Early and Late Mortality of Spontaneous Hemorrhagic Transformation of Ischemic Stroke

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Background: Hemorrhagic transformation (HT), a complication of ischemic stroke (IS), might influence patient's prognosis. Our aim is to evaluate, in a hospital-based series of patients not treated with thrombolysis, the relationship between HT and mortality. *Methods:* We compared mortality of individuals with spontaneous HT with that of individuals without. Medical records of patients diagnosed with anterior IS were retrospectively reviewed. Outcome measures were 30- and 90-day survival after IS onset. Kaplan–Meier estimates were used to construct survival curves. Cox proportional hazards model was used to estimate hazard ratio (HR) for the main outcome measure (death). HT was stratified in hemorrhagic infarction and parenchymal hematoma (PH). We also evaluated the relationship between HT and the main mortality risk factors (gender, age, premorbid status, severity of stroke, and radiological features). *Results:* Thirty days from stroke onset, 8.1% (19 of 233) of patients died. At multivariate analysis, PH (HR: 7.7, 95% confidence interval [CI]: 2.1, 27.8) and low level of consciousness at admission (HR: 5.0, 95% CI: 1.3, 18.6) were significantly associated with death. At 3-month follow-up, mortality rate was 12.1% (28 of 232). At multivariate analysis, large infarct size (HR: 2.7, 95% CI: 1.2, 6.0) and HT (HR: 2.3, 95% CI: 1.0, 5.4) were independent risk factors for mortality. Parenchymal hematoma was, however, the strongest predictor of late mortality (HR: 7.9, 95% CI: 2.9, 21.4). *Conclusions:* Neurological status and infarct size play a significant role, respectively, in early and late mortality after IS. Parenchymal hematoma independently predicts both early and late mortality. **Key Words:** Ischemic stroke—hemorrhagic transformation—prognosis—survival—epidemiology.

Introduction

Hemorrhagic transformation (HT) is a common complication of ischemic stroke (IS).[1] Overall stroke mortality has been widely studied.[2] Thrombolytic therapy determines a significant reduction in the proportion of patients dead or dependent in activities of daily living. This benefit seems, however, to be compensated by an increase in deaths, with most of the excess of them occurring early and explained by intracranial hemorrhage.[3] Most of the authors focused their interest on functional outcome of spontaneous HT,[4-6] and it is still uncertain how much spontaneous HT influences prognosis.[7,8]

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Table 1. *Characteristics of patients by living status at 30 and 90 days from stroke onset*

	30 d			90 d		
	Alive (n = 214)	Dead (n = 19)	*P*	Alive (n = 204)	Dead (n = 19 + 9)	*P*
Age (mean ± SD)	72.3 ± 12.1	77.2 ± 8.5	NS	72.1 ± 12.2	77.4 ± 8.8	.03
Sex (male)	112 (52.3%)	9 (47.4%)	NS	107 (52.5%)	13 (46.4%)	NS
Previous stroke	68 (31.8%)	4 (21%)	NS	65 (31.9%)	7 (25.0%)	NS
Hypertension	160 (74.8%)	12 (63.1%)	NS	153 (75.0%)	18 (64.3%)	NS
Diabetes	79 (36.9%)	5 (26.3%)	NS	75 (36.8%)	8 (28.6%)	NS
Current smoking	87 (40.6%)	9 (47.4%)	NS	84 (41.2%)	11 (39.3%)	NS
Cardioembolic stroke	64 (29.9%)	8 (42.1%)	NS	60 (29.4%)	12 (42.9%)	NS
Severe consciousness impairment	3 (1.4%)	4 (21%)	<.0001	3 (1.5%)	4 (14.3%)	.0002
Presence of early CT signs	59 (27.6%)	10 (52.6%)	.02	57 (27.9%)	12 (42.9%)	NS
Medium/large infarcts	41 (19.1%)	9 (47.4%)	.004	36 (17.6%)	13 (46.4%)	.0005
HT (HI + PH)	23 (10.7%)	6 (31.6%)	.008	20 (9.8%)	9 (32.1%)	.0008
HI	16 (7.5%)	3 (15.8%)	NS	15 (7.4%)	4 (14.3%)	NS
PH	7 (3.3%)	3 (15.8%)	.01	5 (2.5%)	5 (17.9%)	.0002

Abbreviations: CT, computed tomography; HI, hemorrhagic infarction; HT, hemorrhagic transformation; NS, not significant; PH, parenchymal hematoma.

Aims

The current retrospective cohort analysis was designed to analyze, in a hospital-based series of patients with IS not treated with recanalization therapy, the association between HT and mortality.

Materials and Methods

All consecutive patients with anterior IS admitted to our department in the period 2004-2006 were enrolled in this study. Inclusion criteria have been previously reported.[9,10] Briefly, all patients performed a baseline brain computed tomography (CT) scan within 24 hours from symptoms onset and a follow-up CT. Patients with transient ischemic attacks and cerebral hemorrhage were excluded. If living status was not determinable, patients were excluded from current analysis.

Early and late mortality were, respectively, defined as the proportion of patients who died within 30 days and 3 months after stroke onset. Data about mortality were obtained from the public record office of the municipality of Palermo or directly by telephone interview. HT was stratified in hemorrhagic infarction (HI) and parenchymal hematoma (PH).[11,12] HI was defined as a petechial infarction without space-occupying effect, and PH was defined as a hemorrhage with mass effect.[8] Together with HT, the following risk factors for mortality were investigated: gender, age, smoking (ever-smokers versus nonsmokers), previous cerebrovascular accidents (transient ischemic attack, IS, or hemorrhagic stroke), hypertension, diabetes, cardioembolic origin of stroke (classified according to the Trial of Org 10172 in Acute Stroke Treatment criteria),[13] impairment of consciousness at admission (moderate to severe versus normal to mild impairment), early CT signs (hyperdensity of middle cerebral artery, focal hypodensity consistent with the clinical picture, swelling because of developing infarction, blurring of gray matter–white matter distinction), and infarct size (medium–large infarcts versus small ones).[14]

The study has been approved by the local ethics committee.

Statistical Analysis

Clinical characteristics of patients dead or alive at 30-day follow-up were compared using χ^2 test for categorical variables and *t* test for continuous variables. Kaplan–Meier estimates were used to construct survival curves for early and late mortality. Estimates were calculated including only those who were still alive at last follow-up or if dead, whose date of death was known. The statistical difference between groups was tested with the log-rank test. Odds ratios, calculated by Cox proportional hazards analysis, were used as measure of association of poor outcome and the variables investigated (age, gender, clinical characteristics on admission, risk factors for stroke, CT findings, and HT). Multivariate analysis included the variables found significantly associated with death in the univariate analysis. Statistical analysis was performed using SAS 9.2.

Results

During the study period, 240 patients were included in the study. All patients received, together with medical therapies required by concomitant diseases, acetylsalicylic acid and subcutaneous heparin at the dosage recommended to prevent deep venous thrombosis. Living status, 1 month after stroke onset, was available for 233 of the 240 patients initially included in the study (97.1%), whereas at 3 months, 1 more patient was lost at

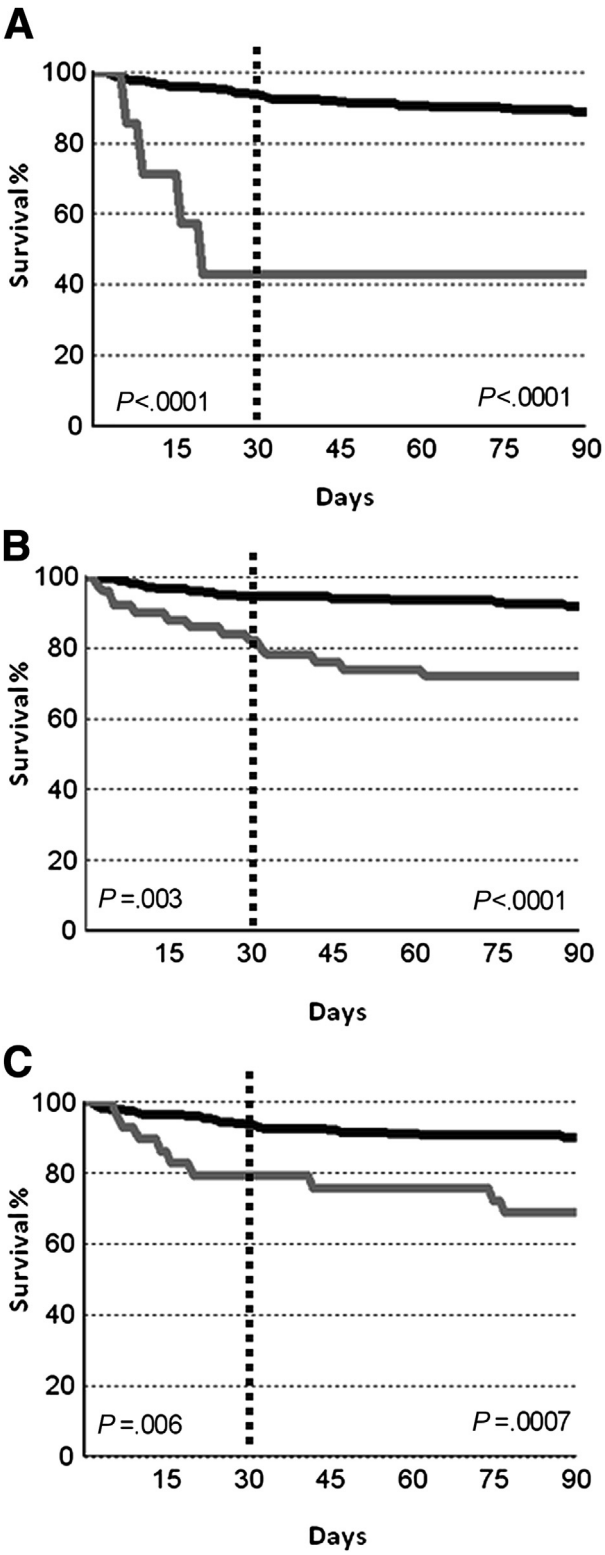

Figure 1. *Cumulative survival probability of patients stratified by impairment of consciousness, lesion size, and HT. Cumulative survival probability stratified by (A) impairment of consciousness (gray line = impairment of consciousness; black line = no impairment of consciousness); (B) lesion size (gray line = medium/large lesions; black line = small lesions); (C) HT (gray line = HT; black line = no HT)* (P *values reported at the left of the vertical line refer to mortality at 30 days, whereas those at the right of the same line refer to mortality at 90 days). Abbreviation: HT, hemorrhagic transformation.*

follow-up (232 of 240, 96.7%). HT did not occur in any of the 8 patients lost at follow-up. At 30 days from stroke onset, 19 of 233 patients died (8.1%). No significant difference was observed for age at admission, gender, and stroke risk factors between patients who died and those who were still alive 30 days from stroke onset (Table 1). Patients who died, compared with those who survived, had a significantly more severe neurological status, larger lesions, and more frequently showed early CT signs at first neuroimaging or HT at a follow-up CT scan (Table 1). A highly significant difference between strata was observed when patients were stratified according to the presence of impairment of consciousness (log-rank test: χ^2 12.22; *df* 1; $P < .0005$), size of the lesions (log-rank test: χ^2 7.09; *df* 1; $P < .008$), and the occurrence of HT (log-rank test: χ^2 5.56; *df* 1; $P < .02$) (Fig. 1). Death, at multivariate analysis, was significantly associated only with a more severe neurological deficit at admission (presence of consciousness impairment). When HT was stratified in HI and PH, HI was not associated with an increased risk of early mortality, whereas PH was associated with an almost 8-fold increased risk of death (Table 2).

At 3-month follow-up, 9 more patients had died (28 of 232, 12.1%). At multivariate analysis, larger lesions and HT were independent risk factors for late mortality.

Discussion

In our study, overall mortality was of 8.1% at 1 month after stroke onset and 12.1% at 3-month follow-up. Only PH and impairment of consciousness were independently associated with an increased risk of mortality at 30 days. Ninety days after stroke onset, individuals with larger lesions or whose IS was complicated by the occurrence of HT had a significantly increased risk of death. Neurological status was still associated with death.

Data on outcome of patients with IS complicated by the occurrence of HT derive mostly from randomized trials looking at the efficacy of thrombolysis (Table 3). A recent analysis identified 16 trials separately reporting data, both in the treated and in the control group, on fatal intracranial hemorrhage occurring within 7-10 days from thrombolysis.[3] Risk of death for intracranial hemorrhage was higher in treated patients (4.45%) compared with controls (.74%), so that most of the excess of early deaths in patients treated with thrombolysis were attributed to intracranial hemorrhage.

Thrombolysis, a proven instrument to reduce stroke severity, influences, in fact, several aspects of stroke especially the occurrence of HT.

Moreover, results of clinical trials may not be easily generalized as characteristics of enrolled participants might be different from patients not enrolled in clinical trial,[15] and therefore, not representative of the general

Table 2. *Predictors of early and late mortality: results of univariate and multivariate analysis*

	30-d mortality				90-d mortality			
	HR (95% CI)	*P*	HRa (95% CI)	*P*	HR (95% CI)	*P*	HRa (95% CI)	*P*
Age	1.0 (.99, 1.10)	NS	1.0 (.97, 1.1)	NS	1.05 (1.0, 1.1)	.03	1.03 (.99, 1.1)	NS
Gender (male)	.8 (.3, 2.1)	NS	—		.8 (.3, 1.7)	NS		
Diabetes	.6 (.2, 1.8)	NS	—		.7 (.3, 1.6)	NS		
Previous stroke	.6 (.2, 1.8)	NS	—		.7 (.3, 1.8)	NS		
Hypertension	.6 (.2, 1.5)	NS	—		.6 (.3, 1.4)	NS		
Cardioembolic stroke	1.7 (.7, 4.2)	NS	—		1.4 (.7, 3.0)	NS		
Severe consciousness impairment	12.0 (3.9, 36.3)	<.0001	5.0 (1.3, 18.8)	.01	8.2 (2.8, 23.6)	.0001	3.0 (.9, 9.9)	NS
Presence of early CT signs	2.7 (1.1, 6.8)	.03	1.8 (.7, 4.8)	NS	1.8 (.8, 3.7)	NS		
Medium/large infarcts	3.5 (1.5, 8.7)	.006	1.8 (.6, 5.5)	NS	3.9 (1.9, 8.0)	.0003	2.7 (1.2, 6.0)	.02
HT (HI + PH)	3.5 (1.3, 9.3)	.01	1.8 (.6, 5.5)	NS	3.6 (1.6, 7.9)	.002	2.3 (1.0, 5.4)	.05
No HT	Ref.		Ref.		Ref.		Ref.	
HI	2.6 (.7, 9.1)	NS	.8 (.2, 3.2)	NS	2.3 (.8, 6.7)	NS	1.0 (.3, 3.2)	NS
PH	5.6 (1.6, 19.8)	.007	7.7 (2.1, 27.8)	.002	6.6 (2.5, 17.6)	.0002	7.9 (2.9, 21.4)	<.0001

Abbreviations: CT, computed tomography; CI, confidence interval; HI, hemorrhagic infarction; HR, hazard ratio; HRa, HI and PH adjusted for impairment of consciousness, presence of early CT signs, and lesion size; HT, hemorrhagic transformation; NS, not significant; PH, parenchymal hematoma.

population, as on the contrary, it is advisable in epidemiological studies.

Interesting findings on outcome come also from stroke registries, where patients are included independently from specific characteristics and that often incorporate unbiased data coming both from academic and community hospitals and department of neurology and internal and geriatric medicine.

This is the case of the German Stroke Register Study Group (ADSR),[16] a network of regional hospital-based stroke register, monitoring quality of stroke care in Germany. The analysis of the ADSR, aimed to investigate predictors of in-hospital mortality of patients treated with recombinant tissue plasminogen activator, found that the occurrence of symptomatic intracranial hemorrhage was the second most important complications of IS predicting early mortality. Patients with symptomatic intracranial hemorrhage had a significant 8-fold increased risk of death.

The Nationwide Inpatients Sample has been investigated for mortality risk for the years 1999-2002,[17] comparing 2594 patients treated with thrombolysis with 246,370 patients not treated. Although intracerebral hemorrhage occurred in very small percentage of not treated patients (.4%), in-hospital fatality rate for intracerebral hemorrhage in this group was 25%.

Frequently, prognosis has been investigated pooling together data on functional outcome and death.

In a small sample of 53 patients with atrial fibrillation and nonlacunar stroke involving the vascular territory of the middle cerebral artery,[4] at 3-month follow-up, severe disability (using a modified Rankin scale score > 2) and death were not significantly associated with HT. However, in this series, HT was nearly 2 times more frequent in the group with worst outcome (38%) compared with those with better outcome (21%).

A larger hospital-based study,[5] including all consecutive patients with IS, reported an overall mortality rate of 7.3% within 3 months after stroke onset. The authors reported a significant correlation between symptomatic HT (defined as HT on neuroimaging with any neurological deterioration) and poor outcome (death and Rankin scale score > 2) at 3 months (odds ratio: 3.57, 95% confidence interval: 1.33-9.54).

Similar results were observed in a multicenter prospective study enrolling 1125 patients with IS.[18] Death or disability (modified Rankin scale score ≥ 3) was seen in 33 of the 36 patients with PH (91.7%), 35 of the 98 patients with HT (57.4%) as compared with 387 of the remaining patients without HT (37.9%). PH, but not HT overall, was significantly associated with an increased risk for death or disability (odds ratio: 15.3, 95% confidence interval: 2.4, 99.4).

More recently, the prospective cohort of the Helsinki Stroke Thrombolysis Registry was investigated to assess the impact of symptomatic intracerebral hemorrhage.[19] Patients with symptomatic intracerebral hemorrhage had a significant increased risk of fatal outcome that, according to the different definitions used, ranged from 1.5 to 4.8.

In our sample, early and late mortality were related to PH independently from infarct size and neurological status at admission. Although it is predictable that HT of IS might influence early mortality, it is interesting to note that still 90 days from stroke onset, individuals who

Table 3. *Results from studies reporting data on mortality of hemorrhagic*

Reference	Patients	Treatment	Outcome	Results
Toni et al[7]	150 Patients with supratentorial IS	No thrombolysis; antithrombotic/i.v. heparin for stroke treatment	By day 30, mortality rate was 16.7%, whereas 41.3% of patients were disabled	HT was not related to bad 30-d outcome (OR: .76; 95% CI: .25-2.37)
Fiorelli et al[8]	609 Patients from ECASS I trial	307 of 609 patients were treated with recombinant tPA	At 3-month follow-up, 18.4% of patients died and 49.3% were disabled (RS score $\geq$ 1)	Only patients with PH2 had a strongly increased risk of 24-hour deterioration (OR: 32.3, 95% CI: 13.4-77.7) and 3-month death (OR: 18.0, 95% CI: 8.05-40.1)
Berger et al[20]	790 Patients from ECASS II trial	Intravenous thrombolysis (406 patients) versus placebo (384 patients)	Assessment of HT type on clinical outcome	Only PH2 was associated with an increased risk for deterioration at 24 hours after stroke onset (OR: 18; 95% CI: 6-56) and for death at 3 months (OR: 11; 95% CI: 3.7-36)
Heuschmann[16]	1658 IS patients from the German Stroke Registers Study Group	All patients were treated with tPA	In-hospital mortality in patients with acute IS	ICH occurred in nearly 30% of patients who died, compared with 4.6% of those who survived (OR: 8.3, 95% CI: 5.0-13.8)
Hong et al[4]	1254 Patients with IS	Antithrombotic therapy	Death within the 3-month period of follow-up occurred in 91 patients (7.3%). 34.9% of patients had a poor outcome at 3 months (RS score 3-6)	Symptomatic HT was independently associated with poor outcome (OR: 3.57, 95% CI: 1.33-9.54)
Paciaroni et al[18]	1125 Patients with IS	5.8% treated with recombinant tPA	At 3 months, 29.2% of patients were disabled (RS score $>$ 2) and 11.5% died	PH, but not HT, was independently associated with an increased risk for death or disability (OR: 15.29, 95% CI: 2.35-99.35)
Goldstein et al[21]	2362 Patients with acute IS (retrospective analysis from database)	311 Patients treated with intravenous tPA, 72 patients treated with intra-arterial thrombolysis	Risk of symptomatic HT and in-hospital mortality	Symptomatic HT was an independent predictor of in-hospital mortality (OR: 32.6, 95% CI: 8.8-120.2)
Strbian et al[19]	985 Patients with anterior IS	Intravenous thrombolysis	Impact of symptomatic ICH on mortality at 3 months	According to different definitions used risk for mortality ranged from 1.5 (95% CI 1.0-2.2) (any ICH) to 4.8 (95% CI 2.8-8.2) (Safe Implementation of Thrombolysis in Stroke Registry)

Abbreviations: CI, confidence interval; ECASS, European Cooperative Acute Stroke Study; ICH, intracerebral hemorrhage; IS, ischemic stroke; OR, odds ratio; PH2, parenchymal hematoma type 2; RS, Rankin scale; tPA, tissue plasminogen activator.

experienced PH have a 2-fold increased risk to die compared with those who did not.

Results from clinical trial on recombinant tissue plasminogen activator administration in patients with IS identified PH type 2 as significantly related to an increased risk of 3-month death.[8,20] As a consequence, cerebral hematoma, either of primitive intracerebral hemorrhage or of HT of IS, seems to play a crucial role in mortality risk. Our study underlines this association even in patients treated with conservative therapy (not thrombolysis).

HT worsen prognosis in patients with IS. In particular, the occurrence of PH increases the risk of mortality even in patients not treated with thrombolytic agents.

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