing the initial stroke severity, accurately predicted the 3-month clinical outcome in previous studies [28, 29]. In the present study, the NIHSS score on admission was associated with an HR = 1.15 (95% CI 1.05–1.25) for 30-day mortality.

Low admission BP, elevated pulse pressure, elevated serum urea levels in patients with diabetes, hyperglycaemia in nondiabetic patients, and the presence of atrial fibrillation have been associated with poor clinical outcome and increased mortality 3 months after stroke onset [30–36]. In our study, hyperglycaemia on admission and the presence of atrial fibrillation were associated with a 30-day mortality in univariate but not in multivariate analysis. It may be that blood glucose levels and atrial fibrillation are related to age and/or stroke severity, thus, the effects they exert on mortality are not independent. The same is true for the association of intra-arterial thrombolysis and early mortality. With univariate analysis they are associated, after multivariate analysis not. Both mean age and median NIHSS score were significantly higher in patients who died than in survivors. This suggests that age and higher NIHSS account for the higher mortality and not thrombolysis. A history of hypertension was associated with a 30-day mortality in univariate analysis but admission BP was not. Previous studies have shown considerable variations of BP in the acute phase of ischaemic stroke [30]. Variables describing the course of BP over the first 2.5 days have a marked and independent relationship with the outcome at 30 days.

CT and early perfusion- and diffusion-weighted MRI have been shown to predict fatal outcome in patients with extensive middle cerebral artery infarction [37, 38]. One of the strengths of the present study is the extensive evaluation of our studied population with modern imaging technologies. All patients underwent CT and CT angiography and/or MRI and MR angiography. The presence of early CT signs of parenchymal

ischaemia or dense artery signs, as well as the CT- or MR-angiographic demonstration of proximal vessel occlusion were significantly associated with a 30-day mortality in univariate analysis (table 2). However, there were no independent radiological predictors of early mortality in multivariate analysis. Obviously, there is a strong correlation between stroke severity as measured with the NIHSS and the above CT and MRI findings. The relationship of proximal vessel occlusion and the NIHSS in acute stroke has been shown in a previous correlative study of the NIHSS and digital subtraction arteriography [39].

Our study has the limitation of being a hospital-based study population. Although our institution is the main stroke center for the canton of Bern and serves a catchment area for almost 1.5 million inhabitants, patients with acute ischaemic stroke included in the present study are not representative of the entire population. In particular, patients who die from their stroke before admission to our hospital have not been analysed. Furthermore, younger stroke victims are more likely

to be referred to a university-based stroke center than older patients with stroke. Consequently, our patients are approximately 10 years younger than would have been expected in a population-based study.

To summarise, the present study reports a 13% mortality rate at 30 days after acute ischaemic stroke. More than two thirds of the deaths were related to the index event. Advanced age and stroke severity on admission were the only independent predictors of early mortality, whilst the results of the laboratory investigations and brain imaging had no independent prognostic value.

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